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CONTROVERSIES IN HEMATOLOGY

Growth Factors and Hematopoietic Cell Fate

A New Feature: Controversies in Hematology

By Kenneth Kaushansky

WITH THIS ISSUE OF *BLOOD* we launch a new feature, *Controversies in Hematology.* The series is designed to identify both long-standing and relatively recent topics in Hematology and Oncology on which considerably diverging opinions exist, and to highlight the critical data supporting each view. The format is one of point and counterpoint. Each discussant will have an opportunity to put forth the critical arguments supporting their position. The papers will be exchanged and each author then allowed to rebut the arguments of the opposing discussant. We feel that this format will allow the readership to quickly appreciate the question being addressed and the nature of the evidence in support of each view. The reader is then left to his or her own conclusions. We also hope each *Controversy* will evoke discussion and stimulate additional investigation in the field.

The inaugural chapter in the series asks what are the mechanisms responsible for commitment of multipotent hematopoietic progenitors to cells of each blood lineage. Evidence from many quarters indicate that growth factors are essential for hematopoietic development. However, the precise role played by these proteins, whether to direct multipotent cells down a particular cellular pathway or to merely support the survival of cells that have intrinsically selected a specific hematopoietic lineage, remains controversial.

Lineage Commitment and Maturation in Hematopoietic Cells: The Case for Extrinsic Regulation

By Donald Metcalf

THE TWO SPECIFIC QUESTIONS at issue in the present discussion are (1) whether extrinsic signaling by hematopoietic regulators can influence the occurrence or nature of the differentiation commitment decisions a cell makes and (2) whether these regulators can initiate or influence maturation events in the progeny of committed cells. These are questions of practical importance if hematopoiesis is to be selectively manipulated in clinical emergencies by the use of hematopoietic regulators.

LINEAGE COMMITMENT

Commitment can be defined as the decision a cell makes to enter, or generate progeny that enter, a particular maturation lineage at some future time. This decision need not necessarily be accompanied by any immediate change in morphology or expression of novel membrane proteins or regulator receptors.

The existence of a lineage-committed state in many hematopoietic progenitor cells is substantiated by the ability of such cells, when in semisolid cultures, to generate colonies of a single lineage even when stimulated by a mixture of growth factors that should have permitted cells of other lineages to survive and proliferate had they been generated in the clones.[1]

In embryonic development, the principle is firmly established that commitment is extrinsically regulated by position effects or inductive gradients and does not occur by random chance. There is clear evidence that commitment events in the initiation and continued production of hematopoietic populations follow the same principle.[2]

Hematopoietic commitment depends on, and is presumably initiated by, activation of a succession of nuclear transcription factors, beginning with SCL/TAL-1 and LMO2 and then involving more lineage-restricted transcription factors such as GATA-1 or PU-1.[3] The extrinsic agents responsible for activation of these nuclear transcription factors are at present unknown.

The earliest of these events occur in cells not expressing hematopoietic receptors and are thus not subject to control by such regulators. However, there are hematopoietic precursors

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