Welcome to the era of interconnecting pathways

Our understanding of hematopoiesis has evolved from the turn of the last century when early hematopoietic cells were identified by morphologic examination of marrow cells after special stains. During the 1960s and 1970s, Till, McCulloch, Metcalf, and Sachs provided us in vivo and in vitro clonogenic assays to help dissect the hematopoietic pathways. Identification of growth factors and their receptors using these assays markedly propelled our knowledge. This was enhanced by a variety of separation techniques that took advantage of cell surface antigens expressed on various hematopoietic lineages. Over the last several years, focus has turned to identifying transcription factors that could act as the control center to mediate lineage-specific differentiation; their importance has been confirmed by their forced over- or underexpression in hematopoietic cells, both in vitro and in mice. One family of transcription factors is C/EBP, which is composed of 6 members (C/EBP-α, -β, -δ, -γ, -e, and -ζ). C/EBP-α is robustly expressed in early myelopoiesis and is thought to help mediate nascent myeloid differentiation. C/EBP-β is believed to be especially important in monocyte-macrophage differentiation. C/EBP-ε is important during the later stages of myelopoiesis as suggested by the following: (1) Specific granule deficiency syndrome can be caused by a mutation of C/EBP-ε; affected individuals have incomplete maturation of their granulocytes, are missing key granulocyte-specific proteins, and get frequent microbial infections. (2) C/EBP-ε knockout mice have the same phenotype. (3) Forced overexpression of C/EBP-ε can induce granulocytic differentiation in myeloid leukemia cell lines and cause expression of granulocyte-specific proteins in NIH3T3 fibroblasts.

Using all of the above-mentioned techniques, Nakajima and Ihle (page 897) now show that a cytokine (G-CSF) can bind to its cellular receptor and through an undefined secondary signal can induce expression of C/EBP-ε to help mediate myeloid differentiation. They also show that granulocytic differentiation can be induced through more than one signaling pathway (STAT3) and that high levels of C-MYC can block both expression of C/EBP-ε and myeloid differentiation. This block can be bypassed by forced expression of C/EBP-ε. Myelopoiesis is a complicated symphony composed of a myriad of extracellular stimuli, numerous intersecting secondary signaling pathways activating a group of transcription factors that orchestrate expression of a variety of myeloid specific targets. Armed with instruments of the past including those acquired from the genome project, we are now in the era of studying interconnecting, melodious cellular pathways.

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Mysteries of HIV pathogenesis explained

Infection and loss of CD4 helper T cells is considered an underlying mechanism for the progressive demise of the immune system in HIV-infected patients. But it fails to provide an adequate explanation for certain clinical observations. For example, why do some patients remain relatively healthy with CD4 counts of fewer than 200 while others with similar or even higher CD4 counts succumb to Kaposi sarcoma? New data from Liu and colleagues (page 1182) suggest that a recently identified subpopulation of blood dendritic cell (DC) able to produce copious amounts of type I interferon may provide some of the answers to this conundrum. These cells are variously termed DC2s, interferon-producing cells (IPCs), or plasmacytoid DCs. The investigation analyzed the number of IPCs in peripheral blood of HIV-infected patients at different stages of disease and showed a progressive depletion with increasing plasma virus load, an observation confirmed by our own recent studies (Donaghy et al, Blood, in press). Furthermore, patients who were able to suppress virus growth and remained healthy for more than 10 years were found to have elevated numbers of IPCs compared with uninfected controls. Perhaps the most striking finding was the correlation between low numbers of IPCs (fewer than 2/μL) was considered critical and opportunistic infections. The finding of Kaposi sarcoma patients with low IPC numbers but high CD4 T-cell counts was also revealing. These findings contrasted with patients showing IPC counts higher than 2 IPCs/μL who remained healthy despite very low CD4 T-cell numbers. The critical role of IPCs in HIV pathogenesis indicated by these studies suggests that monitoring IPC numbers may be of value and that strategies that increase the numbers of these cells, such as treatment with flt-3 ligand, may have therapeutic value.

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