Mechanisms of lineage commitment are of considerable interest in biology, and lineage commitment in the immune system represents no exception to this rule. In the thymus, the TCR α/β lineage diverges into the CD4+8- and CD4-8+ lineages, which exhibit distinct functional programs after antigenic stimulation. To a large extent, these programs are fixed before antigenic stimulation (1-5). The thymus, the TCR α/β lineage diverges into the CD4+8- and CD4-8+ lineages, which exhibit distinct functional programs after antigenic stimulation. To a large extent, these programs are fixed before antigenic stimulation (1-5).

Work with transgenic α/β TCRs has shown that the specificity of the TCR for either class I or class II thymic MHC molecules ultimately decides whether a developing T cell becomes a long-lived, mature CD4+8- or CD4-8+ lymphocyte, respectively (6-9). Before positive selection of immature CD4+8- thymocytes was discovered, it was postulated that CD4/CD8 lineage commitment occurred by an instructive mechanisms such that coengagement of the α/β TCR and the CD8 or CD4 coreceptor by either class I or class II MHC molecules would result in different signals that would direct the differentiation into the CD4+8- and CD4-8+ lineages, respectively (10).

While initial results in TCR transgenic mice were consistent with this notion (6-9), subsequent thinking (11) as well as analysis of various mutant mice revealed that there was room for other, noninstructive explanations (1, 3, 12-15). In particular, the discovery of so-called intermediate CD4+8lo and CD4+8hi subsets (12, 15) in various MHC-deficient mice led to the hypothesis that early CD4/CD8 commitment was of a stochastic nature. This assumed that CD4+8lo and CD4+8hi cells were on their way to becoming CD4+8- and CD4-8+ mature and long-lived T cells, a view that appeared to be supported by the fact that CD4+8- cells with class I-restricted TCRs and CD4-8+ cells with class II-restricted TCRs could be rescued by CD8 and CD4 transgenes, respectively, which were expressed in all α/β T cells (1, 3, 4, 13, 14). Collectively, these data were interpreted to indicate that CD4/CD8 lineage commitment and positive selection could be divided into two steps: in the first step, coengagement on CD4+8- cells of the TCR and coreceptor by thymic MHC molecules in CD4+8- cells would lead to a stochastic lineage commitment accompanied by either CD4 or CD8 coreceptor downregulation, whereas in the second step, coengagement of TCRs and coreceptors by either class I or class II MHC molecules would result in rescue from programmed death of cells with matched receptor molecules only. This view became known as the stochastic/selective model of CD4/CD8 lineage commitment (Fig. 1).

There were, however, concerns with this model too: direct evidence that CD4+8lo and CD4+8hi cells were indeed on their way to becoming CD4+8- and CD4-8+ mature and long-lived cells was lacking. Also, rescue of “unorthodox” subsets with mismatched TCRs and coreceptors by coreceptor transgenes was not as significant as could have been expected if early CD4/CD8 lineage commitment were a stochastic event. Significantly, analysis of CD4+8lo subsets in vivo (16) and in vitro (17) suggested that these cells contained precursors not only for CD4+8- but also for CD4+8+ T cells. This finding and the notion that, at least in vitro, CD4+8- cells could develop from CD4+8low cells even when derived from mice devoid of classical MHC molecules (17) led authors to postulate a default/instructive model in which CD4+8- commitment occurs regularly, even in the absence of classical MHC molecules, whereas commitment to the CD4-8+ lineage requires an instructive signal delivered when TCR and CD8 coreceptor bind to class I MHC molecules. These experiments can obviously only be performed after cell separation, i.e., after binding of CD4 and CD8 antibodies to the cells in question, which may or may not have consequences for further phenotypic changes. Also, there is at present no general consensus that CD4+8low cells, committed to the CD4+8- lineage, exist in MHC-negative mice (12, 17). Finally, the proponents of the default/instructive model do not want to rigorously rule out any class II MHC ligation of the TCR as an initial step in CD4+8- commitment (17). The default/instructive model is illustrated in Fig. 1.

To complete the circle of CD4/CD8 lineage commitment models and experiments that are consistent with them, Itano et al. (18) report in this issue novel experiments that are consistent with an instructive/selective model. As explained above, an instructive model requires different signals that are generated after coengagement of TCR and coreceptor by either class I or class II MHC molecules. Since CD4 and CD8 coreceptors have different cytoplasmic tails, these tails could have a role in generating special signals; in fact, the CD4 tail associates much more strongly with p56lck than does the CD8 tail (19). Therefore, attempts were made to see whether a swap of coreceptor tails would result in changes in CD4/CD8 lineage commitment. This was done previously (20) and in a different way again in the work by Itano et al. described in this issue (18). The authors report that a CD8α/CD4 chimeric transgene, in which the CD4 cytoplasmic tail has been hooked into the CD8α extracellular and transmembrane region (CD884), when
expressed together with a CD8β transgene, engages significantly more p56 lck than a CD8α transgene. The same transgene causes an increase in CD4+8− cells that express a class I MHC-restricted TCR. Although this increase could be attributed to a more efficient rescue of stochastically generated CD4+8− cells with a class I MHC-restricted TCR, the authors argue that this cannot serve as the sole explanation, because there is a concomitant decrease in CD4+8− cells, even when competition for putative selection niches appears to be absent. The authors offer adequate, possible explanations as to why such changes were not seen in an earlier attempt of a similar kind (20). The novel model that emerges from these studies is a modified instructive scheme: quantitative differences in signaling induced by coengagement of TCR and coreceptors by either class I or class II MHC molecules produce a bias in lineage commitment such that the stronger signal favors CD4+CD8− and the weaker signal favors CD4−CD8+. After receptor downregulation, a "confirmatory" step due to coligation of TCRs and coreceptors ensures survival of those cells with matched TCR and coreceptor expression, while others die. This can be named the instructive/selective model as shown in Fig. 1.

Obviously, by now we are (painfully) aware of the fact that we have at least four distinct CD4/CD8 lineage commitment models, each with a set of consistent experiments. Clearly, what we need are experiments that refute any of these hypotheses. However, these recent experiments have also produced some facts that are agreed upon: it appears no longer reasonable to assume that a short-lasting TCR-MHC ligation results in lineage commitment and positive selection. Rather, these events require consecutive if not continual (21, 22) receptor engagement.

Address correspondence to Dr. Harald von Boehmer, Institut Necker, INSERM 373, 75730 Paris Cedex 15, France.

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References


