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on the development of methods that distinguish human CECs derived from tumor and bone marrow. Elucidation of the origin of the patients' apoptotic CECs will clarify the role of host-versus-tumor differences in CEC responses, which will have implications for the broader significance of this study to other types of cancers and treatments. More extensive translational clinical trials that follow a larger number of patients for a longer-term follow-up will determine whether a simple blood test can be used to identify and monitor cancer patients who will benefit from novel antiangiogenic therapies. ■

REFERENCES

1. Kerbel RS, Kamen BA. The anti-angiogenic basis of metronomic chemotherapy. Nat Rev Cancer. 2004;4:423-436.
2. Colleoni M, Orlando L, Sanna G, et al. Metronomic low-dose oral cyclophosphamide and methotrexate plus or minus thalidomide in metastatic breast cancer: antitumor activity and biological effects. Ann Oncol. 2006;17:232-238.
3. Shaked Y, Emmenegger U, Man S, et al. Optimal biologic dose of metronomic chemotherapy regimens is associated with maximum antiangiogenic activity. Blood. 2005;106:3058-3061.
4. Jain RK. Normalization of tumor vasculature: an emerging concept in antiangiogenic therapy. Science. 2005;307:58-62.

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Macrophage diversity and polarization: in vivo veritas

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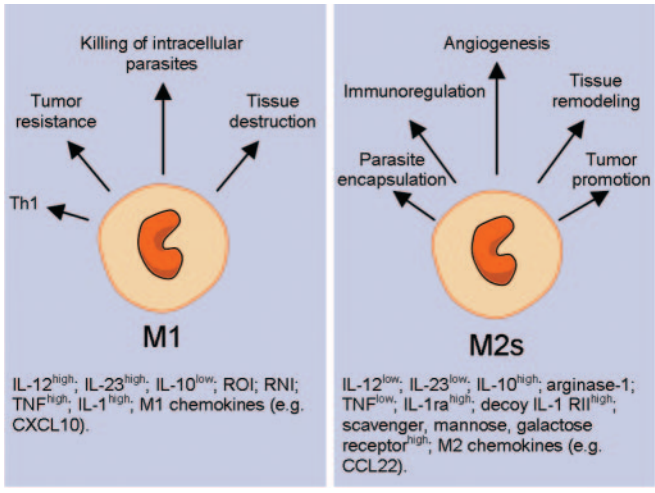
Polarized activation of cells of the monocyte-macrophage lineage into M1 and M2 cells is an operationally useful, simplified descriptor of the functional plasticity of these cells. Ghassabeh and colleagues now put to the test the actual in vivo validity and significance of the M1/M2 paradigm.

The microbial and cytokine milieu drives macrophages to express specialized and polarized functional properties.[1,2] Interferon-γ (IFN-γ), selected cytokines (granulocyte-macrophage colony-stimulating factor [GM-CSF], tumor necrosis factor [TNF]) and microbial products (lipopolysaccharide [LPS]) elicit a classic M1 form of macrophage activation. M1 macrophages are generally characterized by interleukin (IL)–12^{high}, IL-23^{high}, IL-10^{low} phenotype; produce copious amounts of reactive oxygen and nitrogen intermediates and inflammatory cytokines; are part of the afferent and efferent limb of polarized Th1 responses; and mediate resistance against intracellular parasites and tumors (see figure).

M2 is a generic name for various forms of macrophage activation other than classic M1 and includes cells exposed to IL-4 or IL-13, immune complexes, IL-10, and glucocorticoid hormones.[2] The various versions of M2 cells generally share an IL-12^{low}, IL-23^{low}, IL-10^{high} phenotype; have high levels of scavenger, mannose, and galactose-type receptors; orient arginine metabolism to ornithine and polyamine, and hence to growth promotion; and are IL-1 receptor antagonist (IL-1ra)^{high}, decoy IL-1 type II receptor^{high}, IL-1b^{low}, caspase1^{low}.[3] M1 and M2 cells express profoundly different repertoires of chemokines and chemokine receptors (the "chemokinome").[2] M2 cells are diverse, but in general are involved in T helper 2 (Th2) response; have immunoregulatory function; orchestrate encapsulation and containment of parasites; and promote tissue repair, remodeling, and tumor progression. Immature myeloid suppressor cells share functional properties and components of the transcriptome with M2 cells.[4]

The paradigm of macrophage polarization is essentially based on in vitro results. In this issue of *Blood*, Ghassabeh and colleagues report on their systematic effort to characterize macrophages from 3 models of parasite infection (*Trypanosoma brucei brucei*, *Trypanosoma congolense*, and *Taenia crassicens*) and 1 transplanted tumor. Macrophages were obtained at stages of the diseases corresponding to a predominance of M2 orientation. Myeloid cells were profiled using a differential gene expression approach. Using these diverse disease models, Ghassabeh and colleagues identify a gene signature shared by the various ex vivo–obtained M2 populations. The common signature included documented M2-associated genes (eg, arginase 1, mannose and galactose receptors, etc) as well as a new set of molecules not previously associated with M2 macrophage polarization. The functional significance and specificity of the new M2-associated genes remain to be defined. Interestingly, some of these genes could not be induced using M2 stimuli in vitro, emphasizing the importance of the in vivo approach.

This and a study on tumor-associated macrophages[4] complement results obtained in gene-modified mice reviewed in Mantovani et al[5] and provide much needed in vivo evidence of the validity of the macrophage polarization paradigm. However, these results also emphasize the diversity of the activation/differentiation states within the broad "M2" category and caution against a simplistic rigid view of the M1-M2 dichotomy. It will now be important to explore the significance of macrophage polarization in clinical conditions, where information is scanty, and the validity of new



Key properties and functions of polarized macrophages. ROI and RNI indicate reactive oxygen and nitrogen intermediates. M2s refer to diverse forms of M2 activation.

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

REFERENCES

1. Gordon S. Alternative activation of macrophages. Nat Rev Immunol. 2003;3:23-35.
2. Mantovani A, Sica A, Sozzani S, Allavena P, Vecchi A, Locati M. The chemokine system in diverse forms of macrophage activation and polarization. Trends Immunol. 2004;25:677-686.
3. Dinarello CA. Blocking IL-1 in systemic inflammation. J Exp Med. 2005;201:1355-1359.
4. Biswas SK, Gangi L, Paul S, et al. A distinct and unique transcriptional programme expressed by tumor-associated macrophages: defective NF-kB and enhanced IRF-3/STAT1 activation. Blood. 2006;107:2112-2122.
5. Mantovani A, Sica A, Locati M. Macrophage polarization comes of age. Immunity. 2005;23:344-346.

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

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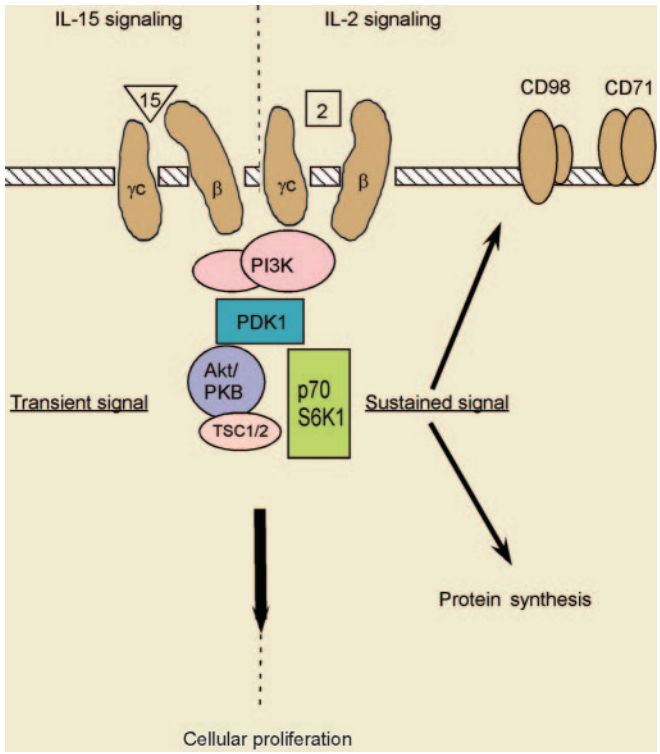
IL-2 and IL-15 transduce distinct signals in the same cell despite their sharing of all signaling receptor components.

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.

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