is a member of the tumor necrosis receptor superfamily and binds to a proliferation-inducing ligand (APRIL) and B-cell–activating factor (BAFF) with, as net effect, promotion of plasma cell proliferation and induction of antiapoptotic proteins.

Others have previously reported the targeting of BCMA with nonengineered mAbs. BCMA is highly and homogeneously expressed in virtually all myeloma patients, with little or no expression in normal tissues including human CD34+ cells, which should limit any mAb-mediated organ and hematopoietic toxicity. GSK2857916 is of particular interest because it displays multiple mechanisms of action and the potency of the native mAb is enhanced in several ways. First, defucosylation of the Fc region carbohydrates of the antibody increases the binding affinity to FcγRIII receptors and potentiates antibody-dependent cell-mediated cytotoxicity (ADCC). Similar glycoengineering helps to explain the enhanced efficacy of the novel anti-CD20 mAb, obinutuzumab. Second, the mAb is conjugated via a noncleavable linker to its cytotoxic cargo, monomethyl auristatin F, which binds to tubulin and inhibits polymerization, thus disrupting mitosis through G2/M arrest with induction of apoptosis. The use of a noncleavable linker has the advantage that GSK2857916 should be more stable in the blood with minimal spontaneous release of the cytotoxic conjugate. The experiments by Tai et al suggested that GSK2857916 is efficiently internalized and spares bone marrow stromal and effector cells. Further mechanisms of action include macrophage-mediated phagocytosis and the interruption of the BCMA/BAFF/APRIL pathway leading to inhibition of nuclear factor-κB signaling.

High levels of soluble BCMA (sBCMA) have been reported in the serum of myeloma patients and have been correlated with progressive disease and worse outcome. Tai et al added MM1s cell supernatants (a source of sBCMA) to ADCC assays and noted some reduction in lysis of myeloma cell lines which was partly reversible by addition of lenalidomide. Clinical studies will have to establish whether a sBCMA “sink” could potentially interfere with the efficacy of GSK2857916. BCMA is expressed by plasma cells and B-cell subsets and anti-BCMA mAb therapy may affect these lineages. However, this potential toxicity is not likely to preclude clinical application. Two other nonglycoengineered ADCs, mBT062 (indatuximab ravtansine) and IMGN901 (lorvotuzumab mertansine), respectively, targeting CD38 and CD36, are presently in phase 1 clinical trial for myeloma. Dose-limiting toxicity of mBT02 was skin and gastrointestinal-related, and objective responses were observed in 2 of 20 patients. IMGN901 elicited a partial response in 1 of 25 patients treated.

BCMA is an interesting molecule from an immunotherapy perspective. Anti-BCMA antibodies have been detected as part of the graft-versus-myeloma response following donor lymphocyte infusion after allogeneic transplant, and patient-derived serum killed primary myeloma cells. BCMA-derived peptides can generate antigen-specific T-cell responses and are candidates for future vaccination strategies. T cells transduced with anti-BCMA chimeric antigen receptors have been reported to kill primary myeloma cells in vitro and in a mouse model, and will likely be tested in clinical trial. GSK2857916 will be both the first defucosylated ADC compound tested in multiple myeloma and the first BCMA-based immunotherapy entering the clinical arena.

Conflict-of-interest disclosure: The author declares no competing financial interests.

COMMENT

Comment on Nelson et al, page 3152

A(nother) RAF mutation in LCH

Kevin Shannon1 and Michelle Hermiston1,2

1University of California, San Francisco

In this issue of Blood, Nelson et al describe a novel somatic ARAF mutation in a child with Langerhans cell histiocytosis (LCH) and demonstrate that the encoded protein has strong gain-of-function properties. Importantly, this mutant A-Raf molecule is sensitive to inhibition by vemurafenib, a potent and selective Raf kinase inhibitor that is Food and Drug Administration (FDA)-approved for the treatment of advanced melanoma. This work thus identifies a new driver mutation in LCH that is potentially actionable in the clinic.

LCH is a rare hematologic disorder that is classified as a unified disease entity based on common histopathologic features and the proliferation of cells with phenotypic and cell surface marker expression characteristic of Langerhans cells. However, the clinical presentation is highly variable, ranging from generally benign single system lesions to life-threatening multisystem disease with organ dysfunction. The antigen-presenting function of Langerhan’s cells, mixed population of infiltrating leukocytes in pathologic specimens,
Beres et al recently associated with a higher incidence of disease bone marrow CD34 cells, circulating CD11c neoplasm. Although evidence that LCH is a hematologic neoplasm, BRAFV600E mutations in each case (45% and 63%, respectively), suggesting a growth advantage for mutant cells. Whereas ARAF mutations were thought to be uncommon in human cancer, a recent paper suggested that it is an oncogenic driver in ~1% of lung adenocarcinomas. Given the potential significance of ARAF as a bona fide LCH oncogene and the complex mutation detected in this case (the mutant allele contains a sequence alteration that results in an amino acid substitution at codon 351 [F351L] and a 6-nucleotide in-frame deletion that removes amino acids 347 and 348), Nelson et al perform elegant functional analyses in which they demonstrate that the mutant A-Raf protein aberrantly activates recombinant MEK, a direct substrate of activated Raf (see figure). They further showed that the relative kinase activity of this mutant A-Raf molecule is comparable to B-RafV600E and that it can transform fibroblasts in a classic 3T3 soft agar assay. Finally and importantly, the authors show that this constitutively activated mutant A-Raf kinase is sensitive to inhibition by vemurafenib.

The identification and functional characterization of this novel ARAF mutation has biological and clinical implications. First, the discovery of a new somatic mutation altering the Ras/Raf/MEK/ERK signaling cascade reinforces the central role of this pathway in LCH pathogenesis and provides further impetus for comprehensive genomic analysis of additional cases lacking BRAF mutations. The unusual nature of the ARAF mutation described by Nelson et al suggested that it would be uncommon. Indeed, sequencing 23 other LCH specimens with normal BRAF failed to uncover additional ARAF mutations. Performing whole exome sequencing of additional patients without RAF gene mutations is a logical next step toward unraveling the pathogenesis of LCH.
this study has implications for establishing a diagnosis of LCH and for identifying patients who might benefit from targeted therapies. Although ARAF mutations appear to be uncommon in LCH, they are straightforward to test for and are clinically actionable. As mutations in other genes are identified and functionally validated, it should be feasible to develop a targeted molecular diagnostics panel for LCH that includes BRAF, ARAF, and other driver genes. Finally, this new study raises questions regarding optimal approaches for implementing pathway-directed treatments for LCH. In addition to vemurafenib, the FDA-approved MEK inhibitor trametinib is a rational therapeutic strategy for patients with LCH with mutations that aberrantly activate Raf/MEK/ERK signaling (see figure). However, because the long-term risks and benefits of these agents are unknown and other effective treatments exist for many patients with LCH, the optimal indications for administering a tyrosine kinase inhibitor—particularly to children—is an open question. A clinical trial of trametinib that is expected to open later this year in juvenile myelomonocytic leukemia, an aggressive myeloproliferative neoplasm of young children characterized by hyperactive Ras/Raf/MEK/ERK signaling, will generate safety data that might be relevant for pediatric patients with LCH. A recent report demonstrating rapid and dramatic responses of 3 adults with Erdheim-Chester disease or Langerhans cell histiocytosis harboring the BRAF V600E mutation.

**PLATELETS & THROMBOPOIESIS**

Comment on Kasirer-Friede et al, page 3156

Platelet αIIbβ3 activation: filling in the pieces

Joel S. Bennett University of Pennsylvania

In this issue of Blood, Kasirer-Friede and colleagues show that the adhesion and degranulation promoter protein (ADAP) promotes αIIbβ3 activation by presenting the cytoplasmic proteins talin and kindlin to the β3 cytoplasmic tail. The integrin αIIbβ3 on circulating platelets is constrained in an inactive conformation by intramolecular interactions involving the stalk, transmembrane, and cytoplasmic domains of its αIIb and β3 subunits to prevent spontaneous platelet aggregation in the...
A(nother) RAF mutation in LCH

Kevin Shannon and Michelle Hermiston