antitumoral properties to sustain their survival and function within the tumor microenvironment.\textsuperscript{1,2} What T-cell type (naïve T cells, memory T cells, virus-specific T cells, T-cell precursors) to engineer “for best results” remains a hotly debated topic.

Antigen specificity is imparted by the genetic transfer of a single antigen receptor, consisting of either physiologic, HLA-restricted T-cell receptors (TCRs)\textsuperscript{3} or artificial, non-HLA-restricted receptors, which vary in the molecular composition and are broadly referred to as chimeric antigen receptor (CARs).\textsuperscript{4} Most CARs use an antibody-derived antigen-binding motif to recognize antigen, and comprise activating and costimulatory signaling domains in their cytoplasmic portion. CARs are thus targeted to cell-surface antigens and do not have to be matched to the patient’s HLA.

In the hematologic malignancies, CD19, which is relevant to chronic and acute leukemias as well as non-Hodgkin lymphomas, has emerged as a pivotal target antigen.\textsuperscript{5,6} It is the focus of more than a dozen active protocols in the United States, all of which are based on the infusion of CD19-targeted T cells. Over 15 centers are planning trials based on this approach in the United States, Europe, and Japan. At a recent meeting of the BMT CTN Network held in May 2010, it was determined that 19 patients had already been treated with CD19-targeted T cells in the United States. CD19 is normally expressed in the B-cell lineage from early B-cell stages to biliary epithelium\textsuperscript{10} and MART-1 in the melanocytes genetically retargeted against carbonic anhydrase IX: a study of the graft-versus-B-lineage leukemia effect. Blood. 2003;101(4):1657-1664. Hudecek M, Schmitt TM, Baskar S, et al. The B-cell tumor-associated antigen ROR1 can be targeted with T cells modified to express a ROR1-specific chimeric antigen receptor. Blood. 2010;116(22):4532-4541.

As the potency of genetically enhanced T lymphocytes gains strength, so does the concern over toxicity, including on-target effects (whereby T cells attack tissues that normally express the targeted antigen). Several reports underscore the ability of genetically targeted T cells to react against normal tissues, for example, carbonic anhydrase IX in biliary epithelium\textsuperscript{10} and MART-1 in the inner ear,\textsuperscript{11} eye, and in patients with renal cancer or melanoma who were given T cells targeted against these antigens. These undesirable effects may, however, be manageable and do not constitute grounds for not investigating differentiation antigens such as CD19 (which is highly restricted to the B-cell lineage) or an oncofetal antigen-like receptor such as ROR1. The consequences of low-level ROR1 expression in adipocytes and possibly some pancreatic cells will have to be closely investigated.

\textbf{References}


**PLATELETS & THROMBOPOIESIS**

Comment on Bao et al, page 4639

**ITP: Tregs come to the rescue**

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In this issue of \textit{Blood}, Bao et al report an increase in regulatory T-cell activity in patients with ITP treated with thrombopoietin receptor (TPO-R) agonists.\textsuperscript{1} This finding implies that TPO-R agonists may have an unexpected immune-regulatory activity. If this is indeed the case, the mechanism by which TPO-R agonists could perform such a function is currently unclear.
T reg suppression of pathogenic immune cells in ITP. (Professional illustration by Marie Dauenheimer.)

ITP occurs because APCs, macrophages, and B cells (which perpetuate the disease) escape the immune surveillance by Tregs. Tregs exert immune control by modifying the functions and numbers of these cells, and consequently return the immune system to homeostasis and health. For example, Tregs can induce apoptosis of the effector cells or can inhibit their activation and functions. These Treg actions are mediated by soluble factors (such as transforming growth factor-β [TGF-β], interleukin-10, perforins, etc) and cell-associated molecules (such as cytotoxic T lymphocyte antigen 4, lymphocyte activation gene-3, LFA-1/CD11a, CD18, CD39, etc). However, how
TPO-R agonists improve Treg activity is still unknown. It may be via a sustained increase in antigen load that induces tolerance or via an increase in anti-inflammatory cytokines such as TGF-β as both antigen and TGF-β can induce Tregs.3 There is no good evidence to support either hypothesis and hence further studies are clearly needed.

Conflict-of-interest disclosure: B.H.C. is a consultant for CSL, Australia for development of Intragram 10NF and is a member of the scientific advisory board of GSK and Amgen, Australia.

REFERENCES

Comment on Zhang et al, page 4684

Safe(r) anticoagulation

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In this issue of *Blood*, Zhang and colleagues demonstrate that targeting factor XI expression by antisense oligonucleotides prevents arterial and venous thrombosis in treated mice without increasing the risk of bleeding.1

Function of FXI in hemostasis and thrombosis. Hemostasis: At sites of injury, fibrin formation is initiated by the tissue factor (TF)/factor VIIa complex. FXI is activated by thrombin and contributes to sustained fibrin production when TF activity is reduced by reaction with tissue-factor pathway inhibitor (TFPI). Thrombosis: On activated platelet surfaces, released polyphosphates (polyP) initiate contact activation of FXII, which in turn activates FXI. Further FXI activity is generated by feedback activation. Targeting FXI with ASO abolishes pathologic thrombosis but has minor impact on hemostasis. (Professional illustration by Kenneth X. Probst.)

Coagulation is a complex process vital to hemostasis—the cessation of blood loss from an injured vessel—but, under pathologic conditions, otherwise life-saving mechanisms can precipitate life-threatening occlusive thrombotic events, collectively the most common causes of disability and death in the developed world. A major goal in anticoagulation therapy is to identify targets for blocking thrombosis without increasing the risk of dangerous bleeding; unfortunately, anticoagulant drugs currently in use (such as heparins, vitamin K antagonists, or direct inhibitors of factor Xa and thrombin) target molecules that are also essential for hemoestasis. Therefore, therapeutic and prophylactic use of anticoagulant agents for thromboprotection is associated with potentially severe and fatal bleeding complications.

In the classical cascade model, fibrin formation is initiated by the intrinsic and extrinsic pathways of coagulation. The intrinsic pathway is activated by “contact” of factor XII (FXII, Hageman factor) to negatively charged surfaces in a reaction involving plasma kallicrein and high-molecular-weight kininogen (contact activation system). Activated FXII (FXIIa) triggers coagulation via activating its substrate, coagulation factor XI (FXI), that in turn contributes to fibrin formation by activating factor IX. Deficiency in factor IX results in severe hemorrhage in patients (hemophilia B), whereas FXI-deficient humans suffer from minor/relatively mild bleeding (hemophilia C), which is characterized by trauma or soft tissue–related hemorrhage, primarily involving tissues with high fibrinolytic activity. Bleeding tendencies vary substantially between patients with similar FXI plasma levels and are not directly related to FXI antigen levels. In contrast, FXII deficiency is not associated with any increased bleeding risk, indicating the existence of FXII-independent pathways for FXI activation.2

Thrombin has been shown to convert FXI to the active protease FXIa, and anti-FXI antibodies were found to interfere with sustained fibrin production by thrombin–driven FXI feedback activation in plasma.3

The role of FXI in hemostasis and thrombosis has been extensively studied in animal models.4-5 In contrast to patients with hereditary FXI deficiency, FXI-null mice do not bleed excessively when challenged by surgical procedures. FXI-null mice have not been systematically analyzed by injury to tissues with high fibrinolytic activity, so it is not known whether the protease is required for normal hemostasis in mice in some situations. Challenging the dogma of a coagulation balance, FXI-deficient mice have severely reduced thrombus formation in response to various
ITP: Tregs come to the rescue

Beng H. Chong