inside blood

1 FEBRUARY 2007 | VOLUME 109, NUMBER 3

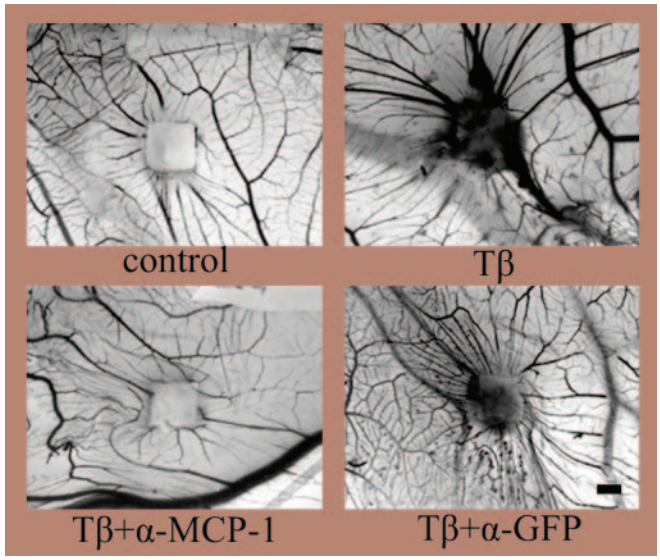
HEMOSTASIS

Comment on Ma et al, page 987

MCP-1 muscles in on pericytes

Simon Karpatkin NEW YORK UNIVERSITY SCHOOL OF MEDICINE

In this issue of *Blood*, Ma and colleagues demonstrate that TGF-β supports angiogenesis through up-regulation of the MCP-1 chemokine, which stimulates the recruitment of vascular smooth muscle cells or pericytes toward endothelial cells.



MCP-1 mediates TGF-β–induced angiogenesis. See the complete figure in the article beginning on page 987.

Angiogenesis, or new blood vessel formation, involves proliferation and migration of endothelial cells induced by vascular endothelial growth factor (VEGF), degradation of subendothelial matrices and basement membrane with metalloproteinases (MMPs), branching, stabilization of newly formed endothelial cords by angiopoietin-1, and disassembly, reassembly, and expansion of endothelial cords by angiopoietin 2. Angiopoietin-1 maintains vascular stability by recruitment of vascular growth smooth muscle cells or pericytes.

Of the numerous proangiogenic growth factors that have been described, some are relatively specific for endothelial cells, such as VEGF and its KDR receptor as well as angiopoietins 1 and 2 and their Tie-2 receptors. Others, such as transforming growth factor-β (TGF-β), basic fibroblast growth factor (bFGF), platelet-derived growth factor (PDGF), and the chemokines interleukin-8 (IL-8), growth-related oncogene-α (GRO-α), and monocyte chemoattractant protein-1 (MCP-1) are less specific for endothelial cells. Their mode of action on endothelial cells is poorly characterized.

Chemokines (chemotactic cytokines) are small heparin-binding cysteine-containing proteins that direct movement of granulocytes, lymphocytes, and dendritic cells to sites of inflammation. They induce various physiologic functions when binding to their receptors, which are present on various tissues, including endothelial cells and smooth muscle cells. They segregate into 4 families.[1,2] The largest family of chemokines is designated CC (first 2 of 4 cysteines adjacent to each other). A subset of a second family of CXC chemokines (first 2 cysteines separated by a nonconserved amino acid) containing the NH-2 terminus ELR amino acid motif have been shown to stimulate angiogenesis by binding to a common receptor, CXCR2, on endothelial cells.

It is of interest that thrombin-induced angiogenesis is also stimulated via the up-regulation of a CXC chemokine, GRO-α, which binds to a CXCR2 receptor, resulting in the up-regulation of VEGF, KDR, angiopoietin-2, MMP-1, MMP-2, and CD31.[3] It is also of interest that TGF-β up-regulates VEGF and PDGF[4,5] as well as MCP-1.

In this issue of *Blood*, Ma and colleagues demonstrate that the mechanism of action of TGF-β on stimulating angiogenesis is through up-regulation of the CC chemokine MCP-1. In a series of elegant experiments they demonstrate that TGF-β activates the promoter region of MCP-1 by initiating binding of the transcription factors Smad3 and Smad4 to the MCP-1 promoter. This leads to the recruitment of pericytes for angiogenic stability. Others have shown that MCP-1–induced angiogenesis is also mediated by VEGF.[6] Thus, a CC chemokine is also capable of stimulating angiogenesis following its up-regulation by VEGF as well as TGF-β and perhaps other vascular growth factors yet to be determined.

These observations tie inflammation to angiogenesis. What is a possible pathophysiologic relevance for these observations? Tumor cells secrete MCP-1. The requirement of tumor-induced angiogenesis for tumor growth is well established. The ability of tumor cells to secrete VEGF, bFGF, and PDGF is well recognized. The addition of the chemokines GRO-α and MCP-1 contributes to this panoply of tumor-secreting angiogenesis growth factors.

The author declares no conflicting financial interests. ■

REFERENCES

1. Strieter RM, Burdick MD, Gomperts BN, Belperio JA, Keane MP. CXC chemokines in angiogenesis. Cytokine Growth Factor Rev. 2005;16:593-609.

2. Charo IF, Ransohoff RM. The many roles of chemokines and chemokine receptors in inflammation. N Engl J Med. 2006;354:610-621.

3. Caunt M, Hu L, Tang T, Brooks PC, Ibrahim S, Karpatkin S. Growth-regulated oncogene is pivotal in thrombin-induced angiogenesis. Cancer Res. 2006;66:4125-4132.

4. Brogi E, Wu T, Namiki A, Isner JM. Indirect angiogenic cytokines upregulate VEGF and bFGF gene expression in vascular smooth muscle cells, whereas hypoxia upregulates VEGF expression only. Circulation. 1994;90:649-652.

5. Taylor LM, Khachigian LM. Induction of platelet-derived growth factor B-chain expression by transforming growth factor-b involves transactivation by Smads. J Biol Chem. 2000;275:16709-16716.

6. Hong KH, Ryu J, Han KH. Monocyte chemoattractant protein-1-induced angiogenesis is mediated by vascular endothelial growth factor-A. Blood. 2005;105:1405-1407.

HEMATOPOIESIS

Comment on Flygare et al, page 980, and comment on Choesmel et al, page 1275

Diamond-Blackfan anemia: "novel" mechanisms—ribosomes and the erythron

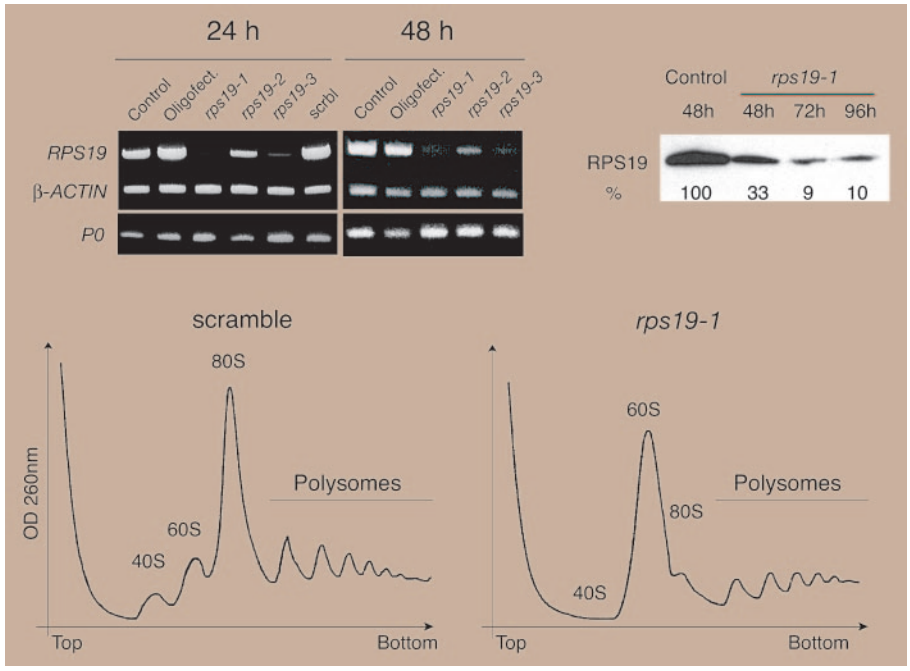
Jeffrey M. Lipton SCHNEIDER CHILDREN'S HOSPITAL and THE FEINSTEIN INSTITUTE FOR MEDICAL RESEARCH

Important studies by 2 groups have each independently provided compelling evidence implicating impaired ribosome biogenesis in the molecular pathophysiology of the dominantly inherited pure red cell aplasia, Diamond-Blackfan anemia.

The rarity of a family of disorders known as the inherited bone marrow failure syndromes (IBMFS) belies their importance. Despite obvious differences in their respective molecular lesions, these disorders share not only a predisposition to hematopoietic failure, but also to birth defects and cancer. It is widely accepted that the propensity of the mutated cells in these disorders to apoptosis is the proximate cause of their demise.[1] Furthermore, it is theorized that "interdicting" mutations that provide a reprieve from this molecular death sentence may explain the cancer predisposition, both hematopoietic and nonhematopoietic, observed in the IBMFS.[2]

Between 1938, when Diamond and Blackfan first described the clinical syndrome erythrogenesis imperfecta, characterized by pure red cell aplasia,[3] and 1997, when the first gene mutated in Diamond-Blackfan anemia (DBA) was reported,[4] myriad explanations for the red cell failure of DBA were proposed with great zeal. Various mechanisms ranging from immune mediation to a marrow stromal defect were championed before strong evidence of an intrinsic hematopoietic progenitor disorder emerged.[1] Subsequently, although the presence of a mutated gene provided very convincing evidence for a defect intrinsic to the erythroid progenitor, the novel nature of that gene created a fair amount of consternation. Indeed, the developing story line did not, for many, permit the required "willing suspension of disbelief." The mutation was in a gene, *RPS19*, which encodes a protein associated with the 40S subunit of the ribosome. That disruption of a fundamental process such as ribosome biogenesis could lead to pure red cell aplasia was not universally accepted, and alternative explanations proposed that the manifestations of DBA might be due to extraribosomal functions of RPS19. Now, 2 new pieces of evidence have emerged almost simultaneously. A second "DBA gene," *RPS24*, has been identified,[5] and in this issue of *Blood*, Flygare and colleagues and Choesmel and colleagues describe a functional defect in ribosome biogenesis attributed to RPS19 dysfunction. Thus, Flygare et al and Choesmel et al have coauthored an important chapter in the story of DBA. The authors have clearly demonstrated that a functional defect in ribosome assembly as a consequence of RPS19 protein insufficiency, characterized by faulty cleavage of ribosomal RNA, results in arrested maturation of the 18S rRNA species and culminates in a decreased number of mature ribosomes (see figure).

The exact mechanism by which this particular molecular lesion results in a failure to generate red cells will carry the plot forward. The simple explanation is that the high demand on protein synthesis in the developing erythron is the culprit, but other protagonists will no doubt emerge. For some, the final chapter will connect the defect in ribosome assembly with the predisposition to malignancy seen in DBA. Recent evidence provides an interesting theme. The nucleolus has been found consorting with p53. That a failure in protein synthesis may result in p53-mediated cell death[6] provides a tantalizing clue that may



Down-regulation of RPS19 expression blocks maturation of the 18S rRNA. See the complete figure in the article beginning on page 1275.