

Preface

From the Cradle to the Work Place: Pleiotropic Roles of Notch in Immunity

The Notch signaling cascade is one of the few basic cellular mechanisms that controls cellular fate specifications, cell growth and cellular differentiation. The pathway is highly pleiotropic and regulates multiple aspects of embryogenesis as well as differentiation processes and homeostasis in adult tissues. One of the first reports linking the Notch pathways with the hematopoietic system was the landmarking study in 1991 by Ellisen et al. who associated altered Notch function with human disease identifying a rare chromosomal translocation in human T cell acute lymphoblastic leukemia (T-ALL) (Ellisen et al. 1991). Subsequently, more than a decade ago the essential role of Notch1 for T lymphopoiesis was established (Radtke F. et al. 1999, Pui J. C. et al. 1999). Since then, Notch signaling has been implicated in many aspects of hematopoiesis and immune function. This collection of reviews summarizes the different roles of Notch signaling within the blood system. Bigas and colleagues review our current understanding of Notch function for the generation, specification and maintenance of hematopoietic stem cells during embryonic development and adulthood. The best-studied function of Notch signaling within the blood system is its essential role during T cell lineage commitment and maturation. Shah and Zuniga-Pflücker focus on the role of the Notch ligands and key molecules involved in ligand endocytosis as well as on the mechanism of Notch activation during T lymphopoiesis. Toribio and colleagues describe the interplay between Notch and cytokine signaling with a particular emphasis on how Notch-driven expression of the IL-7R is important for survival and proliferation during early thymocyte development. Moreover, they explain how aberrant IL-7R expression or gain of function mutations within the IL-7R gene contribute to T cell neoplasms.

Most of our current knowledge of Notch function within the hematopoietic system is derived from studies in mouse models. However, a major breakthrough was made with the establishment of Notch ligand expressing stromal cell culture systems (Schmitt and Zuniga-Pflucker 2002) that made it possible to now study in

vitro also the effects of Notch signaling in human progenitors. These studies revealed the importance of Notch signaling during multiple stages of T cell development, in both mice and men, but they also highlighted species related differences. Taghon and colleagues summarize these findings here for us.

Once thymic T cell development is completed, T cells leave the thymus and orchestrate immunity against pathogens. After receiving and integrating the appropriate signals, T cells differentiate into effector or helper T cell subsets. Different aspects of the role of Notch signaling in T helper cell differentiation and function are described in two reviews by Minter and Osborne and by Tachini-Cottier and colleagues.

More recent evidence also suggests a role for the Notch cascade in alloreactive T cell immunity, which mediates recognition of foreign antigens in recipients of organ transplants. The review by Chung and Maillard highlights these novel findings and they suggest that modulating Notch signaling in T cells could have beneficial effects in an allogeneic transplantation setting.

The family of Notch receptors consists of four family members, of which Notch1, Notch2 and to a lesser extent Notch3 have been shown to mediate physiological relevant functions within the immune system. The review by Sakata-Yanagitoma and Chiba focuses on the specific roles of Notch2 during hematopoietic lineage specification and immune function.

Constitutive Notch1 signaling and activating mutations in the Notch1 gene contribute to and are a major hallmark of T cell lymphoblastic leukemia (T-ALL). The last review by Tzoneva and Ferrando summarizes the recent progress on our understanding of how aberrant Notch1 signaling mediates its oncogenic properties and discusses potential avenues targeting Notch1 therapeutically to fight T-ALL.

Lausanne, Switzerland

Freddy Radtke

References

- Ellisen LW et al (1991) TAN-1, the human homolog of the *Drosophila* notch gene, is broken by chromosomal translocations in T lymphoblastic neoplasms. *Cell* 66(4):649–661
- Pui JC et al (1999) Notch1 expression in early lymphopoiesis influences B versus T lineage determination. *Immunity* 11(3):299–308
- Radtke F et al (1999) Deficient T cell fate specification in mice with an induced inactivation of Notch1. *Immunity* 10(5):547–558
- Schmitt TM, Zuniga-Pflucker JC (2002) Induction of T cell development from hematopoietic progenitor cells by delta-like-1 in vitro. *Immunity* 17(6):749–756



<http://www.springer.com/978-3-642-24293-9>

Notch Regulation of the Immune System

Radtke, F. (Ed.)

2012, XII, 184 p., Hardcover

ISBN: 978-3-642-24293-9