Les récepteurs couplés aux protéines G (GPCR) : de nouveaux marqueurs pour améliorer la greffe de cellules souches hématopoïétiques

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"Les récepteurs couplés aux protéines G (GPCR) : de nouveaux marqueurs pour améliorer la greffe de cellules souches hématopoïétiques"

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Résumé

La transplantation de cellules souches hématopoïétiques (HSCT) reste indispensable dans le traitement de certaines maladies malignes et non-malignes. Toutefois cette procédure et notamment sa phase de conditionnement entraîne de sérieuses toxicités liées au traitement (TRT), qui peuvent s'avérer mortelles (mortalité liée au traitement-TRM). Limiter ces toxicités tout en conservant les bénéfices de la transplantation constitue un axe de recherche essentiel. Dans ce contexte, la famille des récepteurs couplés aux protéines G (GPCR) présente de nombreux atouts pharmacologiques, déjà exploités par un nombre croissant de médicaments.

Afin de faire le point sur le potentiel de cette famille de protéines, nous avons mené une revue systématisée de la littérature sur les associations entre les GPCRs et les résultats cliniques de la transplantation. Cette revue a été publiée et constitue la publication originale de cette thèse.

Notre revue met en évidence la corrélation entre l'expression ou la manipulation de plusieurs GPCRs et la mobilisation des cellules souches hématopoïétiques de la moelle ou encore la prise de greffe (« engraftment ») chez les patients transplantés. Pour améliorer la mobilisation notamment, le plerixafor (Mozobil®), un inhibiteur de CXCR4, est déjà approuvé dans certaines indications, qui demandent à être élargies. D'autres molécules mobilisantes ciblant ce même GPCR sont en cours d'essai clinique. En revanche, des associations entre des GPCRs et les principales TRTs doivent encore être démontrées cliniquement.

Ainsi, notre revue établit le potentiel prometteur des GPCRs pour améliorer les résultats de la greffe et pourrait guider de futures études de même que des revues plus ciblées. Elle rappelle qu'un travail considérable reste à accomplir pour comprendre les mécanismes physiopathologiques des TRTs. A cet égard, notre plateforme de recherche utilise la (pharmaco-)génomique pour identifier les gènes dont les polymorphismes sont associés de manière statistiquement significative à l'une ou l'autre des TRTs. Nous étudions alors la fonction de ces gènes dans le développement des TRTs, ce qui pourrait fournir des cibles de traitement ou des biomarqueurs pour renforcer une approche toujours plus personnalisée de la transplantation.

Mots clés : transplantation de cellules souches hématopoïétiques (HSCT); toxicité liée au traitement (TRT); mortalité liée au traitement (TRM); récepteurs couplés aux protéines G (GPCR); revue systématisée; mobilisation; prise de greffe; plerixafor; pharmacogénomique.

Abstract

Hematopoietic stem cell transplantation (HSCT) remains the only curative treatment for several malignant and non-malignant diseases. However, this procedure and in particular its necessary conditioning phase comes at the cost of serious treatment-related toxicities (TRTs) if not treatment-related mortality (TRM). Limiting these TRTs while retaining the benefits of HSCT, is a major research axis. In this regard, the G protein-coupled receptors (GPCR) family exhibits attractive pharmacological properties and is already targeted by an ever-growing number of drugs.

To survey this protein family's potential, we carried out a systematized literature review of the associations between GPCRs and the clinicals outcomes of HSCT. This review was published and constitutes the original publication of this thesis.

Our review shines the light on the correlation between the expression or manipulation of several GPCRs and the mobilization or the engraftment of hematopoietic stem cells in HSCT patients. To improve mobilization in particular, plerixafor (Mozobil®), an inhibitor of the GPCR named CXCR4, is already approved for certain indications, which shall be expanded. Other mobilizing molecules targeting the same GPCR are in clinical trials. However, associations between GPCRs and the main TRTs have yet to be demonstrated clinically.

Our review establishes the promising potential of GPCRs for improving HSCT and could guide future studies as well as more focused reviews. Yet, a considerable amount of work is warranted to improve the understanding of TRTs physiopathology. In this regard, our research platform applies (pharmaco-)genomics to identify genes whose polymorphisms are statistically significantly associated with one or the other TRT. We then study the function of these genes in the development of TRTs, which could provide new treatment targets or biomarkers to further an ever more personalized approach of HSCT.

Keywords: hematopoietic stem cell transplantation (HSCT); treatment-related toxicity (TRT); treatment-related mortality (TRM); G protein-coupled receptors (GPCR); systematized review; mobilization; engraftment; pharmacogenomics.

1. Introduction

1.1 La transplantation de cellules souches hématopoïétiques (HSCT)

Contexte

Depuis les premiers essais à la fin des années 1950 à Boston [1], le nombre de greffes pratiquées a augmenté rapidement partout dans le monde, malgré des disparités régionales encore importantes [2,3]. Les progrès scientifiques et techniques ont entraîné d'une part l'extension des indications et des sources de cellules souches hématopoïétiques[4]. D'autre part, ils ont rendu possible la greffe chez des patients qui auraient été jugés inaptes il y a encore quelques années. Au moment de la millionième greffe enregistrée en 2012[5], les transplantations dites autologues, soit la réinfusion chez le patient de ses propres cellules souches préalablement prélevées, représentaient 53-58% du total des greffes (monde[6]; Europe[7]). Le myélome multiple et les lymphomes sont les principales indications de la greffe autologue. Les greffes dites allogéniques, représentant 42-47% du total [6,7], recourent à des donneurs, apparentés ou non, et sont indiquées principalement dans le traitement des leucémies, syndromes myélodysplasiques et myéloprolifératifs. En outre, la greffe allogénique est indiquée dans un certain nombre de pathologies non-malignes, qu'elles soient (auto-)immunes (p. ex. déficit immunitaire combiné sévère ou SCID), hématopoïétiques (p. ex. hémoglobinopathies, anémie aplasique) [8] ou encore métaboliques [9].

Malgré une amélioration constante des taux de survie, jusqu'à plus de 80% aujourd'hui [10,11], le cancer reste la troisième cause de mortalité chez les enfants après les accidents de la circulation et les armes à feu aux Etats-Unis [12]. La leucémie est le cancer de l'enfant le plus fréquent, avec, à l'inverse des adultes, 80% de formes lymphoïdes et 20% de formes myéloïdes. La leucémie lymphoblastique aigue (ALL) est la forme la plus commune chez l'enfant avec des taux de survie de l'ordre de 90% actuellement grâce à l'amélioration des traitements et à la stratification du risque [13]. Cependant, les rechutes ou les cas réfractaires à la chimiothérapie sont toujours porteurs d'un pronostic sombre. Même si la greffe allogénique reste le standard dans ces cas, de nouveaux traitements ont vu le jour ces dernières années; les inhibiteurs de tyrosine kinase (TKI) dans certains sous-groupes de patients [14,15], les immunothérapies et notamment les cellules porteuses d'un récepteur antigénique chimérique (CAR-T) [16,17] ou encore de nouveaux anticorps ciblés [18,19]. Toutefois, tout comme pour la greffe, ces traitements s'accompagnent d'effets secondaires importants [20,21]. En ce qui concerne la leucémie myéloïde aigue (AML), on constate les mêmes tendances bien que les progrès soient plus limités, avec une survie de l'ordre de 60%. Le traitement des cas à haut risque repose là aussi principalement sur la greffe allogénique [22–24]. Enfin, la greffe autologue est également utilisée en pédiatrie, notamment pour le traitement de certains lymphomes et neuroblastomes.

« Mobilisation » et prise de greffe

A l'origine, les cellules souches hématopoïétiques étaient extraites directement de la moelle osseuse (BM), mais cette source ne représente plus qu'un quart des greffes aujourd'hui, essentiellement allogéniques [25] (Fig. 1). Une compréhension accrue du microenvironnement de la moelle osseuse, aussi appelé « niche hématopoïétique » [26], a permis de « mobiliser » ces cellules souches de la moelle vers le sang périphérique. A cet effet, on peut utiliser notamment des facteurs de croissance, comme le G-CSF (p. ex. filgrastim), qui normalement, en cas d'infection ou de stress, stimulent la production de cellules souches dans la moelle et leur

mobilisation. D'autres types de molécules « mobilisantes » sont désormais disponibles ou en cours de développement [27]. Les cellules souches ainsi mobilisées peuvent alors être récoltées dans le sang périphérique par leucaphérèse [28]. Le degré de mobilisation est mesuré par le nombre de cellules souches périphériques (PBSC) ou de cellules sanguines nucléées récoltées et corrèle positivement avec la probabilité que la greffe prenne dans la « niche » receveuse [29,30]. Les PBSC ne sont biologiquement pas équivalentes aux cellules souches de la moelle, qui sont encore préférées dans certaines applications. Dans 10% des greffes, les cellules souches sont extraites du sang de cordon ombilical (CB) de nouveau-nés, qui peut être stocké à cet effet dans des biobanques publiques. Le potentiel de production de cellules souches *de novo* à partir de cellules adultes différenciées n'a pas encore été prouvé [31]. La prise de greffe ou « engraftment » (Fig. 1) est définie par une récupération pendant au moins 3 jours consécutifs d'un taux de neutrophiles jugé suffisant ($> 500 \times 10^6$/L) dans le sang périphérique [32]. Dans les cas allogéniques, le niveau de chimérisme peut être testé pour confirmer que les nouvelles cellules hématopoïétiques proviennent bien du donneur [33,34]. Si la greffe ne prend pas ou que les cellules du donneur sont perdues après la prise initiale, on parle alors respectivement de rejet de greffe primaire ou secondaire [35], ce qui peut s'avérer fatal.

Greffe et inflammation

Dans le cas d'une greffe autologue, les PBSC sont prélevées en amont d'un traitement oncologique à visée curative qui s'avère myéloablatif (MA). Dans le cas d'une greffe allogénique, les protocoles cliniques incluent un conditionnement myélo-ablatif ou atténué (« reduced intensity conditioning » ou RIC), c'est-à-dire une phase préparatoire (Fig. 1) durant laquelle on recourt à un traitement chimio- et/ou radio-thérapeutique pour éliminer les cellules malignes, libérer de l'espace dans la moelle mais aussi induire une immunosuppression. Cette dernière permet de diminuer le risque de rejet et de limiter le développement d'une réaction greffon-contre-hôte (GvHD) [36]. L'état de santé du patient ainsi que le type de maladie déterminent l'intensité du traitement préparatoire admise et par conséquent le degré de myélo-ablation [37]. En effet, le conditionnement induit une lyse cytotoxique des cellules malignes mais aussi de nombreuses cellules saines, ce qui entraîne un statut inflammatoire [38,39] (Fig. 1) ainsi qu'une dérégulation du microbiote intestinal [40,41]. En outre, une réaction immunitaire, elle aussi inflammatoire, se développe proportionnellement au degré d'incompatibilité génétique entre le donneur allogénique et le receveur, notamment au niveau des antigènes HLA [42]. Dans les cas oncologiques, l'inflammation promeut une réaction greffon-contre-leucémie/tumeur (GvL), nécessaire à l'élimination des cellules tumorales qui auraient résisté au conditionnement [43]. Mais l'inflammation entraîne également de graves toxicités liées au traitement ou TRTs (Fig. 1), comme les infections, les troubles de la coagulation, la cystite hémorragique, le syndrome d'obstruction sinusoïdale (SOS ; anciennement maladie veino-occlusive ou VOD), les toxicités d'organe (p. ex : pulmonaire, rénale) ou encore la GvHD. Ces toxicités peuvent conduire à une mortalité liée au traitement (TRM). Celle-ci se distingue de la mortalité causée par le rejet de la greffe ou dans les cas oncologiques, de la rechute de la maladie (« relapse ») [44]. En cours de traitement, le niveau d'inflammation peut être adapté. Les traitements immunosuppresseurs permettent de le diminuer tandis que la réinfusion de leucocytes du donneur (DLI) [45] après la greffe augmente la réaction immunitaire et l'inflammation associée, favorisant l'effet GvL. Il s'agit alors de trouver le meilleur compromis entre prévenir une rechute oncologique et minimiser les TRTs. Il existe également des traitements, voire une prophylaxie contre certains TRTs [44,46] mais ils s'avèrent encore trop souvent insuffisants.

Syndrome d'obstruction sinusoïdale (SOS)

Certaines complications précoces de la greffe hématopoïétique, comme la micro-angiopathie thrombotique ou le SOS sont initiées par une atteinte de l'endothélium [47,48]. Dans le cas du SOS par exemple, une lésion des cellules endothéliales sinusoïdales du foie est l'élément central de la pathophysiologie du SOS. Elle entraîne une activation de la cascade de coagulation, une thrombose centro-lobulaire et finalement une hypertension portale qui peut aboutir à une défaillance multi-organique [48]. Sur le plan clinique, le SOS est caractérisé par une jaunisse, une rétention hydrique, une hépatomégalie douloureuse et souvent une thrombocytopénie réfractaire à la transfusion [49,50]. 5 à 60% des patients greffés développent un SOS, en fonction de la prophylaxie [50–52] et de facteurs de risque tels que l'utilisation d'agents alkylants lors du conditionnement, l'âge du patient, ou encore une maladie hépatique préexistante. La mortalité est en diminution, de 20-30% dans les années 90, à environ 10% aujourd'hui, notamment grâce à l'introduction du coûteux défibrotide pour le traitement du SOS [53]. Son utilisation à titre prophylactique est encore débattue.

Réaction greffon-contre-hôte (GvHD)

Une réaction greffon-contre-hôte aiguë (aGvHD) est le résultat de l'activation de cellules T naïves d'un donneur allogénique par les cellules présentatrices d'antigène du donneur ou par celles du receveur [54]. Une fois activées dans les ganglions lymphatiques, ces cellules T attaquent les cellules tumorales résiduelles (GvL), mais également les cellules saines du receveur (GvHD), particulièrement au niveau de la peau, du tube digestif et du foie [55]. Le risque de GVHD aigue est déterminé notamment par la source des cellules souches, l'incompatibilité HLA, l'intensité du conditionnement ou encore le type de prophylaxie [56]. Selon la définition historique, la réaction greffon-contre-hôte chronique (cGVHD) se manifeste à partir de 100 jours post-greffe, mais on sait aujourd'hui qu'elle commence plus tôt et se chevauche avec la forme aiguë. En effet, malgré une pathophysiologie et une expression clinique différentes, les deux formes partagent certains facteurs d'initiation [57]. La pathogénèse de la cGvHD n'est d'ailleurs que partiellement comprise ; elle implique une dérégulation immunitaire et une inflammation chronique qui entraînent une réparation tissulaire aberrante et la formation de fibrose [58]. Les options thérapeutiques contre la cGvHD sont très limitées [59,60], ce qui fait d'elle le principal contributeur à la morbi-mortalité à long terme des survivants de la greffe [61]. En raison de sa chronologie, elle tend également à co-exister avec d'autres conditions chroniques et/ou liées à l'âge, comme le syndrome métabolique, les infections chroniques ou encore les cancers primaires et secondaires [62]. La cGvHD peut toucher n'importe quel organe mais s'attaque particulièrement à la peau et ses appendices, aux muqueuses, aux muscles, aux articulations et aux poumons.

Toxicités pulmonaires

Au même titre que les infections, la surcharge volumique iatrogénique, l'insuffisance rénale ou cardiaque ou encore la cGvHD, le syndrome de pneumonie idiopathique (IPS) peut occasionner de sérieuses complications pulmonaires après la greffe [44]. L'IPS est une complication précoce des greffes allogéniques, aux tableaux cliniques variés. Elle est initiée par une lésion alvéolaire aiguë et étendue, dans un contexte inflammatoire [63]. Le type et l'intensité du conditionnement, notamment l'utilisation de cyclophosphamide, ainsi que l'activation et la migration des cellules T du donneur contribuent à cette lésion [64,65].

La recherche en transplantation

Ces dernières années, la recherche s'active pour améliorer le conditionnement pré-greffe. D'une part, la généralisation des formulations intraveineuses permet le suivi thérapeutique des médicaments (TDM) pour chaque patient et l'adaptation du traitement suite à la première dose. D'autre part, de nouveaux algorithmes ont été développés pour prédire individuellement la première dose la plus adaptée (Fig. 1). Ces algorithmes sont basés sur des modèles pharmacocinétiques et incorporent ainsi des paramètres tels que le poids ou l'âge dans le calcul de la première dose [66]. Depuis peu, on commence à intégrer à ces algorithmes des variations génétiques individuelles (polymorphismes) constituées d'un (SNP) ou plusieurs nucléotides (indels) [67]. Ces variations affectent notamment les enzymes responsables du métabolisme des agents de conditionnement couramment utilisés tels que le Busulfan. On peut citer par exemple GSTM1, CYP2C9 [68], CTH [69] ou encore GSTA1 [70,71]. Certaines variations génétiques pourraient également permettre d'identifier les patients les plus à même de bénéficier d'une prophylaxie ciblée des TRTs, ou encore révéler des cibles potentielles pour le traitement ou la prophylaxie.

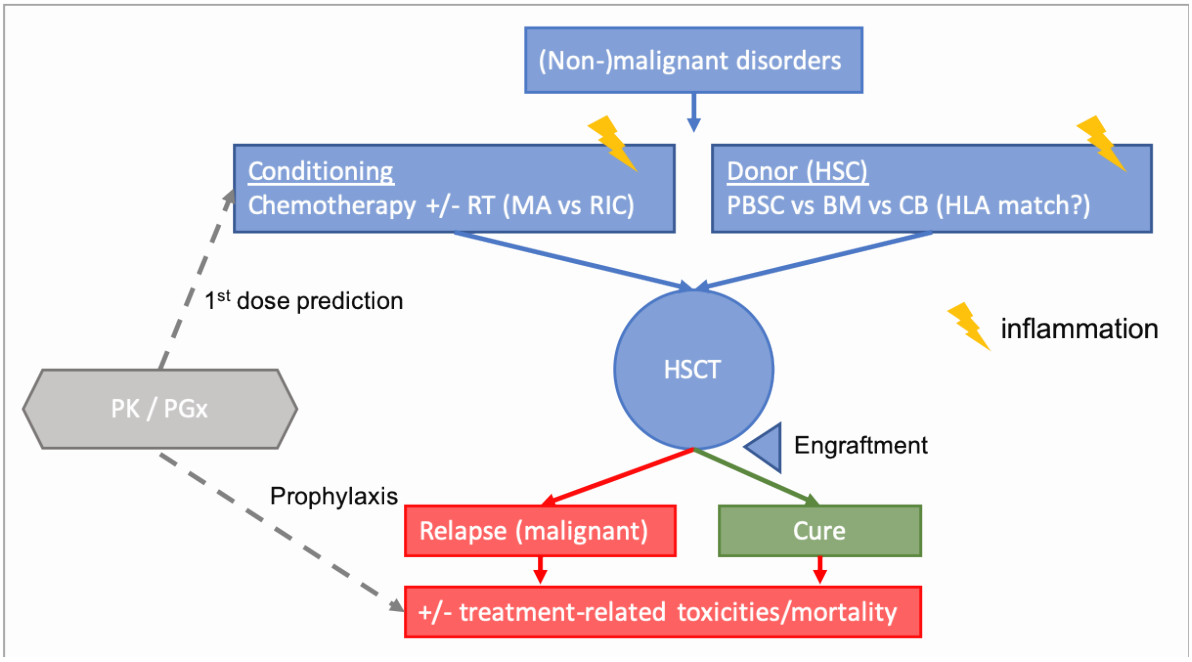

Figure 1 : La transplantation de cellules souches hématopoïétiques (HSCT). Résumé graphique des différentes étapes de la greffe et rôle joué par l'inflammation.

- Les indications à la greffe : maladies malignes et non-malignes.
- Les différentes sources de cellules souches : périphériques (PBSC), moelle (BM), sang du cordon ombilical (CB). Le degré de compatibilité HLA (HLA match), inversement proportionnel à la réaction immunitaire et inflammatoire.
- La phase préparatoire/conditionnement: chimiothérapie +/- radiothérapie (RT) ; elle aboutit à une myélo-ablation totale (MA) ou partielle (RIC) et contribue à l'inflammation.
- La prise de greffe (« engraftment »), par opposition au rejet de greffe primaire / secondaire
- Les différents résultats ("outcomes") cliniques possibles: cure ou rechute dans les cas malins; dans les deux cas des TRTs potentiellement mortelles (TRM) peuvent survenir.
- Le rôle de la pharmacocinétique (PK) et la pharmacogénétique (PGx): intégration aux algorithmes de prédiction de la première dose, prophylaxie ciblée des TRTs chez les patients à risque, identification de nouvelles cibles pour la prophylaxie, voire le traitement.

1.2 Récepteurs couplés aux protéines G (GPCR)

Signalisation moléculaire et pharmacologie

Les cellules humaines expriment quelques 400 GPCRs non-olfactifs [72], qui répondent à une large gamme de ligands endo- et exogènes ; chimiokines, lipides ou catécholamines entre autres. La signalisation cellulaire qui en résulte affecte des fonctions cellulaires clés, comme la survie, la prolifération, la migration ou encore le métabolisme [73]. Tous les GPCRs partagent une structure de base commune constituée de 7 domaines transmembranaires (7TMR) [74]. Les GPCRs peuvent être classifiés en 5 sous-familles en fonction de l'homologie de leur séquence (classification GRAFS) : glutamate, rhodopsin, adhesion, frizzled/taste2, et secretin [75]. D'un point de vue mécanistique, la liaison d'un ligand à son GPCR à la surface de la cellule induit un échange de nucléotides guanine dans la protéine G associée à la partie intracellulaire du récepteur (Fig. 2). Cet échange provoque, au niveau du récepteur, une dissociation de la sous-unité α de ses partenaires βγ, qui forment quant à eux une sous-unité dimérique. Une fois séparées, chaque sous-unité transmet son propre signal en aval. La signalisation cesse lorsqu'une GPCR kinase (GRK) phosphoryle le GPCR lié à son ligand [76], ce qui cause la liaison de molécules de β-arrestines sur le GPCR et son endocytose [77]. Une régulation a lieu à plusieurs niveaux [78,79]. De plus, les GRKs et les β-arrestines sont capables de générer des signaux indépendamment de la protéine G [78–81]. En outre, la signalisation des GPCRs interagit avec d'autres voies de signalisation bien connues comme celles des MAPK, de PI3K/Akt [82–84] ou encore des récepteurs tyrosine kinase [85,86].

Les GPCRs sont déjà la cible d'un tiers de l'arsenal thérapeutique ainsi que de nombreux médicaments en développement [87,88]. En effet, les GPCRs sont impliqué dans plusieurs pathologies humaines ; cancers, maladies cardiaques ou neurologiques entre autres [89–92]. D'un point de vue pharmacologique, leur localisation à la surface de la cellule les rend très accessibles. De plus, les progrès réalisés en cristallographie et en modélisation moléculaire ont grandement facilité le développement de médicaments ciblés [93]. Ces développements ont notamment permis la découverte récente du concept d'agoniste biaisé. Un tel agoniste est capable d'activer différemment les signalisations dépendante et indépendante de la protéine G [94,95], offrant ainsi des options thérapeutiques intéressantes [96]. Certains GPCRs, comme les récepteurs aminergiques sont très fréquemment ciblés, alors que la moitié des GPCRs ne le sont pas encore [97]. Les petites molécules dominent toujours le marché mais on constate une progression des anticorps, comme par exemple l'erenumab (Aimovig ®), le 1er anticorps monoclonal ciblant un GPCR, approuvé en 2018 pour le traitement de la migraine [98].

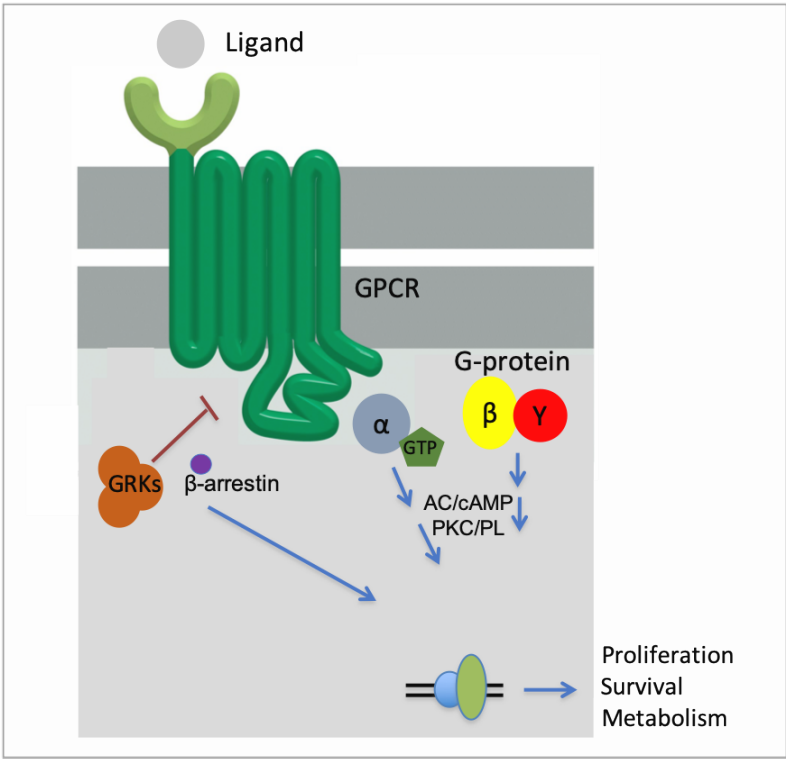

Figure 2 : Signalisation moléculaire d'un récepteur couplé aux protéines G (GPCR). La liaison du ligand à son GPCR provoque un échange de nucléotides dans la protéine G associée. Ceci induit une dissociation entre la sous-unité α et la sous-unité dimérique βγ. Chaque sous-unité active alors d'autres protéines (p. ex l'adenylate kinase ou AC et la protéine kinase C ou PKC) ainsi que des messagers secondaires (p. ex. AMP cyclique et phospholipides). Les voies de signalisation ainsi activées influencent la prolifération, la survie ou encore le métabolisme cellulaire. La phosphorylation par une GPCR kinase induit la liaison de molécules de β-arrestines, entraînant l'endocytose du GPCR. Non montré : cette signalisation interagit avec d'autres voies (e.g. MAPK, PI3K).
Adaptée à partir de « Figure 16-16 Essential Cell Biology, © Garland Science 2010 ».

GPCRs et inflammation

Le rôle des GPCRs dans l'inflammation est de mieux en mieux documenté. Les médiateurs lipidiques produits par les cellules du système immunitaire inné comme les eicosanoïdes, dont font partie les prostaglandines, les thromboxanes ou encore les leukotriènes, sont des ligands de GPCR. Ils sont responsables d'initier l'inflammation aiguë [99]. D'autres ligands GPCR, comme les endocannabinoïdes [100], les sphingolipides [101], le facteur d'activation plaquettaire (PAF)[102] ou encore les médiateurs spécialisés dans la résolution de l'inflammation (SPMs) [103], participent à la régulation de l'inflammation. Les chimiokines quant à elles, peuvent activer, via leurs GPCRs, les cellules immunitaires innées et adaptives, en plus de réguler leur trafic entre la moelle osseuse, les organes lymphoïdes secondaires et les sites inflammatoires [104–106]. Bien qu'elles constituent des cibles très attractives, seulement 3 médicaments approuvés à l'heure actuelle ciblent les chimiokines. Le maraviroc (Celsentri®), un antagoniste de CCR5 utilisé dans le traitement du VIH [107], le mogamulizumab (Potelgeo®) un anticorps anti-CCR4 employé dans le traitement des lymphomes à cellules T de l'adulte [108] et le Plerixafor (Mozobil®), un antagoniste de CXCR4, utilisé pour la mobilisation des PBSC sur lequel nous reviendrons. Finalement, bien que le récepteur beta 2-adrénergique ait été le premier GPCR

cloné de l'histoire [74], le rôle du groupe des récepteurs adrénergiques dans l'inflammation n'a que récemment été mis en lumière [109–111]. Enfin, les GPCRs participent aussi à l'inflammation par leurs interactions avec d'autres voies de signalisations comme par exemple le facteur de transcription NF-κB[112], une molécule clé dans l'inflammation. Les GPCRs et leurs ligands jouent ainsi un rôle à différents sites et à différentes étapes de l'inflammation. Bien que l'expression tissulaire spécifique de certains GPCRs soit partiellement répertoriée dans des bases de données publiques (p. ex. le Human Protein Atlas (HPA), le Genotype-Tissue Expression (GTEx) Portal ou encore Uniprot), la description temporelle et spatiale de l'expression de chaque GPCR est loin d'être acquise.

1.3 Récepteurs couplés aux protéines G et transplantation

Le récepteur C-X-C 4 (CXCR4) est un exemple marquant de la convergence entre les GPCRs et la transplantation de cellules souches hématopoïétiques. Ce GPCR est exprimé sur les cellules hématopoïétiques. Son ligand, C-X-C 12 (CXCL12), est une chimiokine produite par les cellules stromales de la niche hématopoïétique dans la moelle osseuse [113]. Leur interaction est essentielle au maintien des cellules souches dans la moelle [114]. En 2008, la Food and Drug Administration (FDA) américaine a approuvé l'utilisation du plerixafor® (AMD3100), le premier inhibiteur de CXCR4, en association avec le G-CSF, pour la mobilisation des PBSC chez les patients atteints de lymphome non-hodgkinien (NHL) ou de myélome multiple (MM) nécessitant une greffe autologue [115,116]. Afin de rendre compte des derniers développements sur le plerixafor, et surtout d'évaluer l'état des connaissances sur les liens entre d'autres GPCRs et la greffe de cellules souches hématopoïétiques, nous avons entrepris une recherche systématisée de la littérature médicale sur le sujet [117]. C'est l'objet de la publication originale de ce travail. La méthodologie et les résultats seront présentés et discutés dans les chapitres suivants.

2. Méthodes

Afin d'être le plus exhaustif possible, de minimiser les biais et de favoriser la reproductibilité de notre protocole, nous avons utilisé une partie des guidelines PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses)[118], un outil de référence pour les revues systématisées. Dans les bases de données de référence pour ce type d'article (Cochrane, Epistemonikos, Prospero), nous n'avons pas trouvé de revue systématisée pré-existante sur les associations entre le groupe des GPCRs et les « outcomes » cliniques de la greffe, excepté une revue « Cochrane » sur le plerixafor [119]. C'est pourquoi nous avons opté pour une stratégie de recherche inclusive, en prenant en compte aussi bien des études cliniques que précliniques, pour autant que ces dernières aient été basées sur un modèle de transplantation *in vivo*. En ce qui concerne la mobilisation, la recherche étant plus avancée sur le sujet, seules les études réalisées chez l'humain ont été prises en considération. Nous avons optimisé nos équations de recherche pour les bases de données MEDLINE (https://www.ncbi.nlm.nih.gov/pubmed/) et EMBASE (https://www.embase.com/). Les articles sélectionnés (en date du 4 mars 2019) devaient être écrits en anglais, et les publications de type « revue » ont été exclues. Les résultats ou « outcomes » cliniques suivant ont été sélectionnés : mobilisation, prise de greffe (engraftment), SOS, GvHD aiguë, GvHD chronique, toxicité pulmonaire ainsi que TRM. La méthodologie et ses résultats sont détaillés dans la publication originale (« Résultats ») et discutés plus loin dans cette thèse (« Discussion »).

3. Publication originale

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Review

The Biological and Clinical Relevance of G Protein-Coupled Receptors to the Outcomes of Hematopoietic Stem Cell Transplantation: A Systematized Review

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Abstract: Hematopoietic stem cell transplantation (HSCT) remains the only curative treatment for several malignant and non-malignant diseases at the cost of serious treatment-related toxicities (TRTs). Recent research on extending the benefits of HSCT to more patients and indications has focused on limiting TRTs and improving immunological effects following proper mobilization and engraftment. Increasing numbers of studies report associations between HSCT outcomes and the expression or the manipulation of G protein-coupled receptors (GPCRs). This large family of cell surface receptors is involved in various human diseases. With ever-better knowledge of their crystal structures and signaling dynamics, GPCRs are already the targets for one third of the current therapeutic arsenal. The present paper assesses the current status of animal and human research on GPCRs in the context of selected HSCT outcomes via a systematized survey and analysis of the literature.

Keywords: G protein-coupled receptor (GPCR); hematopoietic stem cell transplantation; treatment-related toxicities; mobilization; engraftment; plerixafor

1. Introduction

1.1. Hematopoietic Stem Cell Transplantation (HSCT)

The field of hematopoietic stem cell transplantation (HSCT) has witnessed t remendous progress since its origins in the 1950s [1]#. The number of HSCTs has exploded, along with its range of indications, candidates, and donor sources [2,3]#. HSCT remains indispensable for treating several malignant and non-malignant disorders. The use of peripheral blood stem cells (PBSCs) is well established in autologous transplantation [4]#, and they have become the preferred source of allogeneic hematopoietic stem cells (HSCs), at least in adults [5,6]#. In both scenarios, the number of circulating HSCs mobilized from the bone marrow is closely associated with the engraftment outcome [7]#. Before the graft infusion, most HSCT protocols require a preparation phase, which aims to kill malignant cells to make room for the newly infused HSCs to engraft or to induce immunosuppression. The latter is important to avoid graft rejection and graft-versus-host disease (GvHD) in allogeneic settings. This so-called conditioning regimen comprises high doses of chemotherapeutic drugs and/or radiotherapy that cause a cytotoxic burst of tumor and/or normal cells. This results in a pro-inflammatory status [8,9]#, which is desired

when treating malignant conditions with allogeneic HSCT, as it promotes a graft-versus-leukemia (GvL) effect. On the other hand, uncontrolled inflammation results in serious treatment-related toxicities (TRTs), such as sinusoidal obstruction syndrome (SOS), lung toxicity, or GvHD, the negative counterpart of GvL. Recent research efforts have focused on limiting transplantation- or treatment-related mortality (TRM) and TRTs while improving the beneficial immunological effects after adequate mobilization and engraftment.

1.2. G Protein-Coupled Receptors (GPCRs)

Human cells express some 400 non-olfactory G protein-coupled receptors (GPCRs) [10]# that respond to a large variety of ligands and thereby affect key cellular functions such as survival or proliferation [11]#. GPCRs, also known as seven-transmembrane spanning receptors (7TMRs), are classified into five subfamilies based on sequence homology: glutamate, rhodopsin, adhesion, frizzled/taste2, and secretin [12]#. Mechanistically, a ligand binding to its cognate GPCR induces the dissociation and the activation of α and $\beta\gamma$ subunits in the associated G protein. This signaling ceases upon GPCR phosphorylation by a GPCR kinase (GRK), which causes the binding of a β-arrestin and GPCR endocytosis [13]#. Regulation occurs at multiple levels, whereas GRKs and β-arrestins can also generate G protein-independent GPCR signaling [14–17]#. GPCRs or their ligands are targeted by a third of all approved drugs, and many more are in development [18]#. Their ubiquity and location at the cell surface make them attractive targets. In addition, many GPCR-ligand crystal structures are already available, and steady progress in the fields of crystallization and molecular modeling has facilitated GPCR drug development [19,20]#. For instance, the discovery of "biased" GPCR agonists, which can differentially activate G protein-dependent and G protein-independent signaling, holds the promise of fine-tuning the pharmacological modulation of GPCRs [21,22]#. Importantly, GPCRs have been linked to multiple human diseases [23–26]#, and their roles in regulating inflammation are increasingly recognized. Lipid mediators produced by innate immune cells such as the eicosanoids, which include prostaglandins, thromboxanes, and leukotrienes, signal via GPCRs to initiate acute inflammation [27]#. Other related classes of GPCR lipid ligands, such as endocannabinoids [28]#, sphingolipids [29]#, or even the so-called specialized pro-resolving mediators (SPMs) [30]#, also participate in the regulation of inflammation. In turn, chemokines can activate, via GPCRs, both innate and adaptive immune cells and regulate their traffic between lymphoid organs and inflammatory sites [31]#. Finally, although the Beta-2 adrenergic receptor (B2AR) was the first GPCR ever cloned [32]#, the role of adrenergic receptors in modulating immunity and inflammation has only recently been brought to light [33–35]#. Discussing time and tissue-specific expression patterns of each GPCR is beyond the scope of this review, but this type of information can be found in part in the references above or in public databases such as the Human Protein Atlas (HPA) or the Genotype-Tissue Expression (GTEx) Portal.

1.3. HSCT and GPCR: Plerixafor and Beyond

C-X-C receptor 4 (CXCR4) is a noticeable example of the convergence between GPCRs and HSCT. C-X-C ligand 12 (CXCL12) is a chemokine produced by the stromal cells populating the hematopoietic niche in the bone marrow (BM) [36]#. CXCL12 exerts its function by binding CXCR4, a GPCR present on the surface of hematopoietic cells. That interaction is essential for the homing and the maintenance of HSCs in the BM [37]#. In 2008, the Food and Drug Administration (FDA) approved the use of the first-in-class CXCR4-inhibitor, plerixafor (AMD3100; Mozobil®), in association with granulocyte colony-stimulating factor (G-CSF) for the mobilization and the collection of PBSC in patients with non-Hodgkin's lymphoma (NHL) and multiple myeloma (MM) [38–40]#. In this regard, the present paper assesses the new developments concerning plerixafor, which have occurred since the last systematic review on the topic [41]#. Importantly, this paper also surveys the available evidence linking other GPCRs to HSCT outcomes, for which there was not any existing comprehensive review (see the Appendix A.1). With this in mind, we prepared a systematized search of the medical literature.

2. Results and Discussion

2.1. Mobilization

Mobilization of HSC from the BM into peripheral blood (PB) is usually measured by the number of circulating $CD34^+$ and/or nucleated blood cells harvested using leukapheresis [42]#. The standard mobilization agent is recombinant granulocyte colony-stimulating factor (G-CSF; filgrastim or lenograstim), an endogenous growth factor responsible for inducing granulocyte expansion and maturation in times of infection or stress [43]#.

Within the group of chemokines (Table 1), the *CXCL12 3'UTR A* allele (rs1801157; g.44372809G>A) has shown positive correlation with mobilization in both healthy donors and patients undergoing autologous transplantation [44–46]. The functional consequence of this *CXCL12* (*SDF-1*) polymorphism is still unclear, but it may lead to lower protein levels [47]#. This would concur with abounding evidence on CXCR4, the CXCL12 receptor, whose blockade promotes mobilization when using plerixafor.

As expected, several publications on plerixafor (47) were relevant, with most assessing mobilization for autologous HSCT in MM and lymphoma patients. Although an improvement may be achieved by increasing the dose [48]#, plerixafor has been demonstrated to be less efficient as a monotherapy than in combination with G-CSF [49]. Interestingly, in patients responding poorly to G-CSF ($< 20 \times 10^6$/L CD34+ cells in PB), pre-emptive plerixafor treatment led to a final yield equivalent to a rescue strategy administered to patients with insufficient leukapheresis [50]. Several additional studies have endorsed the use of plerixafor in autologous transplantation for diabetic patients [51] and pediatric patients [52–54], whereas other articles have supported its use in elderly patients and those with renal insufficiency [55,56]#.

Two early studies also showed plerixafor to be efficient in mobilizing healthy allogeneic donors with a reasonable safety profile [57,58], and this was later reported by a phase I/II trial [59]#. Examining these varied studies, an extension of plerixafor indications is to be expected in the coming years, as are new pharmacological alternatives. Indeed, new compounds targeting CXCR4 are in development: small molecules (TG-0054 [60–62]) such as plerixafor, but also peptides (BL-8040 [63], (BK)T140 [64], POL6326 [65], LY2510924 [66]), or oligonucleotides (NOX-A12 [67]). All have already been tested in humans as part of phase I or early phase II clinical trials.

Finally, although the $CD34^+$ count in PB remains the most used predictor for guiding cost-efficient mobilization regimens [68]#, new biomarkers are being eagerly sought to improve individualized prescriptions. Nonetheless, the expression of CXCR4 in $CD34^+$ HSC in correlation with mobilization has thus far shown discordant findings [69–71], and additional studies are needed.

Table 1. Mobilization in human (H) studies. Mobilization is measured by the number of circulating $CD34^+$ (HSC) and/or nucleated blood cells harvested using leukapheresis. See the Methods section regarding the reporting of results (Section 3.2).

Mobilization			
	Studies	**Correlation with outcome**	**References**
C-X-C ligand 8 (CXCL8)	H	+	[72]
C-X-C ligand 12 (CXCL12)	H	0	[73]
	H (rs1801157)	+	[44–46]
C-X-C receptor 4 (CXCR4)	H	–	[49–54,57,58,60–67, 69–71,74–101]
Beta-3 adrenergic receptor (B3AR)	H	+	[102]
Protease-activated receptor 1 (PAR1)	H	+	[103]
Relaxin/insulin-like family peptide receptor 4 (RXFP4)	H	+	[104]

2.2. Engraftment

Engraftment in humans is assessed in PB and defined by the stable recovery of blood cell counts after myeloablative conditioning and graft infusion: platelets $> 50 \times 10^9$/L in the absence of transfusion

(platelet engraftment); or neutrophils > 500×10^6/L (neutrophil engraftment) [105]#. In allogeneic HSCT, additional genetic testing for chimerism is performed to confirm the donor origin of the hematopoietic recovery [106,107]#. The absence of engraftment or the loss of donor cells after initial engraftment constitute primary and secondary graft failure (GF), respectively [108]#. In animal studies, mostly on mice, competitive repopulation assays allow for a much larger toolkit of measurements of HSC engraftment capacity [109]#.

The use of anti-CXCR4 compounds for mobilization in the donor did not preclude engraftment in humans [61,85,94,95,110,111] or mice [112], with some studies reporting even better engraftment in mice [113,114] (Table 2). Targeting CXCR4 could also improve engraftment by vacating the hematopoietic niches in the recipient before HSCT, either via chimeric antigen receptor (CAR) T cells co-expressing CXCR4 and C-kit or via plerixafor [115–117]. Despite discordant results in mice [118], plerixafor administration post-HSCT in human recipients improved engraftment in one phase I/II clinical trial [119]. In this study, "mobilizing" doses of plerixafor were started from day 2 post-HSCT and continued until day 21 or neutrophil engraftment.

Conversely, CXCR4 expression in both mice and human cells correlated positively with autologous and xeno-engraftment [120,121]. In humans, following G-CSF mobilization, CXCR4 expression showed a positive correlation with engraftment [122–124]. Surprisingly, here, the *CXCL12 3'UTR A* polymorphism whose occurrence had been associated with increased mobilization (see the Mobilization subsection) was associated with faster hematopoietic recovery in autologous transplant patients [125]. Indeed, if it really decreased protein expression, one would expect reduced homing of the graft CXCR4+ HSC by CXCL12-expressing stromal cells. However, more research seems warranted to define the timing of CXCR4 requirements both before and during the course of engraftment.

CXCL12-CXCR4 may also act indirectly. Prostaglandin E2 (PGE2) ex vivo treatment of murine HSC improved their BM homing and engraftment through increased expression of CXCR4 [126–129]. Similarly, inhibition of Bone Morphogenetic Protein (BMP) signaling in recipients increased CXCL12 levels and engraftment [130]. In a zebrafish model, CXCL8/CXCR1 expression by endothelial cells in the hematopoietic niche helped HSC engraftment, partly via CXCL12 upregulation [131].

Concerning other chemokines, high levels of interferon gamma-dependent CXCL9 [132,133] have been associated with GF in humans. In mice, knocking out (CXCR2) delayed hematopoietic recovery [134]. On the other hand, CCR1 expression marked human HSC as responsible for high levels of xeno-engraftment in mice [135]. These are some examples of the contribution of chemokines to hematopoietic-niche integrity.

There is less evidence available for other classes of GPCR. For instance, the engraftment of cells mobilized by cannabinoid receptor 2 (CB2) agonism [136] in animals or Beta-3 adrenergic receptor (B3AR) agonism [102] in humans was equivalent to those mobilized by G-CSF. Frizzled-6 (Fzd-6), a class F GPCR for Wnt protein ligands [137]#, is another potential contributor, as it was shown to be necessary for BM reconstitution beyond the homing phase [138]. A potentially clinically relevant finding is the presence of auto-antibodies activating Angiotensin 1 receptor (AT1R) in human allogeneic HSCT recipients, described in auto-immune settings [139]# and solid organ allo-rejection [140]#, and their association with decreased engraftment[141].

Table 2. Engraftment in animal (A) or human (H) studies. In humans, engraftment is measured by either the time to platelet/neutrophil recovery, chimerism, or the absence of graft failure. In animals, genetic manipulation allows for various measures of engraftment. See the Methods section regarding the reporting of results (Section 3.2).

Engraftment			
	Studies	**Correlation with Outcome**	**References**
C-C ligand 15 (CCL15)	A	+	[142]
C-X-C ligand 9 (CXCL9)	H	–	[132,133]
C-X-C ligand 12 (CXCL12)	H (rs1801157)	+	[125]
	A	+	[130]

Table 2. *Cont.*

Engraftment			
	Studies	**Correlation with Outcome**	**References**
C-C receptor 1 (CCR1)	A	+	[135]
C-X-C receptor 1 (CXCR1)	A	+	[131]
C-X-C receptor 2 (CXCR2)	A	+	[134,143]
C-X-C receptor 4 (CXCR4)	A, H	+	[120,121,144–147] (A), [122–124,148] (H)
		0	[112,118] (A), [61,85,94,95,110,111] (H)
		–	[113–117,149] (A), [119] (H)
Gai-coupled chemokine receptors (Pertussis toxin)	A	0	[150]
Angiotensin 1 receptor (AT1R)	H	–	[141]
Beta-3 adrenergic receptor (B3AR)	H	0	[102]
Cannabinoid receptors 1/2 (CB1/CB2)	A	0	[136]
Prostaglandin E2 (PGE2)	A	+	[126–129]
Prostaglandin I2 (PGI2)	A	+	[151,152]
Sphingosine-1-phosphate receptor 3 (S1PR3)	A	–	[153]
Calcium receptor (CaR)	A	+	[154]
Frizzled-6 (Fzd-6)	A	+	[138]
GPCR-associated sorting protein 2 (Gprasp2)/Armadillo repeat-containing X-linked protein 1 (Armcx1)	A	–	[155]

2.3. Sinusoidal Obstruction Syndrome (SOS)

Some early HSCT complications such as thrombotic microangiopathy and SOS are initiated by endothelial cell damage [156,157]#. SOS, formerly called veno-occlusive disease of the liver (VOD), occurs in 5–60% of HSCT patients, depending on prophylaxis and risk factors [158–160]# such as the underlying disease, the use of alkylating agents for conditioning, patient age, or liver disease. Sinusoidal endothelial cell damage is the key step in the pathophysiology of SOS, leading to the activation of the coagulation cascade, centrilobular thrombosis and consequent post-sinusoidal hepatic hypertension and, potentially, multiple-organ failure [157]#. Clinically, SOS is characterized by jaundice, fluid retention, painful hepatomegaly, and often thrombocytopenia refractory to transfusion [160,161]#.

Our review strategy identified no direct associations between any GPCRs and SOS occurrence or severity, yet some additional reports caught our attention. For example, recombinant thrombomodulin (rTM) is approved in Japan to treat disseminated intravascular coagulation (DIC) and has been shown to reduce SOS and the occurrence of thrombotic microangiopathy in HSCT patients [162,163]#. In two murine SOS models, one using monocrotaline (MCT) and the other using busulfan/cyclophosphamide conditioning followed by HSCT, rTM's cytoprotective effect was demonstrated to depend on its fifth epidermal growth factor-like region (TME5) [164,165]#. A murine model of tacrolimus-induced vascular injury showed that the pro-angiogenic functions of TME5 depended on its binding to G protein-coupled receptor (GPR) 15 [165,166]#. rTM was able to mitigate aGvHD in mice in a GPR15-dependent manner [167]#. However, this GPR15 dependency has yet to be demonstrated directly for SOS in vivo. Interestingly, the oligonucleotide—defibrotide—the only FDA/European Medicines Agency (EMA)-approved drug for the treatment of SOS [168]#, was shown to increase thrombomodulin expression in humans [169]#.

A traditional Japanese medicine called Dai-kenchu-to (DKT) was able to attenuate liver damage but not prevent the development of SOS induced by MCT [170]#. As a potential mechanism, MCT-induced CXCL1 (or CINC1) upregulation was suppressed in the DKT-treatment group, which could be a potential mechanism for explaining the associated reduction of neutrophil accumulation in the liver.

2.4. Graft-Versus-Host Disease (GvHD)

2.4.1. Acute GvHD

Acute GvHD (aGvHD) occurs when naïve T cells from an allogeneic donor are activated by recipient or donor antigen-presenting cells to attack recipient cells [171]#. This process is triggered by the inflammatory setting of HSCT. Once activated within lymph nodes, the alloreactive effector T cells migrate to the skin, the gastrointestinal (GI) tract, or the liver, causing further inflammation and damage [172]#. Some of the main determinants of aGvHD risk are the sources of HSCs themselves, donor–recipient HLA mismatches, the intensity of the conditioning regimen, and the absence of any GvHD prophylaxis [173]#. Immunosuppression is systematically used to prevent and treat aGvHD [174]#. Like other immune cells, T cell trafficking is regulated by myriad chemo-attractants, including chemokines. A study of the expression kinetics of a panel of chemokines and receptors in GvHD-target organs following allo-HSCT compared that expression to the histopathological changes occurring in the same organs [175]#. Characterization of the individual contributions of each chemokine/receptor would be needed to make further conclusions, but it highlights that aGvHD is a dynamic process with a complex spatiotemporal network of chemo-attractants at play.

A number of chemokines or their receptors are associated with the development of aGvHD (Table 3). For instance, higher CCL8 levels correlated with more severe murine aGvHD [176], and CCR2 expression on $CD8^+$ effector T cells was necessary for their migration to the murine gut and the liver and for the generation of aGvHD [177]. In contrast, broad inhibition of CCL2, CCL3, and CCL5 reduced murine liver aGvHD [178]. Also in mice, anti-CD3 treatment during preconditioning reduced aGvHD by limiting both $CCR7^+$ dendritic cells homing to lymph nodes and $CCR9^+$ effector T cells homing to aGvHD target organs without reducing GvL [179]. In humans, both a CCL5 (RANTES; Regulated on Activation, Normal T Cell Expressed and Secreted) haplotype of three polymorphisms [180] and the expression of the CX3CL1/CX3CR1 pair [181] positively correlated with the occurrence of aGvHD. Depending on the cells bearing GPCRs, other chemokine receptors can prevent aGvHD. The presence of CCR8 on regulatory T cells (Tregs) is crucial to their anti-GvHD action in mice [182], whereas Chem23R, another chemo-attractant receptor [183], prevents intestinal aGvHD in mice [183]. The *CXCL12 3'UTR A* allele previously discussed for mobilization and engraftment was here associated with reduced risk and severity of aGvHD [184], highlighting the favorable prognosis carried by this allele. The anti-CCR4 antibody, mogamulizumab, is currently approved for human use before HSCT to treat certain adult T-cell leukemias. This might accelerate subsequent aGvHD because it not only targets $CCR4^+$ tumor cells but also $CCR4^+$ Tregs [185,186]. Higher CCR5 and CCR9 levels were detected on children's memory effector T cells before they developed GI aGvHD [187].

CCR5 is particularly interesting and is used by human immunodeficiency virus (HIV) as a co-receptor for entry into $CD4^+$ T cells, thus partly explaining the genetic susceptibility to HIV infection [188]#. Maraviroc, a CCR5-antagonist, was approved in 2016 for the treatment of HIV. In the context of HSCT, the CCR5 Δ32 mutation was first associated with lower aGvHD [189,190]. Several related studies subsequently showed different subgroups of $CCR5^+/CD4^+$ T cells could be associated with intestinal aGvHD [191–193]. Similarly, dendritic cells expressing CCR5 could be associated with aGvHD [194–196], showing that CCR5 could be a chemo-attractant for several causative immune cell types. Two phase I/II trials have now tested the safety and the efficacy of CCR5 blockade using maraviroc for the prevention of aGvHD. The first trial, conducted in adults [197], proved successful and led to follow-up studies by the same group of researchers [198–202] as well as an ongoing phase II study (NCT01785810). Another trial [203], published in 2019, included adults and children but had inconclusive findings due to unrelated toxicities. According to its authors, CCR5 blockade could prevent lymphocyte homing but not their activation, highlighting the temporal complexity of immune activation. In mice, three studies have shown the absence of CCR5 to accelerate aGvHD [204–206]. Nevertheless, more recent studies demonstrated that another anti-CCR5 antibody, (PRO-140) [207], or maraviroc combined with either cyclosporine A [208,209] or CXCR3 blockade [210], could indeed

prevent aGvHD in mice. CXCR3 also demonstrates a compelling case. One study showed that CXCR3-expressing Tregs could mitigate aGvHD [211], and more recent studies indicated a positive correlation between CXCR3 expression and aGvHD in mice [210,212–217] and humans [200,218]. One of these proposed CXCR3-signaling as a resistance mechanism to CCR5 blockade [200]. As for CCR6 and 7 [179,194,195,219–224] or CXCR2 and 4 [225–229], the evidence has been too heterogeneous and conflicting to draw any conclusions. Using combined blockade at several steps in the immune activation underlying aGvHD could create a synergy to reduce its severity. However, additional studies are needed, especially to assess the potential of abrogating the GvL effect with such an approach.

Among adrenergic receptors, alpha-2 adrenergic receptor (A2AR) agonism [230,231] or beta-adrenergic receptor (BAR) activation under stressful conditions [232,233] was associated with lower aGvHD in mice, and so was $P2Y_2$ knock-out [234]. The previously mentioned AT1R auto-antibodies were also revealed to be associated with increased aGvHD in humans [141]. Some interesting candidates have also emerged from the class of lipid mediators. The role played by the endocannabinoid system (ECS) in inflammation is now established [28]#, and the ECS was previously implicated in solid organ rejection [235,236]#. In mice, CB1/2 activation with tetrahydrocannabinol (THC) was able to mitigate aGvHD [237], whereas transplants where CB2 was knocked-down induced higher aGvHD [238]. In a human phase II trial, cannabidiol was also able to prevent aGvHD [239]#. The broad $S1P_1$ agonist, fingolimod, is approved for the treatment of multiple sclerosis and works by sequestering lymphocytes in secondary lymphoid organs [240]#. A more specific agonist (CYM-5442) was shown to reduce the severity of murine aGvHD by inhibiting macrophage recruitment via a reduction of CCL2 and CCL7 expression on endothelial cells [241].

Among the other GPCR classes, complement 3/5 activator fragments receptors (C3aR/C5aR) [242] or platelet-activating factor receptor (PAFR) [243] in mice, as well as a microsatellite in human EGF, Latrophilin, and Seven Transmembrane Domain-Containing Protein 1 (ELTD1) [244], have all shown positive correlation with aGvHD. A frizzled agonist was able to rescue $LGr5^+$ gastric stem cells from murine aGvHD [245], underlining the importance of each target organ's microenvironment. Activated protein C (aPC) signaling using protease-activated receptor 2/3 (PAR 2 and 3) expanded Tregs and mitigated aGvHD in mice [246]. rTM depends on GPR15 to mitigate murine aGvHD [167], whereas human patients receiving rTM were shown to have lower CCL5 levels and aGvHD [247]. The case of GPR43 merits further discussion; it is a sensor of gut microbiota-derived metabolites, such as short-chain fatty acids (SCFAs). These metabolites limit a number of inflammatory processes via action on endothelial cells [248]# by modulating neutrophil recruitment [249]# or the $CD8^+$ T cell's effector function [250]#. In the intestine, GPR43 contributes to epithelial integrity, and GPR43 knock-out in mice was associated with the increased severity of aGvHD [251].

Table 3. Acute GvHD occurrence/severity in animal (A) or human (H) studies. See the Methods section regarding the reporting of results (Section 3.2).

aGvHD			
	Studies	**Correlation with Outcome**	**References**
C-C ligand 2 (CCL2)	A	+	[178]
C-C ligand 3 (CCL3)	A	+	[178]
C-C ligand 5 (CCL5; RANTES)	A	+	[178]
	H	+	[180]
	H (haplotype)	+	[247]
C-C ligand 8 (CCL8)	A	+	[176]
C-X-C ligand 10 (CXCL10)	A	+	[252]
C-X-C ligand 12 (CXCL 12)	H (rs1801157)	+	[184]
C-X-C ligand 13 (CXCL 13)	A	+	[253]
C-X3-C ligand 1 (CX3CL1)	A	+	[181]
C-C receptor 1 (CCR1)	A	+	[175]
C-C receptor 2 (CCR2)	A	+	[175,177]
C-C receptor 4 (CCR4)	H	–	[185,186]

Table 3. *Cont.*

aGvHD			
	Studies	**Correlation with Outcome**	**References**
C-C receptor 5 (CCR5)	A, H	+	[207–210](A), [187,189–202,254] (H)
	H	0	[203]
	A	–	[204–206]
C-C receptor 6 (CCR6)	A, H	+/–	[223] (A, –)/[219] (H, +)
C-C receptor 7 (CCR7)	H	+	[179,194,195]
	A, H	–	[220,221] (A), [222–224] (H)
C-C receptor 9 (CCR9)	H	+	[179,187]
C-C receptor 8 (CCR8)	A	–	[182]
Chemerin receptor 23 (Chem23R)	A	–	[183]
C-X-C receptor 2 (CXCR2)	A	+/–	[226](+)/[225] (–)
C-X-C receptor 3 (CXCR3)	A, H	+	[175,210,212–217](A), [200,218] (H)
	A	0	[255]
	A	–	[211,256]
C-X-C receptor 4 (CXCR4)	A, H	+	[225] (A), [227] (H)
	A	–	[228,229] (A)
Alpha-2 adrenergic receptor (A2AR)	A	–	[230,231]
Angiotensin 1 receptor (AT1R)	H	+	[141]
Beta-adrenergic receptor (BAR)	A	–	[232,233]
P2Y purinoreceptor 2 ($P2Y_2$)	A	+	[234]
Cannabinoid receptor 1 and 2 (CB1/CB2)	A	–	[237]
Cannabinoid receptor 2 (CB2)	A	–	[238]
Sphingosine-1-Phosphate 1 (S1P1)	A	–	[241]
Complement 3/5 activator fragments receptors (C3aR/C5aR)	A	+	[242]
EGF, Latrophilin and Seven Transmembrane Domain-Containing Protein 1 (ELTD1)	H (microsatellite)	+	[244]
G Protein-Coupled Receptor 15 (GPR15)	A	–	[167]
G Protein-Coupled Receptor 43 (GPR43)	A	–	[251]
Leucine-rich repeat-containing G protein-coupled receptor 5 (LGR5)	A	–	[245]
Platelet-activating factor receptor (PAFR)	A	+	[243]
Protease-activated receptor 2/3 (PAR2/3)	A	–	[246]

2.4.2. Chronic GvHD

Chronic cGvHD (cGvHD) historically develops from 100 days after allogeneic HSCT, but it can nevertheless overlap with aGvHD, as it shares some initiating events, although it has different pathophysiology and clinical manifestations [257]#. Although it has not been completely elucidated, cGvHD pathogenesis involves chronic inflammation, aberrant tissue repair, and fibrosis, while the underlying immune dysregulation affects multiple cell types [258]#. The therapeutic arsenal against cGvHD is limited [259,260]#, making cGvHD the main contributor to TRM in long-term HSCT survivors [261]#. Due to its timescale, cGvHD overlaps with other chronic and/or age-related conditions, such as metabolic syndrome, chronic infections, or second primary cancers [262]#. cGvHD can affect virtually any organ but strikes the following systems in particular: skin and its appendages, mucosae, muscles and joints, and lungs.

High levels of several CCL and CXCL chemokines [263–267] have shown positive correlation with cGvHD, although most of the evidence originated from a single animal study [263] (Table 4). The expression of CXCL9 [267–271], CXCL10 [265,266,269,270,272,273], and CXCL11 [270], as well as their common receptor, CXCR3 [269–274], correlated positively with cGvHD in humans. Some

chemokine receptors (CCR1, 3, 6, 7, 9) [263,275–277] showed positive correlation, whereas the correlation with some others (CXCR5, CX3CR1) [278,279] was negative. The available evidence on CCR4 and CCR5 is conflicting. High CCR4/5 levels in the buccal mucosa and salivary glands have been associated with higher T cell infiltrates and cGvHD [265]. However, in another study, $CCR4^+$ $CD4^+$ T cells were associated with lower cGvHD [280], although the authors did not specify the subset of $CD4^+$ T cells in question. Similarly, lower CCR5 on monocytes could be associated with cGvHD in joints [279]. Considering the large variety of immune cells involved in cGvHD, chemokines are naturally expected to play different roles during its course. It is still interesting to note that, as for aGvHD, CB2 knock-out is associated with more severe cGvHD. To date, evidence for the other GPCRs [Prostaglandin D2 receptor (PGD2R), AT1R, smoothened (SMO), CB2] is either conflicting or based on single studies.

Table 4. Chronic GvHD occurrence/severity in animal (A) or human (H)studies. See the Methods section regarding the reporting of results (Section 3.2).

cGvHD			
	Studies	**Effect**	**References**
C-C ligand 2 (CCL2)	A	0	[281]
C-C ligand 3 (CCL3)	H	+	[266]
C-C ligand 5 (CCL5)	A	+	[264]
C-C ligand 6 (CCL6)	A	+	[263]
C-C ligand 7 (CCL7)	A	+	[263]
C-C ligand 8 (CCL8)	A	+	[263]
C-C ligand 9 (CCL9)	A	+	[263]
C-C ligand 11 (CCL11)	A	+	[263]
C-C ligand 19 (CCL19)	A	+	[263]
C-C ligand 22 (CCL22)	H	+	[265]
C-X-C ligand 2 (CXCL2)	A	+	[263]
C-X-C ligand 8 (CXCL8)	H	+	[266]
C-X-C ligand 9 (CXCL9)	A, H	+	[263] (A), [267–271] (H)
C-X-C ligand 10 (CXCL10)	A, H	+	[263] (A), [265,266,269,270,272,273] (H)
C-X-C ligand 11 (CXCL11)	H	+	[270]
C-X-C ligand 12 (CXCL12)	A	+	[263]
C-C receptor 1 (CCR1)	A	+	[263]
C-C receptor 2 (CCR2)	A	0	[281]
C-C receptor 3 (CCR3)	H	+	[276]
C-C receptor 4 (CCR4)	H	+/−	[265] (+)/[280] (−)
C-C receptor 5 (CCR5)	H	+/−	[265] (+)/[279] (−)
C-C receptor 6 (CCR6)	H	+	[275]
C-C receptor 7 (CCR7)	H	+	[282]
C-C receptor 9 (CCR9)	H	+	[277]
C-X-C receptor 3 (CXCR3)	H	+	[269–274]
C-X3-C receptor 1 (CX3CR1)	H	−	[279]
C-X-C receptor 5 (CXCR5)	A	−	[278]
Angiotensin 1 receptor (AT1R)	H	+	[283]
Cannabinoid receptor 2 (CB2)	A	−	[238]
Prostaglandin D2 receptor (PGD2R; CRTH2)	H	+/−	[276] (+)/[280] (−)
Smoothened (SMO)	A	+	[284]

2.5. Lung Toxicity

Pulmonary complications following HSCT are a cause of morbidity and mortality. They arise from infections, iatrogenic fluid overload, idiopathic pneumonia syndrome (IPS), and as a consequence of renal or cardiac failure or cGvHD [285]#. IPS is an early complication of allogeneic HSCT that encompasses a spectrum of clinical presentations arising from acute, widespread alveolar injury [286]#. The type and the intensity of conditioning medication, especially cyclophosphamide, and the activation and the migration of donor T cells are important contributors to that injury [287,288]#. Various

cellular and soluble inflammatory mediators are thought to play a role in the development of IPS [286,289]#. Our systematized search of the literature found several animal studies reporting associations between chemokines and/or receptors and the occurrence of IPS (Table 5). CXCL 9 and 10, and their receptor, CXCR3 [290], in addition to CCL5 (RANTES) [178,291], showed positive correlation with IPS. For CCL2 [178,292,293] and CCL3 [178,294], the evidence was more conflicting. As with GvHD, specific chemokines probably correlate with distinct immune cell functions during the course of IPS [286]#. No reports of associations were found for any other functional classes of GPCR. It is interesting to note that no new studies on this have been published in the last ten years.

Table 5. Lung toxicity occurrence/severity in animals (A) or humans (H). See the Methods section regarding the reporting of results (Section 3.2).

Lung Toxicity			
	Studies	**Effect**	**References**
C-C ligand 2 (CCL2)	A	+/0	[178,292] (+)/[293](0)
C-C ligand 3 (CCL3)	A	+/−	[178] (+)/[294] (−)
C-C ligand 5 (CCL5) or Regulated on Activation, Normal T Cell Expressed and Secreted (RANTES)	A	+	[178,291]
C-X-C ligand 9 (CXCL9)	A	+	[290]
C-X-C ligand 10 (CXCL10)	A	+	[290]
C-C receptor 2 (CCR2)	A	0	[293]
C-X-C receptor 3 (CXCR3)	A	+	[290]

2.6. Treatment-Related Mortality (TRM)

TRM comprises deaths not due to the underlying disease. In cases of malignant diagnoses, this means death not due to a relapse of the disease, also sometimes called non-relapse mortality (NRM) [295]#. GvHD, VOD, lung toxicity, and infections due to HSCT-related immunosuppression are important causes of TRM [285]#. Mortality rates are tightly linked to responses to the initial treatments for each one of those complications; refractory aGvHD, for instance, is fatal in up to 80% of cases [285]#. Animal transplantation models do not usually recapitulate the underlying diseases for which human HSCTs are indicated, thus defining TRM seems futile in animal studies. In contrast, in human studies, two human polymorphisms in CCL2 (rs1024610, NG_012123.1:g.2936T>A) [296] and CXCL10 (rs3921, NM_001565.3:c.*140G>C) [297] have been associated with increased and decreased TRM, respectively (Table 6). The study on CCL2 found no significant associations between the variant and aGvHD, suggesting that another TRT could be the cause of the observed TRM. In contrast, in the study on the CXCL10 variant, lower TRM was associated with lower organ failure. CXCL9 was part of a four-biomarker panel associated with TRM [268]. High CCR5 expression in recipient T cells increased TRM [198,254], whereas a $CD4^+$ $CCR5^+$ cell population was associated with higher TRM [191]. In another study, $CCR7^+$ $CD4^+$ T cells were associated with death from cGvHD [298]. No reports of associations were found for any other functional class of GPCR.

Table 6. Treatment-related mortality (TRM) in humans (H). See the Methods section regarding the reporting of results (Section 3.2).

Treatment-Related Mortality			
	Studies	**Effect**	**References**
C-C ligand 2 (CCL2)	H (rs1024610)	+	[296]
C-X-C ligand 9 (CXCL9)	H	+	[268]
C-X-C ligand 10 (CXCL10)	H (rs3921)	−	[297]
C-C receptor 5 (CCR5)	H	+	[191,198,254]
C-C receptor 7 (CCR7)	H	+	[298]

3. Methods

3.1. Systematized Search

We used MEDLINE (www.ncbi.nlm.nih.gov/pubmed/) and EMBASE (www.embase.com/) databases to carry out a systematized review [299]# of articles published in English up to 4 March 2019 (see Appendix A.4). The search extended to in vivo models and human interventional and non-interventional studies (see Appendix A.3). The following HSCT outcomes were selected: mobilization, engraftment, SOS, acute GvHD, chronic GvHD, lung toxicity, and TRM. The rationale for this selection and the measurement methods are explained in the Appendix A.8. Due to the advances in research on plerixafor and the existence of another recent systematic report reviewing its use for its approved indications [41]#, we restricted our search to human studies where mobilization was the measured outcome. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA; www.prisma-statement.org/) guidelines were followed to ensure a systematized search, although some of the requirements were not applicable due to the quite inclusive selection criteria used [300]#, as explained in the Appendices A.6–A.11. The selection and data collection processes are described in the Appendices A.6 and A.7 as well. The search workflow and its output are reported in Figure 1 below, whereas Figure 2 details the number of published articles per year. In the Results and Discussion section, we report on and discuss the results of the search.

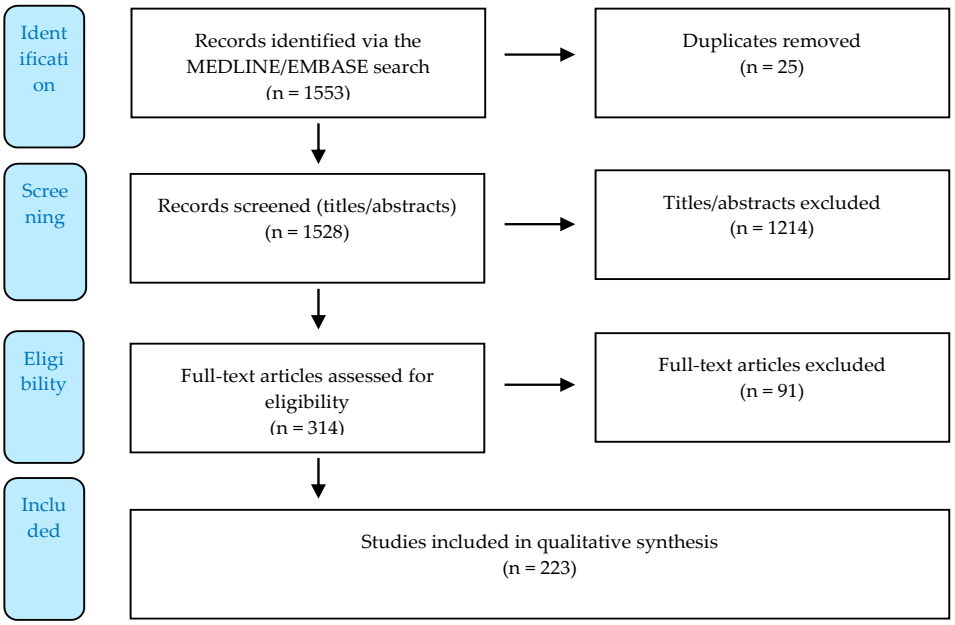

Figure 1. Flow diagram displaying the number of records identified, included, and excluded via a systematized literature review following Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [300]#.

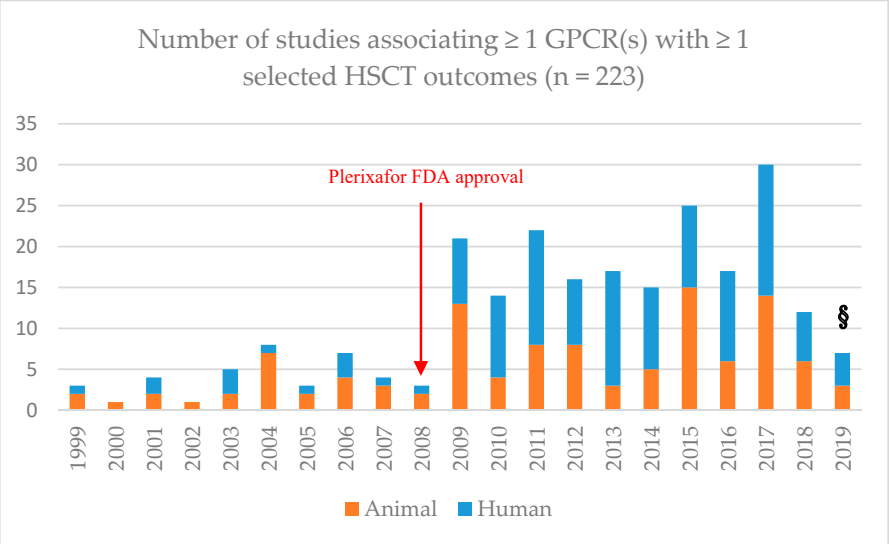

Figure 2. Number of animal (orange) or human (blue) studies per year reporting any association between at least one G protein-coupled receptor (GPCR) and at least one of the selected hematopoietic stem cell transplantation (HSCT) outcomes: mobilization, engraftment, treatment-related toxicities (TRTs) [veno-occlusive disease (VOD), acute graft-versus-host disease (aGvHD), chronic graft-versus-host disease (cGvHD), lung toxicity], and transplantation- or treatment-related mortality (TRM). N = 223. These records were selected via two rounds of systematized screening for eligibility/exclusion criteria (see the Appendix A.6). §: up to 4 March 2019.

3.2. Reporting of the Results

In the Results and Discussion section, each table lists the GPCRs, GPCR ligands, or related proteins whose expression/activity was reported to correlate with the HSCT outcome under consideration, as well as the corresponding reference(s) from the systematized search. Whenever an increase in gene/protein expression or activity of a GPCR, a GPCR ligand, or a related protein was associated with an increase in the incidence/level/severity of the outcome under consideration, the correlation is described as positive (+). The same applies whenever a decrease in a GPCR expression/activity was associated with a decrease in the outcome. Conversely, whenever an increase or a decrease in the GPCR expression/activity was associated with a decrease or, respectively, an increase in the outcome, the correlation is negative (−). Whenever there was no association between a GPCR expression/activity and the outcome, the correlation is null (0). As for polymorphisms (identified as "haplotype", "microsatellite", or by the variant number), their presence can correlate either positively (+) or negatively (−) with the outcome, yet their effect on protein level/function is not necessarily known. GPCRs or their ligands are grouped according to functional classes: chemokines [C-C ligand/receptor (CCL/R), C-X-C ligand/receptor (CXCL/R), C-X3-C ligand/receptor (CX3CL/R) blue], adrenergic receptors (orange), lipid mediators/receptors (green), and "others" (gray). To introduce topics or to enrich the discussion, we considered additional studies, which were not selected by the research query and/or criteria, as well as reviews. These references, along with those cited in the introduction, are specifically identified (#).

4. Conclusions and Perspectives

This systematized review reports on a significant number of GPCRs showing consistent associations with mobilization and engraftment and for which research has moved on to more advanced stages. Although there is some evidence that GPCRs play a role in SOS, GvHD, lung toxicity, and TRM in HSCT settings, there is a flagrant paucity of clinical associations. For several target GPCRs,

the evidence is lacking or conflicting. In contrast, chemokines and their receptors make promising potential targets/biomarkers, as there are numerous potential candidates in various settings. Despite the difficulties in isolating the contributions of individual GPCRs, research has made significant progress for several of them. Targeting CXCR4 for mobilization has proven its utility, with the marketing authorization of plerixafor coming in 2008. Further work is needed to extend plerixafor's indications, and the new anti-CXCR compounds in development could offer interesting pharmacological alternatives. The timing of CXCR4's role during engraftment remains unclear, but CXCR4 blocking during mobilization does not seem to prevent engraftment, and CXCR4 could be manipulated so that it vacates the recipient niche or stimulates engraftment. No direct link between a GPCR and SOS has been consistently demonstrated in vivo. As for aGvHD, CCR5 blockade, such as with the anti-HIV drug, maraviroc, is on track to become a therapeutic option for its prophylaxis. Combined or alternated blockade using CXCR3 and CCR5 might bring further benefits. Activating cannabinoid receptors could be another prospect. GPR43 also merits further investigation as the importance of the gut's microbiota in inflammatory processes is increasingly recognized.

It seems that research on GPCRs in the context of cGvHD is less advanced than in that of aGVHD. The current state of knowledge involves multiple chemokines but is either based on single studies or reports with conflicting findings. Studies on lung toxicity and IPS were scarce, and no relevant contribution to this field has been made in the last ten years. For both cGvHD and IPS, a better understanding of the molecular pathogenesis will probably be required before any useful biomarkers are revealed. As for TRM, it is often multifactorial and may thus prove more challenging to associate death with a single biomarker than individual or even combined toxicities. The absence of an assumed common toxicity-related pathway may explain the paucity of studies revealed by our literature search strategy.

The methodology used in the present paper strived to follow the PRISMA protocols, which, due to the nature of the search performed, could not be followed strictly. However, given the broad range of GPCRs, using the PRISMA methodology helped the authors to guide their search, resulting in a systematized review [299]. Because our search included both pre-clinical and clinical studies, quality, precision, and developmental stage of the evidence was inevitably heterogeneous and could not be reported or summarized using quantitative measures. Despite our best efforts to cover all GPCRs, certain reports that we judged significant enough to mention were missed by the search strategy. Nevertheless, the structure of this article allowed the authors to include such papers in the Results and Discussion section in order to properly cover the subject. Also, time and human resources limitations did not allow for quality or bias assessment by multiple unbiased reviewers, as should be expected from a completely systematic review. Regardless of the limitations to our systematized approach, it did allow for comprehensive scope and was meant to inform scientists and clinicians of the latest developments in a field that is (re-)gaining momentum.

Author Contributions: M.A. is the guarantor and the corresponding author. T.N., S.J.M., and H.G. developed the inclusion/exclusion criteria, the list of outcomes and their measurement, outlined the search strategy, and drafted the piloting form for data collection. H.G. developed and carried out the search strategy, deduplicated and screened the results, collected the data, prepared the summary table, and drafted the manuscript. M.A., S.J.M., V.M., and T.N. supervised the process and provided regular feedback. All the authors revised the manuscript critically. M.A. had final responsibility for the decision to submit for publication. All the authors read and approved the final manuscript.

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Conflicts of Interest: The authors declare no conflicts of interest.

Abbreviations

aGvHD	acute graft-versus-host disease
cGvHD	chronic graft-versus-host disease
aPC	activated protein C
AT1R	angiotensin 1 receptor
AR	adrenergic receptor
BM	bone marrow
BMP	bone morphogenetic protein
CAR	chimeric antigen receptor
CB	cannabinoid receptor
DIC	disseminated intravascular coagulation
DKT	Dai-kenchu-to
ECS	endocannabinoid system
G-CSF	granulocyte colony-stimulating factor
GTEx	Genotype-Tissue expression
GF	graft failure
GPCR	G protein-coupled receptor
GRK	GPCR-related kinases
GvL	graft-versus-leukemia
HPA	Human Protein Atlas
HSC	hematopoietic stem cell
HSCT	hematopoietic stem cell transplantation
IPS	idiopathic pneumonia syndrome
MCT	Monocrotaline
MM	multiple myeloma
NHL	non-Hodgkin lymphoma
NRM	non-relapse mortality
$P2Y_2$	P2Y purinoreceptor 2
PAF	platelet-activating factor
PAR	protease-activated receptor
PB	peripheral blood
PBSC	peripheral blood stem cell
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RANTES	Regulated on Activation, Normal T Cell Expressed and Secreted (CCL5)
7TMR	seven trans-membrane spanning receptor
SCFA	short-chain fatty acid
SMO	Smoothened
SOS	sinusoidal obstruction syndrome
SPM	specialized pro-resolving mediators
THC	tetrahydrocannabinol
TM(E5)	thrombomodulin (fifth epidermal growth factor-like region)
Tregs	regulatory T cells
TRM	transplantation- or treatment-related mortality
TRTs	treatment-related toxicities
VOD	veno-occlusive disease (the term formerly used for SOS)

Appendix A. Methodology

Appendix A.1. Administrative Information

This manuscript is a review using some of the systematic elements recommended in the latest PRISMA guidelines [300]#. Its protocol was not registered prior to its completion. Cochrane, Prospero, and Epistemonikos databases were searched (see Appendix A.4) to verify that this manuscript was not repeating any existing review.

Appendix A.2. Rationale and Objectives

The rationale was explained in the main text. The general objective was to genuinely report on the state of knowledge regarding the identification and the targeting of GPCRs in the management of hematopoietic stem cell transplantation (HSCT) outcomes. Hence, we used an inclusive approach in selecting the types of studies under consideration.

Appendix A.3. Eligibility/Exclusion Criteria

Appendix A.3.1. Study Designs

Clinical studies, both observational and interventional, prospective randomized clinical trials, and retrospective cohort or case-control studies were included in the search. Both adult and pediatric studies were considered. Preclinical studies were included provided they used animal models (mice, rats, primates, zebrafish) that reproduced conditioning and hematopoietic stem cell transplantation comparable to humans. We thus excluded animal studies that only investigated the mobilization stage of HSCT. Conference abstracts were included, whereas reviews, editorials, and case reports were excluded. Only English language literature was included. As there was no existing comprehensive review of the field to start from (see Appendix A.1), we did not set any anterior limit on the time of publication. We ran the search for the last time on 4 March 2019.

Appendix A.3.2. Interventions/Observations

Studies were considered for this review if they reported:

- any association between the expression of a GPCR, a GPCR ligand, or a related protein (e.g. GPCR kinase, beta-arrestins) and one of the selected outcomes (see Appendix A.8) of autologous and/or allogeneic HSCT;
- any intervention on a GPCR, a GPCR ligand, or a related protein to change one of the selected outcomes of autologous/allogeneic HSCT.

The list of GPCRs provided by Uniprot (Available online: www.uniprot.org/docs/7tmrlist.txt) was used as a reference and was sometimes cross-checked with other public databases.

Appendix A.4. Information Sources and Search Strategy

- Cochrane (www.cochranelibrary.com/), Prospero (www.crd.york.ac.uk/prospero/) and Epistomonikos (www.epistemonikos.org/): queried using Medical Subject Headings (MeSH®) descriptors (explode all trees) or free text terms, to probe for already existing systematic reviews.
- MEDLINE (Pubmed interface, 1966 onwards; www.ncbi.nlm.nih.gov/pubmed/) database: queried using either MeSH® or free text terms.
- EMBASE (Elsevier interface, 1947 onwards; www.embase.com/) database: queried using either Embase Subject Headings (Emtree ®) or free text terms.

With the help of SJM and TN, HG created a search equation stepwise for each database, as shown in Table A1 for MEDLINE (Pubmed interface), and all searches were run for the last time on 4 March 2019.

Table A1. Search equation built for MEDLINE (Pubmed interface).

Key Concepts	G Protein-Coupled Receptor	Hematopoietic Stem Cell Transplantation
Free text terms	"G protein-coupled receptor"[Title/Abstract] OR "GPCR" [Title/Abstract] OR "G protein coupled receptor" [Title/Abstract] OR "chemokine" [Text Word]	"Hematopoietic stem cell transplantation" [Title/Abstract] OR "HSCT" [Title/Abstract] OR "haematopoietic stem cell therapy" [Title/Abstract] OR "haematopoietic stem cell transplantation" [Title/Abstract] OR "hematopoietic stem cell (hsc) transplantation" [Title/Abstract] OR "hematopoietic stem cell therapy" [Title/Abstract] OR "hsc therapy" [Title/Abstract] OR "hsc transplantation" [Title/Abstract] OR "Hematopoietic cell transplantation" [Title/Abstract]
MeSH terms	"Receptors, G-protein-coupled"[MeSH Terms] OR "beta-Arrestins"[Mesh Terms] OR "G-Protein-Coupled Receptor Kinases"[Mesh Terms] OR "Receptors, Thyrotropin"[Mesh Terms] OR "Receptors, Thyrotropin-Releasing Hormone"[Mesh Terms]	("Hematopoietic Stem Cell Transplantation"[Mesh Terms] OR "Bone Marrow Transplantation"[Mesh Terms] OR "Hematopoietic Stem Cell Mobilization"[Mesh Terms] OR "Transplantation Conditioning"[Mesh Terms] OR "Cord Blood Stem Cell Transplantation"[Mesh Terms]
Others	"MSH receptor" [Supplementary Concept]NOT "editorial"[Publication Type] NOT "review"[Publication Type] AND "english"[Language]	

Appendix A.5. Data Management

The references were assembled and screened using EndNote X9.1.1 Desktop software for MacOS. The extracted data were stored in an Excel form.

Appendix A.6. Selection Process

Appendix A.6.1. De-Duplications

HG used EndNote's automatic duplication search function and also conducted a manual curation of the assembled articles to remove obvious duplicates before screening. As this review was not completely systematic for the reasons previously explained, we decided against running a thorough de-duplication algorithm [301]#.

Appendix A.6.2. Screening

HG screened the title and the abstract of each article found using the search strategy described above for whether they fulfilled the eligibility/exclusion criteria. A rating system was used to discuss the least obvious exclusions with TN and SJM. Records for which important information was missing, typically the abstract, but for which titles indicated a likely match to our topic were further screened, along with all the included records. HG performed this second screening step based on full-text articles, at the time as he collected the data.

Appendix A.7. Data Collection Process

HG extracted the data from the full-text records using an Excel piloting form drafted with TN and SJM. The investigators undertook no data verification. No systematic publication quality assessment was conducted. The item variables sought were as follows:

- General information: Article ID (1st author's name, 2nd author's name if ambiguity), year of publication, PDF retrievability;
- Study types (if applicable): animal, human, observational, interventional, prospective/retrospective, gene manipulation;
- Intervention (if applicable): drug used, drug type, mode of action, polymorphism;
- Outcome, effect of GPCR, and direction of the effect: mobilization, engraftment, VOD, acute GvHD, chronic GvHD, lung toxicity, treatment-related mortality.

Appendix A.8. Outcomes and Measurement

The search and the ensuing data collection considered the following outcomes, as they were identified as being the most common or the most important issues in HSCT in the latest European Society for Blood and Marrow Transplantation (EBMT) Handbook [285]. The measurement method is indicated in brackets, when appropriate.

- Stem cell mobilization in donors (allogeneic) or hosts (autologous), as measured using circulating $CD34^+$ (HSC) and/or nucleated blood cells harvested through leukapheresis.
- Engraftment (neutrophil and/or platelet recovery, lab diagnosis). Better engraftment was measured by shorter recovery times or lower rates of graft failure.
- Hepatic sinusoidal obstruction syndrome (SOS), formerly known as hepatic veno-occlusive disease (VOD) or liver inflammation (clinical diagnosis).
- Acute graft-versus-host disease (aGvHD) (clinical diagnosis).
- Chronic graft-versus-host disease (cGvHD) (clinical diagnosis).
- Treatment-related mortality.

Appendix A.9. Risk of Bias

Due to the heterogeneity of the studies found and the fact that the screening was executed by one reviewer only, the risk of bias in individual studies was not properly assessed. It is obviously an important shortcoming of this review.

Appendix A.10. Data Synthesis

Data were qualitatively analyzed and the results summarized in Tables 1–6. Due to the heterogeneity of the studies, no quantitative analysis could be reasonably carried out.

Appendix A.11. Meta-Biases and Cumulative Evidence

Due to the heterogeneity of the studies reviewed, no meta-bias analysis was undertaken, and this is a shortcoming of this review. No systematic approach was undertaken to assess the quality of individual studies due to the constraints and heterogeneity previously underlined.

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4. Discussion

La revue systématisée de la littérature, présentée comme publication originale de ce travail, a montré que plusieurs GPCRs sont associés à la mobilisation et/ou à la prise de greffe (Fig.17). Pour certains d'entre eux, les progrès sont significatifs. L'utilité du plerixafor n'est plus à prouver, et des études sont en cours pour en étendre ses indications ou pouvoir l'utiliser en monothérapie. D'autres études explorent son utilité chez les patients souffrant de co-morbidités telle que le diabète ou l'insuffisance rénale, chez les enfants, ou encore chez les donneurs de greffe allogénique sains. D'autres études présentent de nouvelles molécules ciblant CXCR4 afin d'offrir des alternatives pharmacologiques, dont certaines sont déjà en cours d'essai clinique. Ceci est d'autant plus intéressant que contrairement à ce que sa fonction pourrait laisser penser, le blocage de CXCR4 ne semble pas diminuer la prise de la greffe par la suite. Certaines études ont même montré que cibler CXCR4 chez le receveur permettrait de vider la niche hématopoïétique pour faire place au futur greffon [120,121]. D'autres proposent même de stimuler la prise de greffe par un blocage transitoire de CXCR4 [122]. Il semble que le moment le plus opportun pour bloquer CXCR4 n'a ainsi pas encore été déterminé.

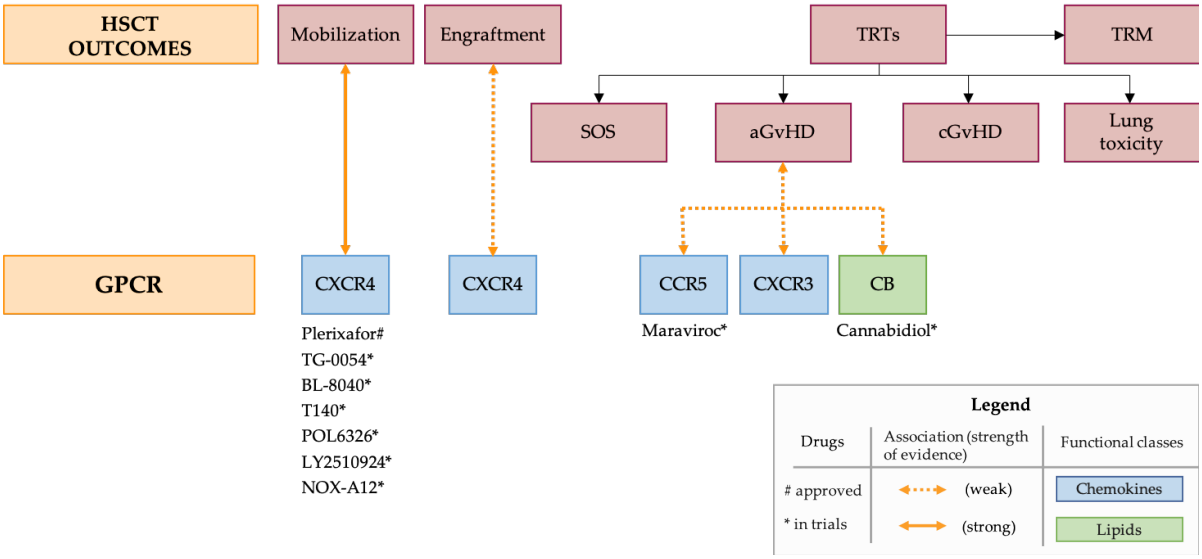

Figure 17: Résumé graphique tiré de la publication originale (Golay et al, 2019). Il présente les associations entre GPCRs et « outcomes » cliniques déjà testées chez l'homme. Le niveau de développement des molécules (approbation, essai clinique), une estimation qualitative de la force de l'association, ainsi que la classe fonctionnelle des GPCRs sont indiqués (légende).

Pour ce qui est des TRTs, comme le SOS ou l'aGvHD, les associations cliniques sont moins claires, avec même parfois des résultats contradictoires. C'est au sein du groupe des chimiokines et de leurs récepteurs que l'on trouve les cibles les plus prometteuses (Fig. 4). Malgré tout, davantage de recherche sera nécessaire pour isoler les contributions individuelles des différentes chimiokines. Dans le cas du SOS, aucun lien avec des GPCRs n'a pu être démontré *in vivo*. Pour ce qui est de la GvHD, le blocage de CCR5, notamment par le maraviroc, un médicament utilisé contre le VIH, pourrait bien devenir une option prophylactique dans un futur proche. Un blocage combiné de CXCR3 et CCR5 pourrait même s'avérer encore plus efficace. L'activation des récepteurs cannabinoïdes ou la manipulation de GPR43, un senseur des métabolites produits par le microbiote, sont d'autres pistes intéressantes à suivre. En ce qui

concerne la GvHD chronique et les toxicités pulmonaires, malgré un lourd impact sur le bilan des greffes à long terme, les mécanismes pathologiques ne sont pas encore assez bien compris au niveau moléculaire. La recherche sur les toxicités pulmonaires semble d'ailleurs s'être interrompue, puisque les dernières études datent d'il y a plus de dix ans. Finalement, la TRM est souvent multifactorielle, ce qui pourrait expliquer la difficulté de trouver un marqueur associé unique.

La méthodologie de cette revue est décrite en détail dans l'annexe de la publication originale. Les guidelines PRISMA ont permis une systématisation du processus de recherche de littérature ainsi que de la façon d'en rendre compte. Toutefois, ils n'ont pas pu être suivis à la lettre. C'est pourquoi, pour éviter toute confusion, nous présentons cette revue comme systématisée et non comme systématique au sens strict. Premièrement, le protocole n'a pas été publié avant d'être exécuté, comme recommandé par PRISMA pour favoriser la transparence et la traçabilité. D'autre part, l'adhésion stricte aux standards PRISMA aurait nécessité plus de temps et de ressources humaines, afin que plusieurs réviseurs « indépendants » puissent évaluer la qualité et les éventuels biais de chacune des études prises en considération. Nous avons par contre pu discuter, entre co-auteurs, des exclusions les moins évidentes. Comme expliqué dans le chapitre « Méthodes », nous n'avons pas pu trouver de revue compréhensive pré-existante sur le sujet dans les bases de données de référence comme Cochrane, Prospero ou encore Epistemonikos. Ceci nous a poussé à recourir à des critères de sélection très inclusifs, prenant en compte à la fois des études cliniques et précliniques, aussi bien interventionnelles que non-interventionnelles, sans restriction sur la date de parution. Dès lors, le résultat fut nécessairement hétérogène, empêchant d'attribuer un « poids » qualitatif à chaque étude. En effet, une étude réalisée chez la souris ne peut pas être comparée directement à une étude clinique. De même, une étude clinique de cohorte rétrospective est difficile à comparer à un essai clinique prospectif randomisé. Or ces comparaisons auraient été nécessaires pour déterminer d'un point de vue quantitatif la force de l'évidence de chaque association.

Les case reports, éditoriaux et revues ont été exclus de notre recherche. Toutefois, lorsqu'une revue permettait d'éclairer un concept ou offrait un éclairage historique, elle a été utilisée et dès lors clairement identifiée dans l'article au moyen d'un signe distinctif (#). Nous avons procédé de la même façon avec des études qui nous semblaient significatives, mais qui n'ont pas pu être trouvées au moyen de nos équations de recherche. Ceci met en évidence la difficulté de trouver la meilleure équation de recherche, malgré le recours à une combinaison de termes libres et indexés (MeSH, Emtree). Ces derniers permettent d'éviter les problèmes de synonymes et d'acronymes mais ne sont pas toujours disponibles (documents non indexés) ou pas assez spécifiques. Les termes libres nécessitent quant à eux l'inclusion de toutes les variantes possibles d'un même terme et de déterminer dans quelle partie des articles ils seront recherchés (titre, résumé, corps principal). Afin de mieux comprendre ces problématiques, nous avons consulté des bibliothécaires de la bibliothèque médicale universitaire. Le résultat de ces réflexions méthodologiques a d'ailleurs été l'objet d'une présentation publique (CANSEARCH seminar) le 10.05.2019.

Utiliser plus d'une base de données pour la recherche de littérature implique une étape de déduplication pour éliminer les doublons, ce que nous avons effectué manuellement. Des algorithmes de déduplication existent [123], mais nécessitent du temps et de l'expérience dans leur utilisation pour offrir un réel avantage. La collection de données a été guidée par un formulaire

Excel que nous avions pré-défini. Toutefois nous avons dû parfois le réviser pour prendre en compte différentes sous-catégories dans nos variables cliniques. Ceci souligne l'importance de planifier l'ensemble du protocole à l'avance, pour éviter une possible introduction de biais par des changements ultérieurs. La méthode de mesure pour chaque résultat (« outcome ») clinique est décrite dans la méthodologie de la publication.

Afin de s'assurer que cette revue ne plagiait pas les études inclues, nous avons utilisé le programme en ligne « compilatio.net » en utilisant l'accès UNIGE. Les seules similarités rencontrées sont des descriptions d'abréviations, comme PRISMA ou RANTES.

Cette revue avait pour but d'informer aussi bien des chercheurs en biologie ou pharmacologie que des cliniciens des derniers développements d'un domaine qui gagne en importance. Elle est d'ailleurs publiée dans la section de « pharmacologie clinique » du « International Journal of Molecular Sciences » (IJMS). Les concepts cliniques y ont été brièvement introduits dans un but informatif et vérifiés avec les cliniciens travaillant dans notre équipe. Les « outcomes » cliniques choisis sont parmi les plus fréquents et/ou les plus graves [44]. Notre revue pourrait servir de base à de futures études et à des revues plus ciblées, sur certains GPCRs ou certains « outcomes » cliniques.

5. Conclusion et perspectives

Les toxicités et la mortalité liées au traitement continuent d'assombrir le bilan des greffes de cellules souches hématopoïétiques chez les patients pédiatriques. Déterminer comment les prévenir ou les traiter, sans perdre les bénéfices indispensables de la greffe, est un défi majeur de la recherche. Dans ce contexte, la revue systématisée que nous avons menée établit le potentiel encore largement inexploité des membres de la famille des GPCRs, notamment les récepteurs de chimiokines, pour améliorer les résultats de la greffe. Des progrès intéressants ont été réalisés pour la mobilisation des cellules souches et la prise de greffe, alors que dans le cas des TRTs, il reste du travail à accomplir pour démontrer des associations cliniques univoques. Notre revue avait justement pour but de faire le point sur ces avancées.

Pour améliorer les résultats de la greffe, notre plateforme de recherche en oncologie pédiatrique s'est spécialisée dans la (pharmaco-)génomique. Le faible nombre de cas dans les cohortes pédiatriques pose certes un challenge statistique récurrent. Les études d'association permettent néanmoins d'identifier des polymorphismes statistiquement associés à l'une ou l'autre des TRTs et suffisamment fréquents dans la population pour être pertinents (« minor allele frequency »). Ces polymorphismes peuvent d'une part fournir des biomarqueurs permettant de mieux stratifier le risque individuel de chaque patient, notamment en fonction du régime de conditionnement. Intégrés aux algorithmes existants, ils permettraient par exemple de mieux personnaliser la prédiction des premières doses de chimiothérapie, un enjeu majeur dans la préparation à la greffe. D'autre part, la fonction des gènes ainsi identifiés peut être étudiée, afin de mieux comprendre la physiopathologie des TRTs et éventuellement développer de nouveaux traitements. Cette approche nécessite le développement d'outils expérimentaux permettant de construire des modèles *in vitro* et *in vivo* pertinents, comme par exemple le silençage de gènes d'intérêt. C'est dans cette perspective que nous avons, en parallèle de la réalisation de notre revue, testé et optimisé un certain nombre de techniques de génie génétique, afin d'étudier la fonction d'un GPCR dont un polymorphisme était associé à certaines TRTs dans nos cohortes cliniques. Ce travail était toujours en cours au moment de la rédaction et de la correction de cette thèse.

6. Abréviations

Les abréviations anglophones ont été préférées pour plus de clarté et faciliter les références à la littérature. Une traduction de chaque abréviation, si elle existe, est proposée dans le tableau ci-dessous.

	English	Français
(T-)ALL	T-cell acute lymphoid leukemia	Leucémie lymphoïde aigue à cellules T
AML	Acute myeloid leukemia	Leucémie myéloïde aigue
BM	Bone marrow	Moelle osseuse
CB	Cord blood	Sang du cordon ombilical
EBMT	European Society for Blood & Marrow Transplantation	Société européenne pour la transplantation de moelle osseuse
G-CSF	Granulocyte colony-stimulating factor	Facteur de croissance hématopoïétique spécifique de la lignée granulocytaire
GvHD	Graft-versus-host disease	Réaction du greffon contre l'hôte
GvL	Graft-versus-leukemia	Réaction du greffon contre la leucémie/tumeur
Indels	Nucleotide(s) insertion or deletion	Insertion ou délétion de nucléotide(s)
HR	Homologous recombination	Recombinaison homologue
HSCT	Hematopoietic stem cell transplantation	Greffe de cellules souches hématopoïétiques
IPS	Idiopathic pneumonia syndrome	Syndrome de pneumonie idiopathique
MA	Myelo-ablation	Myélo-ablation
MAF	Minor allele frequency	Fréquence de l’allèle mineur

NCBI	National Center for Biotechnology Information	Idem
NHEJ	Non-homologous end-joining	Jonction d'extrémités non homologues
PBSC	Peripheral blood stem cells	Cellules souches hématopoïétiques périphériques
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses	Lignes de conduite pour les revues systématiques et méta-analyses
rTM	Recombinant thrombomodulin	Thrombomoduline recombinante
SNP	Single nucleotide polymorphism	Polymorphisme d'un seul nucléotide
SOS	Sinusoidal obstruction syndrome (formerly veno-occlusive disease or VOD)	Syndrome d'obstruction sinusoïdale (anciennement maladie veino-occlusive hépatique)
TDM	Therapeutic drug monitoring	Suivi thérapeutique pharmacologique
TRT	Treatment-related toxicity	Toxicité liées au traitement
TRM	Treatment-related mortality	Mortalité liée au traitement
7TMR	Seven-transmembrane receptor protein	Protéine récepteur à sept domaines transmembranaires (récepteurs serpentins)

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