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REVIEW

Notch signaling in hematopoietic cell transplantation and T cell alloimmunity

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ABSTRACT

Notch signaling can regulate both hematopoietic progenitors and alloimmune T cells in the setting of allogeneic bone marrow or hematopoietic cell transplantation (allo-HCT). Ex vivo culture of multipotent blood progenitors with immobilized Delta-like ligands induces supraphysiological Notch signals and can markedly enhance progenitor expansion. Infusion of Notch-expanded progenitors shortened myelosuppression in preclinical and early clinical studies, while accelerating T cell reconstitution in preclinical models. Notch also plays an essential role in vivo to regulate pathogenic alloimmune T cells that mediate graft-versus-host disease (GVHD), the most severe complication of allo-HCT. In mouse allo-HCT models, Notch inhibition in donor-derived T cells or transient blockade of Delta-like ligands after transplantation profoundly decreased GVHD incidence and severity, without causing global immunosuppression. These findings identify Notch in T cells as an attractive therapeutic target to control GVHD. In this review, we discuss these contrasting functions of Notch signaling with high translational significance in allo-HCT patients.

1. Introduction

Allogeneic bone marrow or hematopoietic cell transplantation (allo-HCT) is a potentially curative therapy for many patients with hematological diseases [1,2]. In the absence of underlying cancer, allo-HCT provides a source of healthy progenitors to replace failing or diseased cells (e.g. in bone marrow failure syndromes, congenital immunodeficiencies and hemoglobinopathies). However, the majority of allo-HCT procedures are performed for patients with leukemias, lymphomas and other clonal hematological disorders. In these cases, the allogeneic graft provides T cells and other immune cells that play major therapeutic roles through recognition and elimination of cancer cells in the host (graft-versus-tumor, or GVT, effect) [3–5]. Unfortunately, donor-derived T cells also lead to immune-mediated damage in normal host tissues, a life-threatening complication referred to as graft-versus-host disease (GVHD) [6–8].

Multiple shortcomings limit the success and broader applicability of allo-HCT: absence or insufficient numbers of adequately matched progenitors in some patients; prolonged myelosuppression and lymphopenia after transplantation; high morbidity and mortality associated with GVHD; and insufficient graft-versus-tumor effects leading to post-transplant relapse [2]. Progress in the field requires creative new solutions to these problems. Interestingly, the Notch signaling pathway was recently identified as a target for intervention to mitigate several complications of allo-HCT. Both ex vivo and in vivo observations have been reported, reflecting diverse effects of Notch signaling, different target cells (hematopoietic progenitors vs. T cells) and contrasting interventions (induction vs. blockade of Notch signaling). In this paper, we review emerging work describing important effects of Notch signaling in allo-HCT with a focus on potential translational impact in patients.

2. Use and limitations of allogeneic hematopoietic cell transplantation

The devastating health effects of radiation exposure from nuclear warfare in World War II prompted pioneering studies and ultimately the first bone marrow transplantations, which were of limited benefit [1]. Intense subsequent clinical and laboratory research improved success rates and made allo-HCT available to an expanding number of patients. Recent estimates indicate that ca. 25,000 allo-HCT procedures are being performed annually worldwide. Multiple advances contributed to this success, including progress in HLA matching and donor selection, improved donor registries, access to alternative sources of hematopoietic progenitors such as cord blood, better conditioning regimen and supportive care, as well as systematic use of prophylactic immunosuppression to control GVHD.

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Despite advances in transplant care, several major problems limit the safety and effectiveness of allo-HCT. First, a sizable subset of patients lacks a related or unrelated donor with a sufficiently high degree of HLA matching [9,10]. This problem affects ethnic minorities to a disproportionate extent. In these cases, cord blood transplantation (CBT) can be considered as an alternative approach, as a higher degree of HLA mismatch can be tolerated with this source of hematopoietic progenitors and T cells [11]. However, a significant limitation of CBT especially for adult recipients is the low progenitor content of cord blood grafts. Low progenitor numbers typically lead to delayed engraftment with prolonged myelosuppression and an increased risk of serious infections. Slow lymphoid reconstitution is also particularly prevalent and severe after CBT. The first historic use of Notch signaling in allo-HCT addresses these significant issues via enhanced ex vivo expansion of cord blood progenitors [12].

As a second major problem, acute and chronic GVHD remains a source of high morbidity and mortality after allo-HCT [6,7]. Current strategies to prevent GVHD rely either on T cell depletion from the donor inoculum or on global immunosuppression (typically with calcineurin inhibitors such as cyclosporin A or tacrolimus, plus other agents) [13]. However, severe acute GVHD still occurs in a high proportion of patients (up to 50% or even more depending on donor/recipient characteristics, conditioning and GVHD prophylaxis). Patients with severe acute GVHD are treated with steroids, but only about half demonstrate a sustained response. Allo-HCT recipients with steroid-refractory acute GVHD have unacceptably high mortality (>70%) [14]. Furthermore, T cell depletion and global immunosuppression increase the risk of opportunistic infections and also decrease the potency of graft-versus-tumor activity [4,7]. This problem is best illustrated by studies of T cell depletion as a preventative approach for GVHD: improved GVHD control was counterbalanced by a markedly increased risk of tumor relapse, so that overall patient outcome was not improved [15–17]. Finally, chronic GVHD represents a major unmet clinical need, as all current treatment strategies perform poorly in this condition [18]. Altogether, the field would benefit from novel interventions that control GVHD without causing global immunosuppression and without eliminating potent GVT activity. Notch inhibition in T cells is emerging as an attractive new strategy to achieve these goals [19–22].

3. Overview of Notch signaling

Notch is a highly conserved intercellular communication pathway with important functions in health and disease [23,24]. In mammalian organisms, four Notch receptor genes have been identified (*Notch1–4*) (Fig. 1). Notch1–4 receptors are expressed as transmembrane proteins after constitutive cleavage at the S1 site during transport through the Golgi complex. Notch receptors interact with ligands of the Delta-like (Dll1, 3, 4) or Jagged family (Jag1, 2) on adjacent cells. Ligand–receptor interaction generates a physical force that displaces a negative regulatory region of the Notch receptor and opens access to proteolysis at the S2 site by an ADAM-family metalloprotease [25–27]. S2 cleavage generates an unstable intermediate that becomes a substrate for intramembrane proteolysis

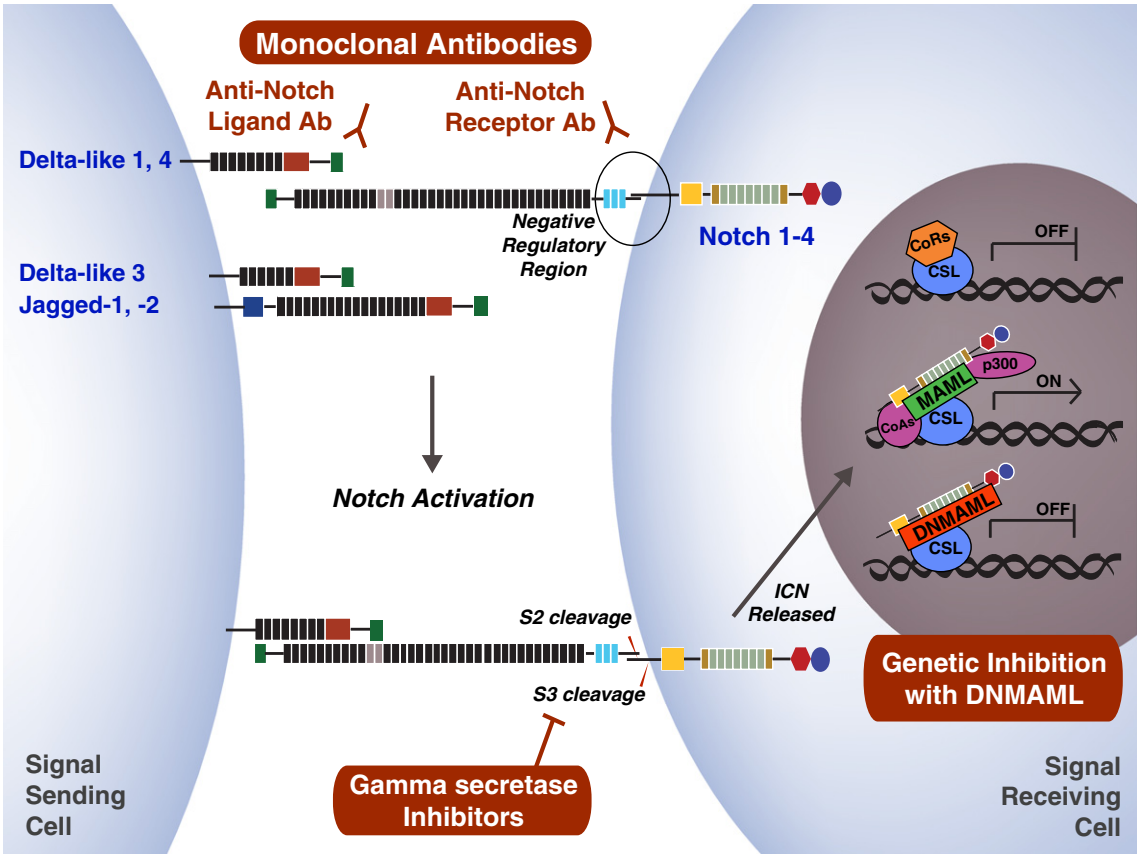

Fig. 1. Overview of Notch signaling. Activation of Notch signaling is triggered by the interaction between one of five Notch ligands (Delta-like1, 3, 4; Jagged-1, 2) with one of four mammalian Notch receptors (Notch1–4). Ligand-receptor binding induces a mechanical change in the Notch receptor, displacing the negative regulatory region to allow proteolytic cleavage at the S2 site by an ADAM family metalloprotease. S2 is rapidly followed by S3 cleavage mediated by the γ-secretase complex, releasing the intracellular portion of the Notch receptor (ICN) into the cytoplasm. ICN migrates into the nucleus to assemble a transcriptional activation complex together with the transcription factor CSL (CBF-1/Suppressor of Hairless/LAG-1) and a co-activator of the Mastermind-like family (MAML). During Notch activation, co-repressors (CoRs) are displaced and co-activators (CoAs) recruited, stimulating target gene transcription. Selected strategies of Notch inhibition are highlighted in red: neutralizing monoclonal antibodies against Notch ligands or receptors; pharmacologic inhibition of γ-secretase; and genetic blockade of the Notch transcription activation complex with dominant negative Mastermind-like (DNMAML). Other methods include gene inactivation of *Notch1–4* or *Rbpj* (encoding CSL).