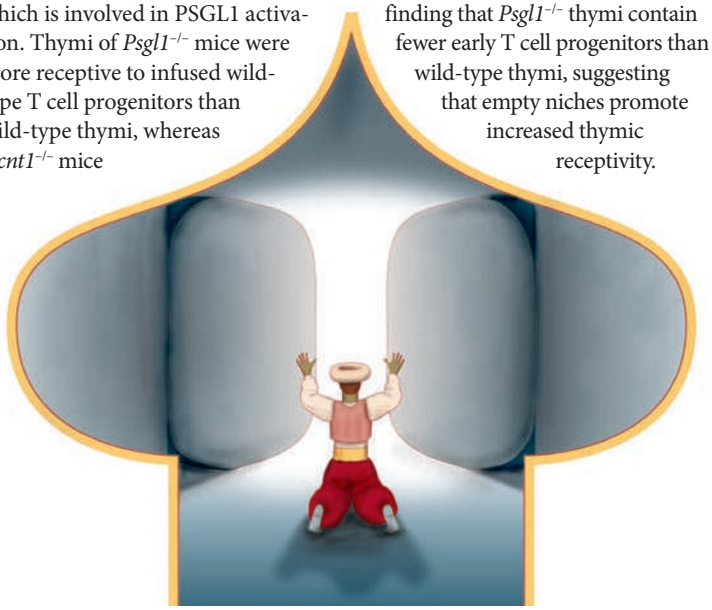
T CELL DEVELOPMENT

Open sesame! Thymic entry commands revealed

To sustain a constant supply of T cells, the thymus must be seeded by T cell progenitors from the blood. Precursor entry to the thymus occurs in waves separated by several weeks and is therefore thought to be a 'gated' process. A recent study provides important new findings showing that the commands that control the opening of thymic gates come from occupied thymic niches and the peripheral lymphocyte pool.

Previous studies have shown that thymic entry of T cell progenitors requires interaction with P-selectin on thymic vessels through P-selectin glycoprotein ligand 1 (PSGL1; also known as SELPLG), responsiveness to CC-chemokine ligand 25 (CCL25) and available space in thymic niches that provide thymocyte survival and differentiation factors. To further explore the correlation between niche occupancy and the expression of molecules needed for thymic entry, the authors examined mice deficient in P-selectin, PSGL1 and core 2 *N*-acetylglucosaminyltransferase 1 (GCNT1; also known as C2GNT1), which is involved in PSGL1 activation. Thymi of *Psgl1*$^{-/-}$ mice were more receptive to infused wild-type T cell progenitors than wild-type thymi, whereas *Gcnt1*$^{-/-}$ mice showed no or only modest increases in thymic receptivity. By contrast, thymi from mice that lack recombination-activating genes (RAGs) had reduced receptivity, which is consistent with the failure of progenitors from these mice to mature and vacate early thymic niches. Importantly, thymic receptivity positively correlated with the level of expression of P-selectin by thymic endothelial cells, such that P-selectin levels were high in *Psgl1*$^{-/-}$ mice but low in *Rag*$^{-/-}$ mice (compared with wild-type mice). Similarly, thymic expression levels of CCL25 were increased in *Psgl1*$^{-/-}$ mice but decreased in *Rag*$^{-/-}$ mice.

In further support for a relationship between thymic receptivity and homing molecule expression, the authors showed that in wild-type thymi P-selectin and CCL25 expression levels fluctuate in parallel with the approximately fortnightly waves of progenitor entry to the thymus, suggesting that the periodic filling and emptying of thymic niches provide feedback signals to control thymic entry. This is also consistent with the finding that *Psgl1*$^{-/-}$ thymi contain fewer early T cell progenitors than wild-type thymi, suggesting that empty niches promote increased thymic receptivity.



Next, the authors observed that immature and mature thymocytes accumulated in *Psgl1*$^{-/-}$ but not *Gcnt1*$^{-/-}$ thymi, leading them to suggest that impaired thymic export and the consequent reduction in size of the peripheral lymphocyte pool might explain why thymic entry is increased in *Psgl1*$^{-/-}$ but not *Gcnt1*$^{-/-}$ mice. Indeed, transfer of wild-type lymphocytes to reconstitute the peripheral T cell population in *Psgl1*$^{-/-}$ mice led to reduced thymic P-selectin expression and thymic receptivity. Conversely, depletion of peripheral T cells from wild-type mice led to rapid increases in P-selectin expression and thymic receptivity.

Finally, the authors identified sphingosine 1-phosphate (S1P) as a key mediator linking peripheral T cell numbers to thymic receptivity. Changes in S1P levels in the blood seemed to positively correlate with changes in thymic P-selectin expression, and treatment of wild-type mice with the S1P agonist FTY720 or with a S1P lyase inhibitor (to disrupt the S1P gradient between the thymus and the blood) resulted in reduced P-selectin expression and thymic entry.

Together, these data led the authors to conclude that thymic entry is controlled by two feedback mechanisms: the first depends on the occupancy status of thymic niches and the second depends on the peripheral lymphocyte pool and involves S1P.

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ORIGINAL RESEARCH PAPER Gossens, K. *et al.* Thymic progenitor homing and lymphocyte homeostasis are linked via S1P-controlled expression of thymic P-selectin/CCL25. *J. Exp. Med.* 16 Mar 2009 (doi:10.1084/jem.20082502)
FURTHER READING Cyster, J. G. Settling the thymus: immigration requirements. *J. Exp. Med.* 6 Apr 2009 (doi:10.1084/jem.20090458)