Chapter 9

ANGIOGENESIS IN LEUKEMIA AND LYMPHOMA

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1. INTRODUCTION

Increased bone marrow blood flow in hematologic malignancies was described about 50 years ago.\(^1\) However, it was only after the publication in 1997 of a study by Judah Folkman’s group, demonstrating increased angiogenesis in acute lymphoblastic leukemia,\(^2\) that the field received a major fillip, and attracted a lot of attention. Since then, as in any nascent field, the number of publications has grown exponentially, and there are now over 300 publications on this subject. The purpose of this review is to describe the progress in this field and to explain the significance of angiogenesis in leukemia and lymphoma.

2. A BRIEF OVERVIEW OF TUMOR ANGIOGENESIS

The hypothesis that tumor growth is angiogenesis-dependent was first proposed in 1971.\(^3\) Many lines of evidence indicate that growth of tumors beyond a diameter of 2-3 mm requires formation of new blood vessels.\(^4\)\(^-\)\(^6\) These blood vessels supply oxygen and nutrients to the growing tumor, and also promote metastasis.\(^5\) Specific anti-angiogenesis agents such as endostatin\(^7\)\(^-\)\(^9\) and anti-VEGF antibodies\(^10\) suppress tumors in animal models,
providing strong support for the hypothesis that tumors are angiogenesis-dependent.

There are numerous inducers of angiogenesis including vascular endothelial growth factor (VEGF), basic fibroblast growth factor (bFGF), hepatocyte growth factor (HGF), the ephrins, and the angiopoietins.\textsuperscript{5, 11} VEGF is the best-characterized vascular growth factor, and is critical for blood vessel formation. Deletion of a single allele in knockout mice results in embryonic lethality.\textsuperscript{12} Apart from VEGF, the VEGF family also includes VEGF-B, VEGF-C, VEGF-D, VEGF-E, and placental growth factor (PlGF).\textsuperscript{13, 14} VEGF itself has multiple splice isoforms, encoding (most commonly) polypeptides composed of 121, 165, 189 and 206 amino acids.\textsuperscript{14} The actions of VEGF are mediated by its receptors, including VEGFR-1 (also known as flt-1), VEGFR-2 (KDR, flk-1), VEGFR-3 (flt-4), and neuropilin. Deletion of the flt-1 gene\textsuperscript{15} or flk-1 gene\textsuperscript{16} results in lack of organized vascular channels, and embryonic lethality, illustrating the importance of the VEGF system in the formation of blood vessels.

There are also many endogenous inhibitors of angiogenesis, including thrombospondin-1, prolactin, angiostatin and endostatin.\textsuperscript{5, 6} Angiogenesis is a tightly regulated process, and is triggered by an “angiogenic switch”, i.e. a shift in the balance between the inducers and inhibitors of angiogenesis.\textsuperscript{5, 6} There is now considerable evidence for a genetic basis of regulation for this angiogenic switch, based on the actions of tumor suppressor genes and oncogenes.\textsuperscript{6, 17-19}

For a more detailed overview of angiogenesis, readers are referred to reviews on the subject by Folkman,\textsuperscript{5} Zetter,\textsuperscript{20} and Kerbel,\textsuperscript{6} and to reviews on VEGF and its receptors by Ferrara\textsuperscript{14} and Dvorak.\textsuperscript{13} A historic account of the progress in angiogenesis research was recently published by Ferrara.\textsuperscript{21}

### 3. ANGIOGENESIS IN MYELODYSPLASTIC SYNDROME (MDS) AND ACUTE MYELOID LEUKEMIA (AML)

Numerous groups have documented increased vascularity in bone marrow biopsies of patients with AML\textsuperscript{22-29} and MDS,\textsuperscript{23, 29-31} as compared to normal control bone marrow biopsies. In our study\textsuperscript{26} we specifically looked at angiogenesis in acute promyelocytic leukemia (APL), which is a subtype of AML. We showed that bone marrow angiogenesis is increased in APL, and is decreased after treatment with all-\textit{trans} retinoic acid. A similar decrease in angiogenesis, after therapy, has been seen in other subtypes of AML.\textsuperscript{25}