The emerging role of sST2 blocking in the therapy of graft-versus-host disease

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Suppression of tumorigenicity 2 (ST2) is an interleukin-1 (IL-1) receptor family member with transmembrane (mST2) and soluble isoforms (sST2) (1).

The mST2 is expressed on many types of cells including group 2 innate lymphoid cells (ILC2s), natural killer (NK) cells, Th1 cells, Th2 cells, regulatory T (Treg) cells and $CD8^+$ T cells (2,3). While sST2, a soluble truncated form of mST2 without the transmembrane and intracellular domains, is secreted into the circulation.

Until now, the only known ligand of ST2 is IL-33, a member of the IL-1 family and mainly expressed in the nucleus of tissue lining cells, stromal cells, and activated myeloid cells (3). In the latest research we also found that IL-33 is highly expressed in the central nervous system (CNS) (4), in which IL-33 is over 10 fold more than in liver, spleen and lung (unpublished data from our lab). IL-33 is mostly released as a damage-associated molecular pattern (DAMP) molecule from damaged cells (2,3,5) or be processed and released from activated cells (2,4,6) to the extracellular milieu and plays an important role in many indicated diseases such as inflammatory bowel disease, allergy, autoimmune disease, transplantation rejection, graft-versus-host disease (GVHD), infectious disease, and cancers (3,5,7).

IL-33 exerts its cellular functions by binding a receptor complex composed of mST2 and IL-1R accessory protein to induce MyD88-dependent signaling. On the other hand, IL-33/mST2 signaling will be inhibited by sST2 which always functions as a "decoy" receptor to sequester free IL-33 (1,8). In multiple clinical trials, sST2 has emerged as a clinically useful prognostic biomarker in patients with cardiac diseases (1,9) and allergic and nonallergic pulmonary disease (10).

Zhang *et al*. are to be congratulated for revealing a potential therapeutic target of sST2 in GVHD, a devastating complication after allogeneic hematopoietic stem-cell transplantation (HSCT) (11). Allogeneic HSCT can cure haematological malignancies and inherited or acquired non-malignant disorders of blood cells, such as sickle-cell anaemia and aplastic anaemia. After chemotherapy, patients are transplanted with the bone marrow or peripheral-blood stem cells (PBSCs) from donors. Whereas bone-marrow cells and granulocyte colony-stimulating factor (G-CSF)-mobilized PBSCs are enriched for haematopoietic progenitors, and contain mature $CD4^+$ and $CD8^+$ αβ T cells. These T cells promote haematopoietic engraftment, reconstitute T-cell immunity (particularly in adults with reduced thymic function) and mediate a potent beneficial antitumour effect, known as graft versus leukaemia (GVL). Unfortunately, both of these donor T-cell subsets also cause graft-versus-host disease (GVHD), the broad attack against host tissues by donor T cells (12).

Clinical GVHD has two forms: acute GVHD is characterized by damage to the skin, liver and the gastrointestinal tract; whereas chronic GVHD has more diverse manifestations. Zhang *et al*. demonstrated that in the development of GVHD, as the main target organ, the intestine $CD45^-EpCAM^-$stromal cells and $CD45^-EpCAM^-CD146^+$ endothelial cells, as well as donor T cells circulated in the intestine produced a large number of sST2 into plasma. When the full-length anti-ST2 mAb was applied, the severity and mortality of GVHD were reduced

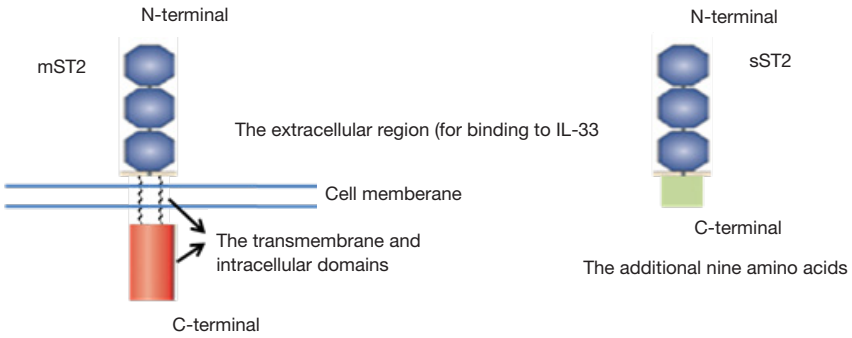

Figure 1 The difference between mST2 and sST2.

significantly (11). As for the probable pathway, there were four main points as follows: (I) ST2 blockade decreased the percentages of pathogenic TH1 cells and TH17 cells, so as the inflammatory cytokines IFN-γ, IL-17, and IL-23 were decreased; (II) the anti-ST2 mAb neutralized the sST2 and more free IL-33 bond to mST2-expressing T cells to drive the production of type 2 cytokines, which was responsible for protective type 2 inflammatory responses and promoted the expansion of regulatory T cells (Tregs) and myeloid-derived suppressor cells (MDSCs), so as the release of anti-inflammatory cytokine IL-10 was increased; (III) the anti-ST2 mAb restrained sST2-producing T cells (such as TH17 and Tc17) to produce sST2; (IV) the anti-ST2 mAb inhibited the expansion of immunogenic $CD103^+$ dendritic cells and the expression of MHC class II and costimulatory molecules (CD40, CD80, and CD86) on $CD11c^+$ dendritic cells. In the meanwhile, sST2 blockade preserved substantial antitumoral cytotoxicity and GVL activity. Above all, it suggests that sST2 is a therapeutic target for severe GVHD in clinical trials.

The main promoter used for the expression of the *ST2* gene is distinct among different cells or species (13,14). sST2 and mST2 mRNA in rats were generated by use of the proximal and distal promoters, respectively. In mice, differential mRNA processing within the *ST2* gene generates two mRNAs of 2.7 and 5 kb, corresponding to shorter secreted sST2 and longer, membrane-anchored mST2 respectively. Hence, sST2 is identical with the extracellular region (for binding to IL-33) of mST2 except for an additional nine amino acids presented at the C terminus of the molecule (15,16) (*Figure 1*). Seemingly, it is difficult to develop a specific anti-ST2 mAb only against sST2 but not mST2.

Commendably, Zhang *et al*. demonstrated that the anti-ST2 mAb they used specifically inhibited sST2 by forming a stable complex with sST2 in circulating blood and also verified that the inhibitory effect was limited to the soluble form by measuring the frequency of $ST2^+$ Tregs after treatment (11). The methods account for the effects of anti-ST2 antibody on distinct ST2 forms, but they remain far from enough. And administration of sST2 to ST2-knockout mice or selectively expressing either sST2 or mST2 in transgenic mice may be a feasible approach to disentangle the involvement of distinct ST2 forms in GVHD. It also accords with what Trajkovic *et al*. speculated in infection and autoimmune diseases (15). Thus, it seems that sST2 might present an important role in GVHD and more direct evidences for such hypothesis are urgent need.

In the research from Zhang *et al*., *ex vivo* systemic injections of IL-33 did not lead to improvement in the treated animals though anti-ST2 mAb did reduce the severity and mortality of GVHD (11). Despite of different disease model, we also observed the similar phenomenon in experimental autoimmune encephalomyelitis (EAE). Although IL-33 alone cannot relieve the progress of EAE, anti-IL-33 polyclonal antibody aggravated the disease apparently (unpublished data from our lab). Zhang *et al*. explained that endogenously produced IL-33 and exogenously administered IL-33 have different (I) circulating doses, (II) pharmacokinetics, and (III) binding properties in vivo. We consider another possibility that the mST2 in vivo is limited, so as the endogenous IL-33 is excessive that the exogenous IL-33 have no chance to exerts its cellular functions at all. While the endogenous IL-33 is blocked largely by anti-IL-33 antibody, its' protective role emerges in the reverse direction.

In summary, Zhang *et al*. found that sST2 was an effective target to relieve GVHD in a minor histocompatibility

antigen (miHA)–mismatched model of allo-HCT and a human-to-mouse xenogeneic model. It highlights the unique antagonistic action of anti-ST2 antibody to sST2 which also needs more to prove. sST2 blocking overcomes the difficulty that there is no effective strategy to control GVHD without decreasing GVL activity and the risk of leukemia relapse .

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Footnote

Provenance: This is a Guest Commentary commissioned by Section Editor Tingting Wu, MD (Department of Cardiology, the First Affiliated Hospital of Nanjing Medical University, Nanjing, China).
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