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# Interleukin-22 in Graft-Versus-Host Disease after Allogeneic Stem Cell Transplantation

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Allogeneic hematopoietic stem cell transplantation (allo-HSCT) is a potential curative treatment for hematologic malignancies and non-malignant diseases. Because of the lower toxicity of reduced intensity conditioning, the number of transplants is in constant increase. However, allo-HSCT is still limited by complications, such as graft-versus-host disease (GVHD), which is associated with important morbidity and mortality. Acute GVHD is an exacerbated inflammatory response that leads to the destruction of healthy host tissues by donor immune cells. Recently, the contribution of innate immunity in GVHD triggering has been investigated by several groups and resulted in the identification of new cellular and molecular effectors involved in GVHD pathogenesis. Interleukin-22 (IL-22) is produced by both immune and adaptive cells and has both protective and inflammatory properties. Its role in GVHD processes has been investigated, and the data suggest that its effect depends on the timing, the target tissue, and the origin of the producing cells (donor/host). In this review, we discuss the role of IL-22 in allo-HSCT and GVHD.

**Keywords:** interleukin-22, graft-versus-host disease, allogeneic stem cell transplantation

## INTRODUCTION

Allogeneic hematopoietic stem cell transplantation (allo-HSCT) is a potential curative treatment for hematologic malignancies and non-malignant diseases. Because of the lower toxicity of reduced intensity conditioning, the number of transplants is in constant increase. However, allo-HSCT is still limited by complications, such as graft-versus-host disease (GVHD), which is associated with important morbidity and mortality. Acute GVHD is an exacerbated inflammatory response that leads to the destruction of healthy host tissues by donor immune cells. Pioneer studies from Ferrara's group suggested that the acute GVHD physiopathology consists of three major steps involving both innate and adaptive immune cells: (i) intestinal damage consequent to the conditioning regimen's triggering of pathogen-associated molecular patterns (PAMPs) and inflammatory cytokine release, which activate antigen-presenting cells (APC), (ii) activation of donor alloreactive T cells, and (iii) proliferation, migration, and destruction of host tissues (1). Since T cells seemed crucial in the pathogenesis process, an important number of studies focused on T cell pathways and associated cytokines. More recently, the contribution of innate immunity in GVHD triggering has been investigated by

several groups and resulted in the identification of new cellular and molecular effectors involved in GVHD pathogenesis (2). Interleukin-22 (IL-22) is produced by both innate and adaptive cells and has both protective and inflammatory properties. Its role in the GVHD process has yet to be determined, but most data suggest that its effect depends on the timing, the target tissue, and the origin of the producing cells (donor/host). In this review, we will discuss the new insights on IL-22 and its role in allo-HSCT and GVHD.

## IL-22 AT A GLANCE

Interleukin-22 has been identified as IL-10-related T cell-derived inducible factor (IL-TIF) (3, 4). This cytokine is a member of the IL-10 family, together with IL-19, IL-20, IL-24, IL-26, IL-28, and IL-29. In humans, IL-22 is an ~20-kDa protein composed of 146 amino acids and shares 80.8% sequence homology with the murine protein. The *IL22* human gene is located on chromosome 12q15, close to the *IL26* and *IFN $\gamma$*  genes (5). Although IL-10 and IL-22 share only 22.8% sequence homology, both cytokines present a similar secondary structure of multiple  $\alpha$ -helices, which is specific of the IL-10 family (6). At the functional level, glycosylation of IL-22 seems to be more crucial for its binding to its receptor than for its spatial conformation (7).

Murine IL-22 production was reported for the first time in a lymphoma cell line after stimulation by IL-9 and also in lymphocytes treated with concanavalin A, independently of IL-9 (3). In humans, IL-22 expression was initially described in anti-CD3 or concanavalin A-stimulated T cells (4, 8). In the immune system, it has been shown that only T cells, innate lymphoid cells (ILC), and neutrophils produce IL-22. By contrast, B cells (activated or not), monocytes, macrophages, dendritic cells (DC), or non-hematopoietic cells are unable to secrete IL-22 (9–13).

Among TCR  $\alpha\beta$ -chain-expressing T cells, CD4<sup>+</sup> T cell is the main source of IL-22. Initially, it was thought that only Th1 and Th17 produced IL-22 (10). Later, a new T cell population secreting, exclusively, IL-22 has been described in humans and called Th22. These cells are dependent on the AHR transcription factor and express CCR10, which induces skin-homing properties (14, 15). To a lesser extent, IL-22 can be produced not only by IL-17-producing CD8<sup>+</sup> T cells (Tc17) (16, 17) but also by a CD8<sup>+</sup> population secreting exclusively IL-22 but not IL-17, called Tc22 (18). As Th17,  $\gamma\delta$  T cells also secrete IL-22, they express the ROR- $\gamma$ t transcription factor, in addition to IL-23R, CCR6, and pattern recognition receptors (PRR), such as TLR1, TLR2, and Dectin-1. In addition to IL-22,  $\gamma\delta$  T cells secrete IL-17 and IL-21, when stimulated with IL-23 and IL-1 $\beta$ , independently of TCR activation (19–21). Similar to what is found in Th17 cells, the transcription factor AHR is required for IL-22 expression but not for IL-17 in the latter cells. In humans, a specific subset of  $\gamma\delta$  T cells that secrete only IL-22 (T $\gamma\delta$ 22) has been recently described. Its differentiation requires IL-1 $\beta$ , IL-23, and TGF- $\beta$  stimulation (22).

Interleukin-22 secretion by non-T cells has been reported for the first time in murine models with *Citrobacter rodentium* infection (23). In this model, Rag2<sup>-/-</sup> mice, characterized by the lack of T cells, produced IL-22 at levels equivalent to those found in wild-type (WT) mice. Using immunocytochemistry methods, the

authors initially attributed IL-22 secretion to CD11c expressing cells and speculated that DC could secrete IL-22. Nevertheless, in *in vitro* experiments using IL-23 stimulation, myeloid cells, such as DC, produced a very limited amount of IL-22. These data indicated that secretion of IL-22 by myeloid cells seems unlikely (24). Interestingly, CD11c expression can be enhanced in other cell types and more particularly in ILCs (25). These cells represent a small fraction of the immune cells in lymphoid organs, in epithelial barriers, and other tissues, but they were described as an important source of IL-22 (25–28). Like B and T cells, ILCs are derived from a common lymphoid progenitor. ILCs form a heterogeneous group of different subsets presenting a profile of cytokine secretion and transcription factors similar to that of helper T cell subsets. Spits and Cupedo's review notably describes functions and phenotypes of these populations (29). Among these heterogeneous populations, only group 3 ILCs produce IL-22. These cells are dependent on GATA-3 and ROR- $\gamma$ t transcription factors for their development and cytokine production, respectively (30).

## IL-22 TARGET TISSUES AND CELLS

The IL-22 receptor is a heterodimeric protein composed of IL-22R1 and IL-10R2 (4). Since IL-10R2 is ubiquitously expressed, only IL-22R1 expression conditions cellular sensitivity to IL-22. Expression of the latter is mainly observed not only in tissues with a direct interface with the external environment, such as respiratory mucosa (31), gastrointestinal mucosa (32, 33), and skin (13), but also in liver, pancreas, kidney, and thymus (8, 34–36). In these tissues, the responding cells include keratinocytes, dermic fibroblasts, intestinal and bronchial epithelial cells, intestinal subepithelial myofibroblasts, hepatocytes, and acinous pancreatic cells. Importantly, cells from hematopoietic origin, such as monocytes, T and B cells, ILCs, macrophages, and DC, do not express IL-22R1 (10) and, consequently, IL-22 cannot directly activate or inhibit immune cells. In addition to IL-22R1, a soluble receptor for IL-22 called IL-22-binding protein (IL-22BP) is encoded by another independent gene *IL22R2a* (37, 38). IL-22BP is homologous to the extracellular chain of IL-22R1 but is only a secreted protein that does not result from a cleaved membrane protein. It is constitutively expressed in several tissues, such as lymph nodes and intestine (39–41). IL-22BP is secreted by DC expressing CD103 and CD11b in murine intestine (42, 43). In humans, IL-22BP is also expressed by DC and is drastically decreased in the presence of IL-18, or after DC maturation (42, 43). More recently, it has been shown that eosinophils are the most important source of IL-22BP in human healthy gut and contribute to an overproduction of IL-22BP in the inflamed mucosa of inflammatory bowel disease (IBD) patients (44).

## BIOLOGICAL FUNCTIONS: BETWEEN TISSUE REGENERATION AND INFLAMMATION

Interleukin-22 signaling *via* its receptor induces Jak1 and Tyk2 activation, leading to the activation of signal transducer and

activator of transcription (STAT) family transcription factors, especially STAT3 (11, 12), but also STAT1 and STAT5 (4, 8, 45, 46). Moreover, mitogen-activated protein kinases (MAPK) pathways, including Erk1/2, JNK, and p38 phosphorylation, are also induced by IL-22 (12, 32, 47, 48). Animal models using IL-22-deficient mice or IL-22 neutralizing antibodies led to the identification of inflammatory or protective roles of IL-22. Interestingly, the IL-22 protective properties are associated with crucial biological functions of STAT3 activation in target cells (49). Indeed, STAT3 induces cell activation, proliferation, and survival *via* anti-apoptotic genes. Thus, IL-22 participates on mucosal homeostasis and epithelial barrier integrity. Murine models suggest that IL-22 plays a major role in intestinal regeneration. For instance, after mechanical wound of the colon, IL-22-deficient mice showed a delayed wound healing as compared to WT animals (46, 50). In dextran sulfate sodium (DSS)-induced or after CD4<sup>+</sup>CD45RB<sup>high</sup>CD25<sup>-</sup> transfer colitis models, IL-22-deficient mice showed a more important loss of weight and a decreased survival as compared to WT mice (33, 51). Furthermore, in a murine model of IBD, IL-22 can be therapeutic. Indeed, Sugimoto's group used an interesting microinjection-based gene-delivery approach to directly transfer the *IL22* gene into the large intestine of mice *via* a non-microbial vector and observed a decrease in inflammation, notably by the induction of mucins, which limit microbial flora and host cell interactions (33). In addition, IL-22 induces the secretion of several antimicrobial proteins by epithelial cells such as the regenerating islet-derived proteins Reg3 $\gamma$  and Reg3 $\beta$ , thus limiting infection by extracellular pathogens (52). IL-22 participates in antimicrobial defense by the induction of S100 family proteins, such as S100A7, S100A8, and S100A9, which sequester essential elements of bacteria, including iron and zinc. IL-22 also induces  $\beta$ -defensins that are able to destabilize bacterial membranes (11). In skin, *in vitro* tests showed that IL-22 treatment of keratinocytes after a lesion favors cutaneous regeneration (53). In conclusion, IL-22 is essential for epithelial barrier integrity and tissue regeneration after different lesions. Although transgenic mice overexpressing IL-22 presented induction of psoriatic keratinocyte alterations and a high early mortality (54), IL-22 administration to healthy mice does not seem to induce acute or severe inflammation (11, 55). These data suggest the possibility of using this cytokine in human therapy targeting tissue regeneration.

Recently, a phase I clinical trial evaluating IL-22 safety in healthy volunteers has been initiated<sup>1,2</sup> (56).

Despite its protective properties, IL-22 is also known to be negatively involved in several inflammatory diseases. In this context, the correlation between the level of IL-22 expression and the severity of the disease has been reported. In an endotoxemia model, IL-22 administration does not inhibit the pro-inflammatory cytokine production, such as TNF- $\alpha$ , IL-6, and IFN- $\gamma$ , during the early phases of the disease. Moreover, in

the late phase, IL-22-deficient mice presented a better survival, showing that IL-22 takes part in the systemic inflammation (57). This notion is also illustrated by another study showing that transgenic mice that artificially express IL-22 receptor on the surface of T cells showed a normal growth initially but presented a multi-organ systemic inflammation after 2 or 3 months of life (58). More specifically, IL-22 participates in the pathogenesis of rheumatoid arthritis both in humans and mice (48, 59). In a murine model of collagen-induced arthritis, the incidence of the disease is decreased in IL-22-deficient mice, associated with a decrease of synovial expression of IL-1 $\beta$ , IL-6, TNF- $\alpha$ , and MMP9 (60). Psoriasis is another disease in which IL-22 is clearly pathogenic and is a key mediator in its late stage, leading to keratinocyte lesions. Thus, a strong expression of IL-22 mRNA is observed in skin lesions from patients as compared to that in healthy skin (61). The serum level of IL-22 is also correlated with disease severity (12). In animal models, IL-22 blockade or IL-22 deficiency is associated with a less severe form of experimental psoriasis (62). Finally, mice that artificially overexpress IL-22 develop psoriasis-like spontaneous lesions (54). The main effects of IL-22 in the skin consist of keratinocyte differentiation and induction of pro-inflammatory effectors, such as CXCL5, IL-20, MMP1, and MMP3 (45, 63, 64). Overall, the effects of IL-22 seem to be protective or pathogenic according to the inflammatory context, the inflammation site, and affected tissue, as well as the cytokines present in the environment.

## IL-22 IN THE PATHOPHYSIOLOGY OF GRAFT-VERSUS-HOST DISEASE: INCREASE OF INFLAMMATORY RESPONSE OR TISSUE PROTECTION?

Graft-versus-host disease results from activation of donor T cells that recognize and destroy host tissues, such as skin and intestine. Given the IL-22 properties in these tissues, several groups assessed IL-22 contribution in acute GVHD models. We and others used IL-22-deficient grafts and observed that acute GVHD severity was decreased as compared to transplantation with WT grafts (65, 66). These data are in line with the critical role of IL-22 in systemic inflammation. Indeed, in a model where systemic IL-22 administration was performed *via* an adenovirus strategy, it was observed that such exposure of IL-22 induced an acute-phase response that could be detected in the blood and the liver (67). Zhao's group showed that the main producers of IL-22 involved in the alloreactive immune response of GVHD were donor CD4<sup>+</sup> T cells that carried CD62L<sup>-</sup> CD44<sup>high/low</sup> surface markers, corresponding to effector memory or recently activated T cells (68). Their group also demonstrated that systemic administration of IL-22 exacerbates murine GVHD, confirming the deleterious contribution of IL-22 to this disease (69). Similarly, they showed that IL-22 contributes to effector T cell expansion and Treg decrease. These data are in line with our observations showing that Treg were increased in the spleen and mesenteric lymph nodes of recipient mice transplanted with IL-22-deficient grafts (66). Several experimental reports suggest that Treg can limit alloreactive responses and reduce GVHD severity in mice

<sup>1</sup> <http://www.businesswire.com/news/home/20120906005611/en/Generon-Initiates-Phase-Clinical-Study-F-652-Australia>

<sup>2</sup> <https://clinicaltrials.gov/ct2/show/NCT02406651?term=IL-22&rank=1>

(70, 71). The expansion of Treg in the absence of IL-22 could be a consequence of reduced inflammation in the GVHD context, rather than an active mechanism.

In a chronic GVHD murine model, Okamoto's group reported that more than 70% of IL-22-producing cells are CD4<sup>+</sup> T cells. They treated recipient mice with an anti-IL12p40 mAb and observed a decrease of pathogenic Th1/Th17 cells that secrete IL-22. This decrease was associated with those of GVHD severity and IL-22 levels in the serum of recipient mice (72). In human GVHD, the effect of IL-22 has not yet been fully established, although its expression seems to be increased in both acute and chronic GVHD. In acute GVHD, Brügggen et al. found a clear increase of IL-22 messenger RNA and IL-22-producing CD4<sup>+</sup> T cells in the skin (73). In active chronic GVHD pediatric patients, a recent report demonstrated an increase of IL-22 expression in peripheral blood mononuclear cells as compared to that in patients with no GVHD (74).

One of the pathogenic mechanisms of donor-derived IL-22 may be due to its synergy with type-I IFN that is produced during the allogeneic response. Recently, we showed that donor-derived IL-22 can synergize with type-I IFN to increase murine GVHD (75). At the protein level, this IL-22/type-I IFN synergy could result from the direct interaction between their relative receptors: the IFNAR physically interacts with the IFN- $\gamma$  receptor and facilitates phosphorylated STAT1 (PSTAT1) homodimer generation (76). A similar interaction has also been reported between the IFNAR and IL-6 receptors (gp130) (77). It is not yet known whether the IFNAR/IL-22R interaction is physiologically relevant.

Interestingly, intracellular STAT1/STAT3 polarization can be controlled by IL-22 through the SOCS proteins (78). SOCS1 and SOCS2 are responsible for STAT1 inhibition (79). Recently, a report showed that SOCS1 expression was abolished in acute or chronic GVHD patients, suggesting that IL-22-induced STAT1 is no longer inhibited in this context (80). In host cells, it was shown that GVHD induction is associated with a rapid phosphorylation of STAT1 in the spleen and the liver (81). In that model, the use of a histone deacetylase (HDAC) inhibitor to limit murine GVHD led to a local and systemic decrease of STAT1 activation, together with a decrease of pro-inflammatory cytokine production. In chronic GVHD patients, STAT1 activation by type-I IFN seems to be critical in oral mucosal inflammation. Indeed, a higher level of activated STAT1 in keratinocytes has been reported in severe chronic GVHD patients as compared with those patients with no oral lesions. In this context, STAT1 activation is associated with an increase of Th1 inflammation mediators, such as CXCL9 (82). These data are in line with our observation showing that both STAT1 and CXCL10 activation is increased in the colon of gastrointestinal GVHD patients (75).

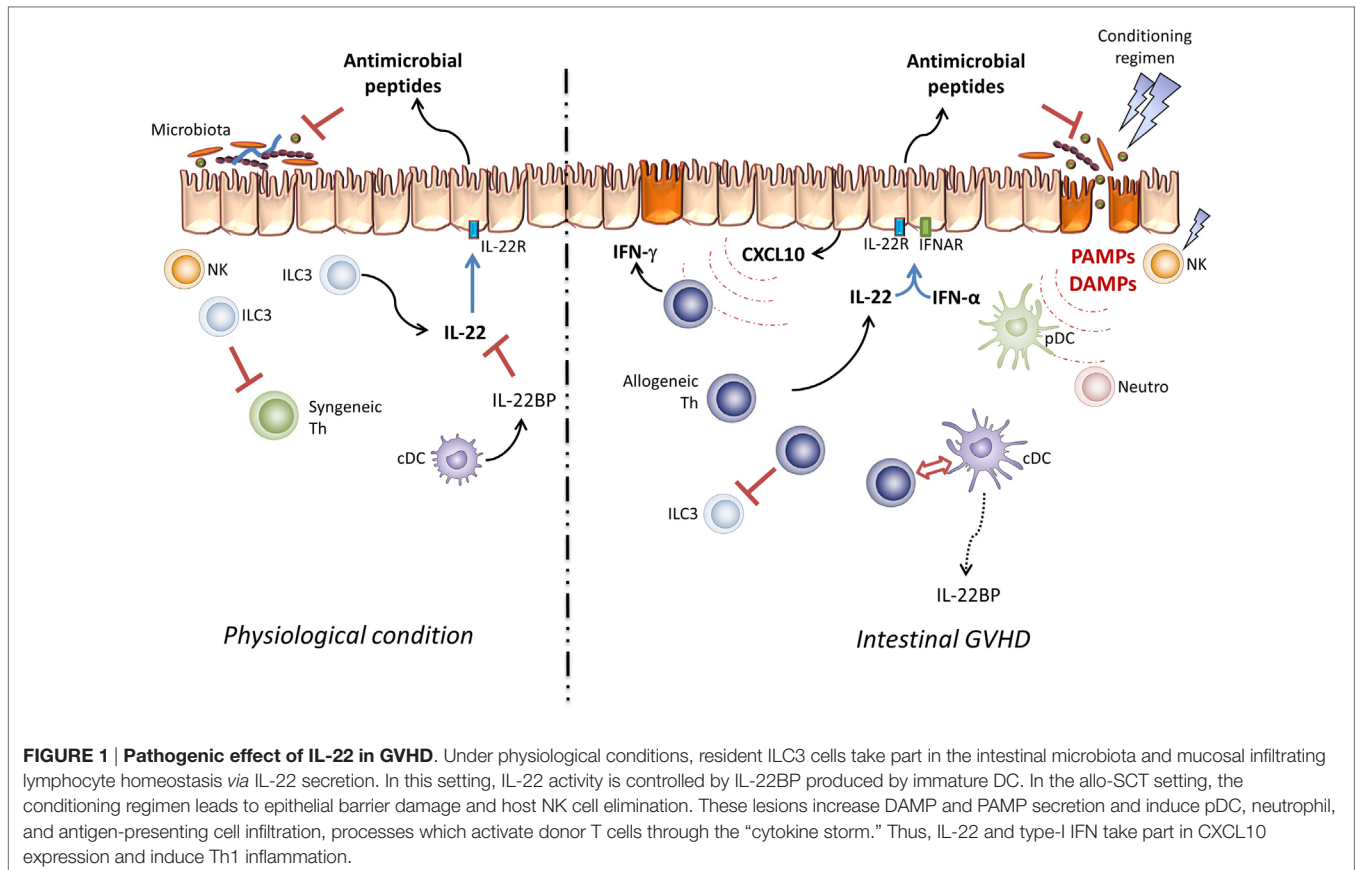
Given the critical role of pro-inflammatory cytokines in GVHD, signal transduction inhibition seems to be a promising therapeutic approach. Janus kinases (Jak) are intracytoplasmic proteins that trigger cellular signalization leading to cytokine secretion through activation of STAT proteins (83). In preclinical models, Jak2 and Jak3 inhibitors are efficient to limit GVHD (84–87). Our recent results showed that treatment with Jak inhibitors could also limit STAT1 activation and CXCL10 expression in intraepithelial cells (IEC).

There has been recent progress in the knowledge on the effects of CXCL10 family of chemokines in the inflammatory process. CXCL9 and CXCL10 can induce naive T cell differentiation to Th1 in a STAT1-dependent manner. Paradoxically, CXCL11 is known to bind another epitope of CXCR3 and to induce IL-10 producing T cells (88). CXCL10 expression induced by IL-22/type-I IFN synergy and STAT1 activation in host mucosal cells could participate in both Th1 recruiting and Th1-like inflammation maintenance by influencing T cell polarization. Interestingly, we previously showed that plasmacytoid dendritic cells (pDC) able to secrete IFN- $\alpha$  infiltrated both intestinal mucosa and cutaneous tissues in GVHD patients (89, 90). The relationship between IL-22 and pDC is suggested by data showing that IFN- $\alpha$  produced by pDC can increase the expression of IL-22R1, the specific subunit of IL-22R, in keratinocytes (91). Moreover, in humans, the differentiation of Th22, which express CCR10, CCR6, and CCR4 and secrete IL-22 but not IL-17, seems to be pDC dependent (14). Thus, IFN- $\alpha$  and IL-22 may participate in epithelial lesions at the skin or intestinal level, by an amplifying loop to sustain Th1 inflammation.

Despite our observations, we cannot conclude on the negative impact of IL-22 in allo-HSCT context. In addition to donor-derived T cells, other cells could secrete IL-22 during allo-HSCT. For instance, ILCs located in the gut of host mice were shown to secrete large amounts of IL-22 under IL-23 stimulation and could resist the conditioning regimen. In the absence of GVHD reaction, host ILC-derived IL-22 is protective to intestinal stem cells (65). A high level of donor-derived ILCs in the blood of allo-HSCT patients is associated with a less severe GVHD (92) but their capacity to infiltrate GVHD target tissues and their effects remain to be deciphered. A recent report from van den Brink's group showed that IL-22 can promote ISC-mediated epithelial regeneration. Using *ex vivo* organoid culture, they demonstrated that group 3 ILCs secrete IL-22, which increases the growth of small intestinal organoids. Recombinant IL-22 treatment induced STAT3 activation in Lgr5<sup>+</sup> ISC and was crucial for IL-22-mediated epithelial regeneration. Moreover, IL-22 treatment *in vivo* also enhanced the recovery of ISC and intestinal regeneration and reduced mortality from GVHD in transplanted mice (93). These observations clearly underline the essential role of IL-22 in damage-induced regulation and maintenance of the ISC compartment.

## IS IL-22 A POTENTIAL THERAPEUTIC TARGET IN GVHD?

The effect of IL-22 in allo-HSCT seems complex (Figure 1). Thymic ROR $\gamma$ <sup>+</sup>CCR6<sup>+</sup>NKp46<sup>-</sup>ILCs are crucial to secrete IL-22 that contributes to thymic regeneration after total body irradiation in mice (36). Post-transplantation IL-22 neutralization could have a direct impact on thymus regeneration and negatively influence immune reconstitution. The thymus regeneration seems more important during the first 2 weeks post-transplantation after IL-22 treatment, but after the second week, the size of the thymus is comparable to that of non-treated mice (69). However, a recent report showed that IL-22 administration to host mice

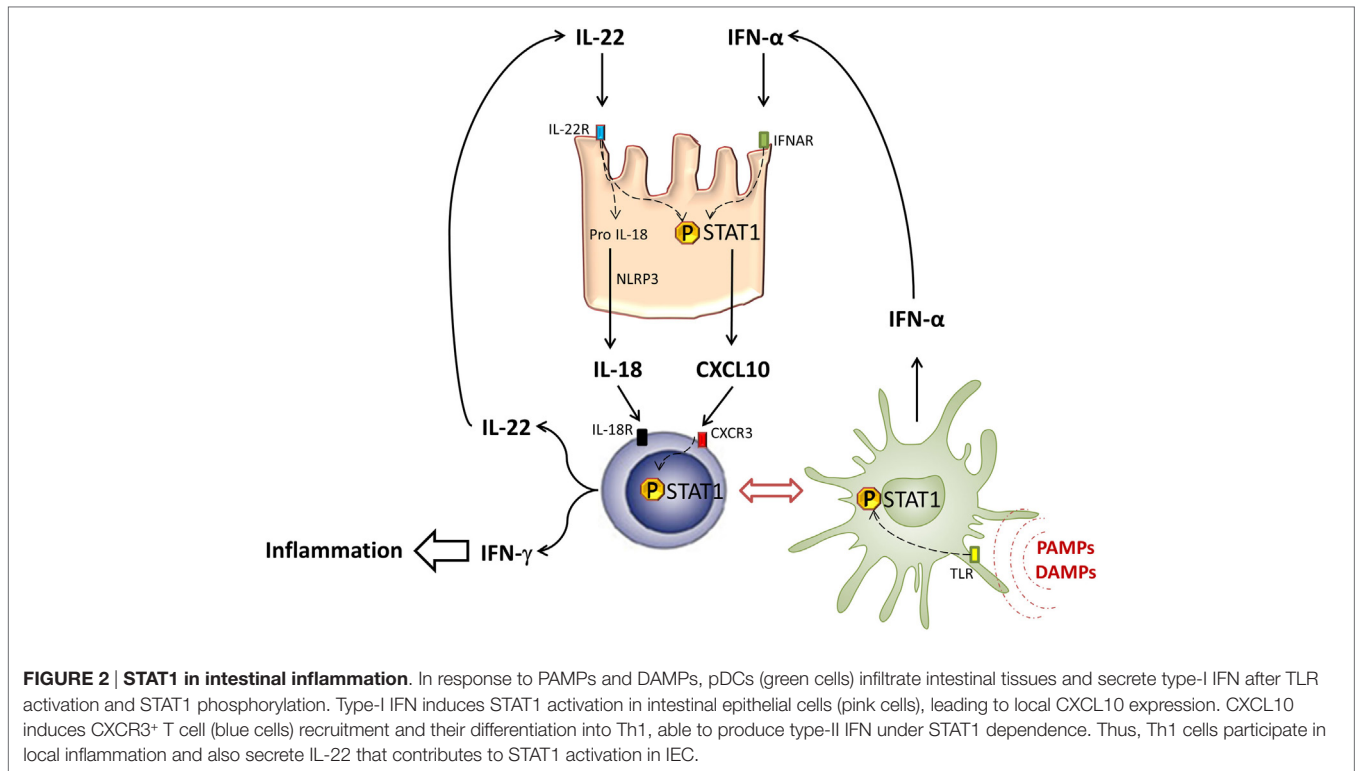


is associated with a more severe intestinal GVHD. These data suggest that an increase in IL-22-dependent thymus regeneration is not correlated with less GVHD, but that IL-22 could be pathogenic for some tissues and protective for others in the same allogeneic context.

Paradoxically, donor-derived IL-22 aggravates intestinal damage during GVHD (66). It has been recently reported that IL-22BP expression is maximal when the intestinal barrier is preserved (42). Conversely, tissue lesions and bacterial translocation decrease IL-22BP expression. The mechanism underlying the expression of IL-22BP by DC is inflammasome dependent (94). Thus, IL-18 can inhibit IL-22BP expression by DC (95). In the GVHD context, the contribution of IL-18 remains controversial (96, 97). Nevertheless, Munoz and colleagues recently described an important property of this cytokine. They showed that IL-22 maintains homeostatic IL-18 expression in epithelial cells and IL-18 can be augmented during infection. Moreover, active IL-18 is responsible for a unique inflammatory feedback loop to amplify Th1 cell-mediated immune response (98). Whether donor-derived IL-22 can amplify Th1 response through IL-18 secretion in the GVHD context remains to be addressed (Figure 2). The decrease of IL-22BP expression probably increases bioactive IL-22 at local level. These observations should be confirmed in allo-HSCT patients. Interestingly, antimicrobial peptides, such as Reg3 $\alpha$ , that are produced by Paneth cells in response to IL-22 are detected in the blood of GVHD patients and have been validated

as intestinal GVHD biomarkers (99). These data are in line with Eriguchi's group observations, which showed an increase of defensin expression in GVHD mice, which confirm that IL-22 is well active in intestinal tissue during allo-HSCT (66, 100).

On the other hand, a tight relation between IL-22 and microbial flora has been observed. Thus, microbiota can directly induce IL-22 secretion by group 3 ILCs (25). Moreover, in epithelial tissues, IL-22 induces antimicrobial peptides, such as  $\beta$ -defensins 2 and 3, S100A8, and S100A9, which are able to specifically target certain microorganisms. An alteration in the composition of the microbiota was described in IL-22<sup>-/-</sup> mice, and it largely increases the susceptibility to induced colitis (101). This particularity should be kept in mind when IL-22<sup>-/-</sup> mice are used as recipients in gastrointestinal acute GVHD models. In addition to bacteria, the characterization of viral and fungal components of intestinal flora is in progress. It is probable that these components influence immune and also allogeneic responses. Recently, the role of the mycobiome has been addressed in different diseases (102, 103). Certain PAMPs, such as  $\beta$ -glucan or  $\alpha$ -mannan polysaccharide chains that are part of the fungal membranes, can be, respectively, recognized by Dectin-1 and Dectin-2 receptors expressed by APC (104, 105). The recognition of certain patterns leads to Th17 responses and IL-17 and IL-22 production that control pathogens (106, 107). Thus, IL-22 can participate to the inflammation process in tissues in the context of fungal infection (108). In allo-HSCT,



colonization by *Candida* is associated with an increase in GVHD severity (109). Interestingly, in patients with Dectin-1 polymorphism associated with a decreased Th17 response and an increase in *Candida* colonization, GVHD is not more severe (110). These data clearly suggest that the allogeneic response can be influenced by the mycobiome, but the relation between this and IL-22 and remains to be elucidated.

## CONCLUDING REMARKS

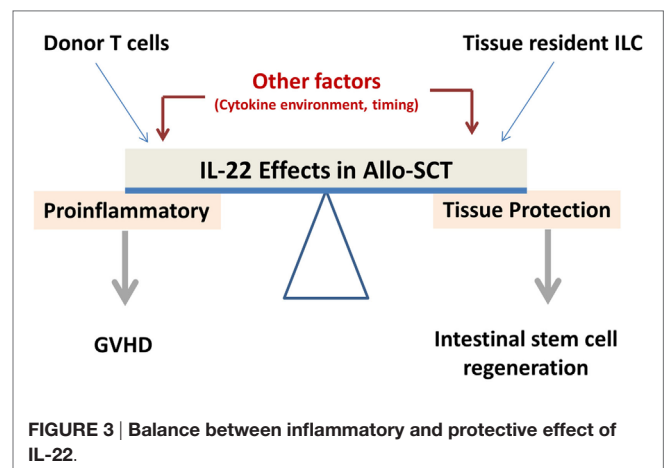
A solid basis of data from *in vitro* and *in vivo* models is now accumulating to support IL-22s pleiotropic function. In particular, its dual pro-inflammatory and anti-inflammatory nature constitutes the largest obstacle to developing therapeutics based on this molecule (Figure 3). Therefore, further studies are required, especially in the human setting, to comprehensively explore the role of IL-22 in allo-HSCT.

## AUTHOR CONTRIBUTIONS

BL wrote the manuscript and designed the figures, FM wrote the manuscript, PS and MM commented on the manuscript, and BG wrote the manuscript.

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**Conflict of Interest Statement:** The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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