inside blood

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LYMPHOID NEOPLASIA

Comment on Sauer et al, page 2265, and Schliemann et al, page 2275

There will be blood: targeting tumor vasculature

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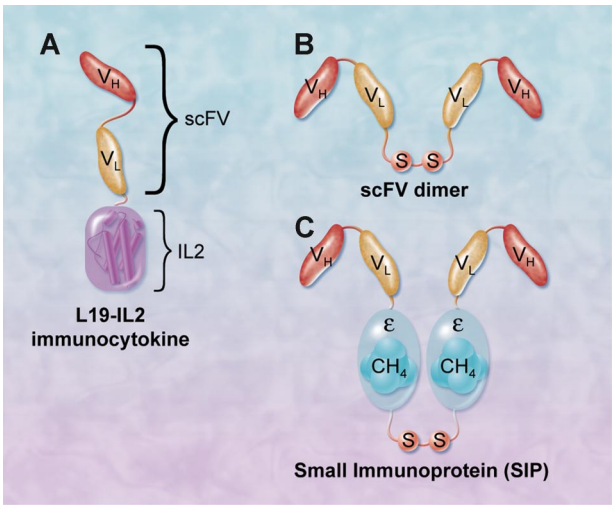
Extradomain B of fibronectin (ED-B FN) is expressed in the vasculature of hematopoietic malignancies and appears to be an effective target for monoclonal antibody–based therapies.

Wherever there is cancer, there will be blood and blood vessels to support tumor growth. While the majority of anticancer drugs are designed to directly kill tumor cells, recent strategies are focusing on drugs that indirectly kill cancer cells by targeting the tumor microenvironment and tumor vasculature. This strategy gained a significant boost with the approval of the angiogenesis inhibitor bevacizumab by the Food and Drug Administration (FDA) for the treatment of a variety of solid tumors. In addition to angiogenesis inhibitors, which primarily target the vascular endothelial growth factors (VEGFs) and their receptors, novel antivascular agents are currently under development for cancer therapy.

Fibronectin (FN) is a large adhesive glycoprotein found in plasma and tissue extracellular matrix.[1] FN binds to a large number of cell-surface transmembrane proteins called integrins. FN was one of the first genes reported to undergo alternative splicing, resulting in 3 isoforms, IIICS, extradomain (ED)-A, and ED-B. The ED-B, which was identified more than 20 years ago, consists of 91 amino acids that are identical in several vertebrates, including mice and humans.[2] This domain arises by alternative splicing exclusively at the sites of tissue remodeling and is considered a marker of angiogenesis. Extradomain B of fibronectin (ED-B FN) is usually absent in plasma and normal adult tissues, but abundantly present around newly formed blood vessels, including cancer neovasculature. Thus, the preferential localization of ED-B FN to tumor vasculature makes it a good target for cancer therapy. To test the potential clinical activity of ED-B FN–targeted therapy, a 150-kDa human IgG1 antibody to ED-B FN (termed L19) was developed. Furthermore, L19 derivatives, including a dimeric single-chain Fv (scFv) fragment (50 kDa), and a small immunoprotein (SIP), were also developed for preclinical and clinical testing. The SIP-L19 (80 kDa) consists of 2 scFv fragments fused by a CH4 domain of the human IgE, which mediates its homodimerization. Because ED-B FN was originally described to be associated with neovasculature of solid tumors, L19 and its derivatives, including radiolabeled SIP and immunocytokine conjugates, were evaluated in animal models bearing a variety of solid tumors with promising early results.[3]



L19 monoclonal antibody derivatives that target ED-B FN. (A) L19-IL2 immunocytokine consists of a single-chain Fv fragment fused to IL-2 molecule. (B) Single-chain Fv dimer. (C) Small immunoprotein (SIP) consists of 2 scFv fragments fused by a CH4 domain of the human IgE, which mediates its homodimerization. SIP can be further conjugated with radioisotopes to deliver radiation to the site of tumors. Professional illustration by A. Y. Chen.

In this issue of *Blood*, investigators extend the knowledge previously obtained from solid tumor models to hematologic malignancies. In the first study, Sauer and colleagues used immunohistochemistry methods to examine ED-B FN expression in a large panel of hematologic malignancies.[4] They found ED-B, which was absent in normal lymph nodes and bone marrow biopsies, to be expressed in the vast majority of Hodgkin and non-Hodgkin lymphoma (NHL) cases. Importantly, these investigators used a ^{131}I-labeled L19 SIP therapeutically to treat patients with relapsed lymphoma and reported achievement of partial remissions in 2 patients with Hodgkin lymphoma. Furthermore, using single photon emission computed tomography (SPECT) imaging, the authors convincingly showed selective ED-B FN targeting of malignant lesions.

In a different approach, Schliemann and colleagues conjugated a high-affinity L19 derivative to ED-B with interleukin (IL)-2.[5] This novel immunocytokine conjugate can bind to lymphoma vasculature and deliver IL-2 to the tumor microenvironment, which

in turn recruits natural killer cells and macrophages to tumor sites. When given with rituximab, the conjugate showed dramatic and prolonged efficacy in xenograft models of NHL. The idea of combining systemic cytokines with monoclonal antibodies to enhance the antibody-dependent cell-mediated cytotoxicity has been previously evaluated in clinical trials in patients with lymphoma with mixed results. However, this approach has not been widely adopted to clinical practice, because of either the toxicity induced by the systemic administration of these cytokines, or the lack of proven superiority to the antibody therapy alone. The ability to deliver cytokines directly to tumor sites through selective targeting may reduce toxicity associated with the high doses of cytokines required for many previous trials.

In recent years, several naked and conjugated antibodies have been approved by the FDA for the treatment of hematologic malignancies, including rituximab, the radiolabeled antibodies tositumomab and ^{90}-Y ibritumomab tiuxetan, and the immunotoxin conjugate gemtuzumab ozogamicin. Other antigens and receptors are also being evaluated as potential therapeutic targets for lymphoma with promising early results, including C30, CD22, CD40, CD80, CD19, and TRAIL death receptors.[6] The identification of ED-B FN as a marker of lymphoma neovasculature adds additional potential therapeutic strategy for this disease. A potential advantage of targeting the tumor vasculature and the microenvironment is that these targets could have a broad therapeutic applicability across various tumor types. Collectively, these two experiments suggest that L19-based therapy is a promising new treatment strategy for patients with lymphoma and warrants evaluating these molecules in clinical trials.

Conflict-of-interest disclosure: The authors declare no competing financial interests. ■

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Comment on Bussel et al, page 2161

Romiplostim: chronic therapy for a chronic disease?

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In this issue of *Blood*, Bussel and colleagues report on the safety and efficacy of long-term administration of romiplostim, a recently FDA-approved TSA, for the treatment of chronic ITP.

In adults, immune thrombocytopenic purpura (ITP) is largely a chronic disorder. Unfortunately, currently available medical therapies for ITP are not well suited to chronic use. Corticosteroids are associated with a well-known litany of cumulative toxicities. Like corticosteroids, immune globulin and anti-Rh(D) are highly effective as rescue therapy, but their use in the maintenance setting is limited, in part because of the inconvenience of regular intravenous infusion. Many thirdline medical therapies are similarly plagued by agent-specific cumulative toxicities and limited response rates. Although splenectomy, the most widely recommended "chronic" therapy, is effective in the majority of patients, some have persistent thrombocytopenia. In addition, splenectomy is associated with approximately a 1% risk of overwhelming sepsis that endures for the lifetime of the patient. Hence, in spite of the multitude of treatments available for ITP, some patients with chronic severe disease have few good options and suffer substantial treatment-related morbidity.

In this light, the study by Bussel et al is greeted with cautious enthusiasm. In previously reported trials, all of which were less than or equal to 24 weeks' duration, romiplostim increased platelet counts and was well tolerated in a majority of subjects.[1-3] Nonetheless, a small number of patients developed reticulin deposition in the bone marrow, raising concerns about the safety of long-term romiplostim administration. In the present analysis, an ongoing, single-arm, open-label extension study of 142 subjects who participated in previous romiplostim trials, patients were treated for a mean of 69 weeks (maximum 3 years).[4] Platelet response, defined as a platelet count greater than or equal to 50×10^9/L and a doubling from baseline, was achieved in 87% of subjects. As the figure illustrates, this response was sustained for the duration of the study, though it may be inflated by dropout bias, a phenomenon in which subjects with a diminished response are more likely to drop out of the study than those maintaining a good response to romiplostim. Nonetheless, consistent with the observed rise in platelet count, bleeding events decreased over time.

Despite these promising results, concerns persist about the safety of long-term romiplostim use, particularly with respect to the risk of bone marrow fibrosis. In a planned subgroup analysis, 9 patients underwent a bone marrow biopsy before entering the extension study and after 3 to 9 months of therapy. Of the 6 patients with evaluable baseline and follow-up biopsies, 1 patient demonstrated mildly increased reticulin staining after 3 months of therapy. Biopsies on at least 7 additional subjects were performed, presumably for clinical indications, such as new abnormalities on the peripheral blood smear or loss of response to romiplostim, and showed varying degrees of reticulin deposition. Trichrome staining for type I collagen fibrosis, performed in 5 of the 8 patients with marrow reticulin, was absent. Immunophenotyping and cytogenetics, also performed in a subset of these patients, did not demonstrate evidence of a clonal disorder. Follow-up bone marrow biopsies were performed in only 2 patients after discontinuation of romiplostim and demonstrated improvement in 1 patient and no change in the other. However, neither patient showed complete regression of marrow reticulin.