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## The role of retinoic acid signaling in thymic function

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Retinoic acid (RA) is a vitamin A metabolite and member of the large family of retinoids that have been used in treatment of various forms of cancer and skin disorders. Also, vitamin A deficiency is associated with impaired ability to fight infections and RA has been shown to shape peripheral immune responses. However, little is known about the role of RA in the development of immune cells. We are currently investigating the role of RA signaling in thymic function. In the thymus, thymic epithelial cells (TEC) are providing the specialized microenvironment that supports T cell development and proper TEC maturation and homeostasis is required for the generation of a functional T cell pool. TEC development and differentiation is dependent on crosstalk with immune and stromal cells in the thymus and previous work of our group has suggested RA as a potential key player in this process.

To study the role of RA signaling in TEC homeostasis and function *in vivo* we are using a transgenic mouse model where RA signaling is blocked in the TEC compartment. Thereby we could show that RA controls TEC subset composition and maturation postnatally, preferably in the cortical TEC compartment. Block of RA signaling in TEC also affects T cell development and results in reduced numbers of single positive (SP) thymocytes and naive CD8<sup>+</sup> T cells in the periphery.

These findings provide first *in vivo* evidence for a role of RA signaling in the adult thymus regarding TEC function and T cell development.

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## NK cells with constitutively active WASp display hyperactivity and increased tumor cell killing

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To kill target cells, natural killer (NK) cells organize signaling from activating and inhibitory receptors to form a lytic synapse. X-linked neutropenia (XLN) patients have gain-of-function mutations in the actin regulator WASp and suffer from neutropenia and immunodeficiency. XLN patients have reduced number of NK cells in peripheral blood, however, the NK cell responsiveness in XLN remains unknown. We have generated mouse models of XLN that harbor the XLN patient mutations, WASp<sup>L272P</sup> and WASp<sup>I296T</sup>, to study NK cell synapse formation and functionality. Using high resolution imaging, XLN NK cells showed highly polarized F-actin in response to low stimulation. In contrast, wild-type NK cells needed specific receptor stimulation via NKp46 for F-actin polarization. To investigate the functional consequence of increased F-actin polarization in XLN NK cells, we assessed their responsiveness to different stimulations. Wild-type and XLN NK cells formed similar synapses with YAC-1 tumor cells *in vitro*, characterized by F-actin and granule polarization toward the YAC-1 tumor cells as determined by ImageStream analysis. When compared to wild-type NK cells, XLN NK cells showed increased degranulation and IFN $\gamma$  production in response to stimulation via activating receptors NKp46 and NK1.1, and tumor cell stimulation *in vitro*. When challenged with tumor cells or MHC class I deficient ( $\beta 2 m^{-/-}$ ) splenocytes *in vivo*, XLN mice showed increased rejection capacity of both tumor cells and  $\beta 2 m^{-/-}$  spleen cells. Together, our data suggests that NK cells from mice with constitutively active WASp show an augmented and unregulated actin polymerization associated with increased capacity to kill tumor cells.