regulated by Dicer-generated small RNAs.

These data indicate that functional Dicer is required for the generation and survival of $\alpha\beta$ -TCR⁺ T cells, although it is not required for CD4/CD8 lineage choice or for the specification of lineage-specific gene expression. The mechanisms by which Dicer regulates $\alpha\beta$ -TCR⁺ T-cell development and survival remain to be determined. However, although Dicer has been shown to mediate heterochromatin silencing through the generation of siRNAs, the authors found no evidence of a defect in either constitutive or facultative heterochromatin silencing in DP thymocytes isolated from the *lckCre Dicer^{ΔΔ}* mice.

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References and links

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LYMPHOCYTE MIGRATION

Rolling lymphocytes come to an abrupt stop

Before circulating lymphocytes can enter lymph nodes or inflamed peripheral tissues, they must come to a stop on the target endothelium — a process known as lymphocyte arrest, which largely depends on activation of the integrin lymphocyte function-associated antigen 1 (LFA1). It is thought that sequential chemokine signals mediate the stepwise activation of LFA1 until a threshold level of active LFA1 is reached. However, this view has been challenged by a report in *Nature Immunology* indicating that lymphocytes come to an abrupt stop after encountering endothelium-presented chemokines and the LFA1 ligand intercellular adhesion molecule 1 (ICAM1).

LFA1 exists in several conformations: an inactive, bent conformation, which is found at the cell surface of most circulating immune cells; and two extended conformations that have either intermediate or high affinity for ligand, depending on the conformation of the ligand-binding I domain (inserted domain). To assess whether *in vivo* activation of LFA1 occurs as a result of an accumulation of successive chemokine-mediated signals, Shamri *et al.* used intravital microscopy to analyse the behaviour of rolling lymphocytes in high endothelial venules. Surprisingly, rolling lymphocytes were observed to arrest abruptly, rather than to gradually decelerate. Another surprise was that LFA1-dependent arrest occurred in the presence of endothelium-presented chemokines — such as CXC-chemokine ligand 12 (CXCL12) and CC-chemokine ligand 21 (CCL21) — but not after activation by soluble forms of the same chemokines. Similarly, under conditions of shear flow, lymphocytes became arrested *in vitro* on purified ICAM1 in the presence of immobilized chemokines, but this did not occur after activation by soluble chemokines. Because arrest through LFA1 occurred immediately after encounter with endothelium-presented chemokine, this indicates that LFA1 can be activated within a fraction of a second of contact with co-immobilized chemokine and ICAM1.

Using antibodies specific for distinct LFA1 conformations, it was shown that, under conditions of shear flow, exposure of lymphocytes to the soluble forms of CXCL12 and CCL9 induced the high-affinity conformation of LFA1, which is incompatible with lymphocyte

arrest under conditions of shear flow. By contrast, when immobilized, these chemokines induced LFA1 extension to the intermediate conformation but did not generate the high-affinity conformation. Therefore, surprisingly, the ability of chemokines to induce lymphocyte arrest on ICAM1 correlated with their ability to induce extension of LFA1 but not the high-affinity conformation. In further analysis, an inhibitor of the I domain — which prevents the I domain entering the high-affinity conformation (but does not prevent LFA1 entering the extended, intermediate-affinity conformation) — markedly impaired lymphocyte arrest induced by immobilized chemokines. These results indicate that LFA1 extension to the intermediate-affinity conformation can be dissociated from lymphocyte arrest and that the conversion of extended LFA1 to fully activated LFA1 (which is required for lymphocyte arrest) must occur during its very short and localized interaction with ICAM1.

These results indicate that endothelium-immobilized chemokines induce LFA1 to enter the extended, intermediate-affinity conformation. This primes LFA1 such that it can bind ICAM1, triggering the full activation of the integrin that is required for lymphocyte arrest. This mechanism of lymphocyte arrest is incompatible with the idea that sequential chemokine-mediated signals are required to mediate LFA1 activation in a stepwise manner.

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References and links

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