molecules as markers and, possibly, targets for therapeutic intervention. ■

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Comment on Cornish et al, page 600

Time to restore individual rights for IL-2 and IL-15?

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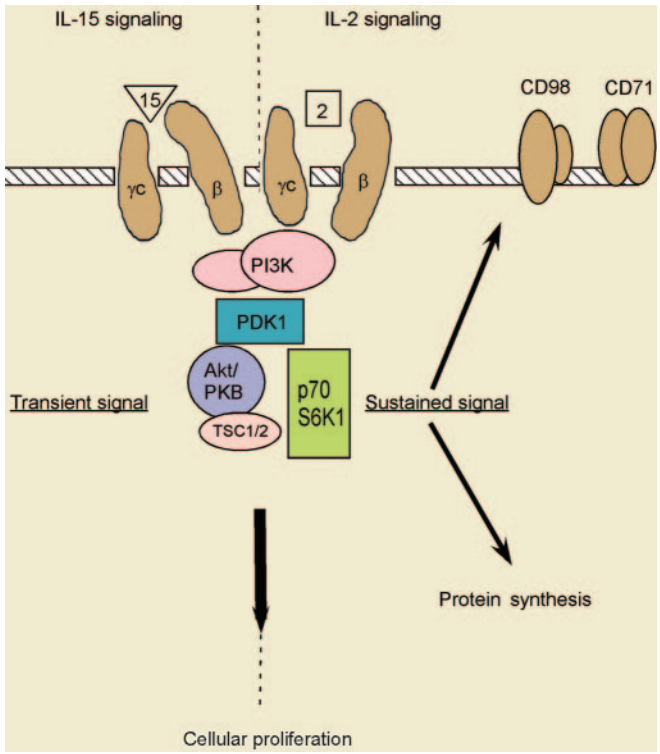
IL-2 and IL-15 transduce distinct signals in the same cell despite their sharing of all signaling receptor components.

The immune system uses many cytokines to accomplish diverse functions. It is sometimes amazing that the system can avoid confusion, especially given that many cytokines share receptor and signaling components. While most cytokines share only part of the signaling receptor components, the case of interleukin (IL)–2 and IL-15 seems unique because they share all the signaling receptor components (ie, CD122 and CD132). Each of these cytokines requires a private α chain (CD25 and IL-15Rα) for stable binding to the CD122/132 complexes in vivo, and these α chains have different cellular distribution, which may explain why IL-$2^{-/-}$ and IL-$15^{-/-}$ mice have totally different phenotypes. Thus, the question of whether IL-2 and IL-15 transduce distinct signals at a single-cell level has been controversial. Ku et al[1] demonstrated that IL-2 and IL-15 display contrasting effects on the survival of memory-phenotype CD8 T cells, which could indicate signaling differences between these two cytokines. However, the basal interpretation of this study has been challenged recently by Boyman et al,[2] who discovered that the anti–IL-2 antibody used in the original study bound IL-2 in vivo but converted it into a "superagonist" by forming stable IL-2/anti–IL-2 complexes, rather than neutralizing the effect of IL-2. Such superagonistic IL-2 can expand memory phenotype CD8 T cells even in IL-$15^{-/-}$ mice; thus, the action of these complexes seems similar to that of IL-15 in this context.[2] So do these 2 factors have distinct in vivo functions only because they act on different target cells? It has been suggested that IL-15Rα transduces its own signal upon binding by IL-15, but the process does not seem to operate in vivo, because IL-$15^{-/-}$ and IL-15Rα$^{-/-}$ mice did not manifest any defects that are not seen with the CD122$^{-/-}$ mice. Moreover, Kovanen et al[3] demonstrated that IL-2 and IL-15 (and IL-7) induce very similar gene activation profile using cDNA microarrays, basically suggesting that the IL-2/IL-15 receptors do not distinguish these 2 cytokines functionally at a single-cell level.

In this issue of *Blood*, Cornish and colleagues present elegant and interesting insights into this question. They demonstrated that IL-15 primarily activates proliferation (and thus acts as a mitogen), whereas IL-2 activates more diverse pathways including proliferation, amino acid uptake, and protein synthesis (hence, IL-2 is a genuine growth factor) in ex vivo CD8 T cells. IL-2–cultured and IL-15–cultured CD8 T cells consistently exhibited distinct morphology and expressed different cell-surface antigens. They also demonstrated that such differences might arise from differential kinetics of the signaling through the Akt (PKB)–PDK1 pathway (see figure). These observations do not seem to contradict the earlier microarray study,[3] because the difference in the signaling kinetics may be translated into cellular events at later points that the microarray analyses did not cover. While the mechanism underlying these observations needs to be investigated, Cornish et al's study undoubtedly sheds new light on how we interpret and design in vivo experiments. In parallel, Dubois et al[4] and other groups demonstrated that IL-15 is presented to target cells in *trans*, which may be the dominant way IL-15 operates in vivo.[5] It is reasonable to assume that *trans*-presented IL-15 may signal very differently from IL-2, since such IL-15 signals inevitably include elements coming from cell-to-cell contact. Finally, IL-15 is being considered as a clinical therapeutic agent as a replacement for IL-2 because of its less-toxic nature, but the current study poses a challenge to this concept and



Differences of IL-2 and IL-15 signaling in CD8 T cells.

urges us to consider IL-2 and IL-15 as distinct factors. ■

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Comment on Schnell et al, page 591

Per aspera ad astra: from early T-cell development to accelerating late T-cell apoptosis

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A sophisticated hunt for genes differentially expressed during early T-cell development has led to the identification of *Gimap4*, a gene with a promising expression profile during T-cell development. However, gene-knockout reveals that *Gimap4* does not play a role in T-cell development, selection, and activation, but that instead it acts as an accelerator of T-cell death during the final transition from a cell with apoptotic morphology to one with a disintegrated plasma membrane.

In this issue of *Blood*, Schnell and colleagues report on the identification of Gimap4, a protein that is differentially expressed during T-cell development, and its surprising function in programmed cell death. Gimap4 is a member of the GTPase of the immunity-associated protein (Gimap) family,[1] also known as the immune-associated nucleotide-binding (IAN) protein family.[2]

The original aim of the study was to identify genes involved in early T lymphocyte development. To identify such genes, the Jacobs group applied a sophisticated screening approach: they performed differential display of mRNA from sorted subsets of thymocytes obtained from *Rag2*–deficient mice that had either been treated with anti-CD3ε or been left untreated.[3] The analysis found that *Gimap4* was one of the most prominently differentially expressed genes. The expression pattern of Gimap4 in early T-cell development also looked promising: while being induced in precursor T cells, *Gimap4* expression was shut off during thymic-positive selection, but Gimap4 was re-expressed thereafter and, interestingly, remained expressed throughout T-cell life.

Because everything indicated that it would be worthwhile to generate *Gimap4*-deficient mice, Schnell and colleagues did so. Needless to say, the authors were not amused and were probably very disappointed to learn that *Gimap4*-deficient mice showed completely normal early T-cell development. They then submitted these mice to an extensive immunologic analysis, but again, no effect of *Gimap4* knockout on T-cell development, selection, and activation could be detected. So did Jacobs' group end up identifying and then even knocking out a gene without a function in the immune system? Well, they did not give up at this point.

As mentioned, the authors had observed that Gimap4 remained expressed in mature peripheral T cells. Intriguingly, *Gimap5* is the gene that is spontaneously mutated in the BioBreeding diabetes-prone (BB-DP) rat; this mutation is responsible for the severe lymphopenia (*lyp* mutation) and the development of insulin-dependent diabetes mellitus (*iddm1* mutation) in these rats.[4,5] In addition, it had been shown that other Gimap family members can influence T-cell survival and proliferation.[6] Consequently, Schnell et al examined whether apoptosis of peripheral T cells from *Gimap4*-deficient mice was normal. When they serum-starved splenic T cells from wild-type and *Gimap4*-deficient mice or treated them with etoposide, dexamethasone, or γ-irradiation, Schnell et al consistently observed that the ratio of apoptotic to necrotic cells was about 4-fold higher in T cells from *Gimap4*-deficient mice than in controls. At the same time, the total number of dead cells and cells with activated caspase-3 were unaffected. Thus, Gimap4 acts as an accelerator for a late step in the cell death program; that is, at the transition from a late zeiotic or "blebbing" cell with an intact plasma membrane—an "apoptotic" cell—to a cell in which the plasma membrane is disintegrated—a "necrotic" cell.

It is currently not well understood how plasma membrane disintegration is achieved during cell death induction, let alone the functional consequences of a shift in the ratio of apoptotic to necrotic cells like that observed in this study. However, it is tempting to speculate that the induction of autoimmunity as well as the ability to mount an immune response against cancer cells may be affected by the ratio of apoptotic to necrotic cells and that a shift in this ratio might influence the immunologic outcome of cell death induction. It will be interesting to see how the role of Gimap4 in apoptosis and immunity will unfold in the future. ■

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