allosteric inhibitory effects, KPT-7523 is shown to bind the C-terminal kinase but not the N-terminal regulatory domain of PAK4. Furthermore, and based on improved absorption, distribution, metabolism, and excretion/pharmacokinetic (ADME/PK) properties, a KPT-7523 analog, KPT-9274, is shown to be highly cytotoxic to myeloma cell lines and primary myeloma cells (50% inhibitory concentration [IC50] in the nanomolar range), with an even enhanced toxicity in cells harboring a t(4;14) or FGFR3 gene mutation. Of interest, the authors identified a direct binding between PAK4 and FGFR3, suggesting that PAK4 may be directly interacting with FGFR3. However, the authors did not provide any evidence or mechanistic explanation of how this interaction regulated FGFR3 signaling, in particular in cell lines such as OPM2 harboring a K650E mutation that results in the strong and constitutive activation of the FGFR3 tyrosine kinase. Lastly, the authors also provide evidence that PAK4 formed a stable complex with nicotinamide phosphoribosyltransferase (Nampt), a key regulator of the intracellular nicotinamide adenine dinucleotide. This interaction was also disrupted by KPT-9274 and hence may represent another mechanism through which PAK4 inhibition may affect myeloma cells survival (see figure).

Is there enough reason to believe that KPT-7532 and its analogs will succeed where other PAK family inhibitors thus far fell short? A couple of features may indeed support this statement. First, the selectivity for PAK4 targeting coupled with its high affinity and low cytotoxic IC50s are surely in favor of KPT-9274. Indeed, its allosteric inhibitory properties (not competing for the evolutionarily conserved ATP-binding pocket) overcome the selectivity challenge that often hinders the therapeutic development of kinase inhibitors and may also minimize the risk of acquired clinical resistance that usually results from acquired mutations in the kinase ATP-binding domain. In addition, the targeting of oncogenic FGFR3 signaling and its destabilizing interaction with Nampt may offer additional therapeutic benefits. On the other hand, and because the prosurvival effects of PAK4 in myeloma cells appear to be largely mediated through MEK-ERK signaling, it is reasonable to argue that PAK4 inhibition may not offer any benefit beyond that of a direct MEK inhibitor (already in the clinic). Furthermore, PAK4 is ubiquitously expressed in normal tissues, raising some concerns regarding the potential toxicities that may be associated with the targeting of this kinase. Surely, “the proof of the pudding is in the eating.” A phase 1 trial of KPT-9274 is currently underway and will examine the clinical safety and feasibility of PAK4 inhibition (#NCT02702492, www.clinicaltrials.gov). Nevertheless, and while awaiting the results of this ongoing phase 1 trial, Fulciniti et al provided us in the meantime with convincing evidence that PAK4 represents a legitimate target in myeloma cells, and perhaps it is about time for myeloma cells to start PKing!

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

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LYMPHOID NEOPLASIA

Comment on Bhatt et al, page 2246

Anti-CD20-IL-21 fusokine: the tail wags the dog

Stephen M. Ansell  MAYO CLINIC

In this issue of Blood, Bhatt et al have shown that fusing interleukin 21 (IL-21) to an anti-CD20 antibody results in a molecule that has superior antilymphoma activity than each of its individual components. They find that the fused IL-21 induces direct cytotoxicity to the lymphoma cells but also activates immune effector cells that enhance the efficacy of the anti-CD20 antibody. The addition of IL-21 to an anti-CD20 antibody to form an anti-CD20-IL-21 fusokine therefore provides enhanced activity in 2 ways: firstly, it increases cytotoxicity directly targeting the malignant cell, and secondly, it modulates and augments the anti-tumor immune response (see figure).

Established anti-CD20 antibody treatments such as rituximab have made a profound impact on the treatment of B-cell non-Hodgkin lymphoma (NHL). In multiple studies in both indolent and aggressive B-cell NHL, the addition of rituximab has resulted in increased response rates, prolonged progression-free survival, and in many cases, improved overall survival. Although various approaches have been attempted to improve CD20 antibody efficacy, fusing a cytokine to the antibody is a unique approach and profoundly enhances its benefit. The presence of IL-21 in close proximity to rituximab clearly is significantly beneficial and may be due to activating immune cells in close proximity to the malignant clone.

In the past, IL-21 has been administered systemically in combination with rituximab. This resulted in generalized, systemic immune activation rather than specific activation at the site of lymphoma. In a phase 1 clinical trial, IL-21 was IV administered, but did result in toxicities including nausea, vomiting, diarrhea, hypotension, and edema. Although clinical
responses were seen, even in rituximab refractory patients, and the durability of response to the combination appeared longer than the previous response to rituximab-based therapy, the systemic administration of IL-21 did not appear to significantly enhance the efficacy of rituximab.

In the study by Bhatt et al, they found that fusing IL-21 to rituximab to generate a fusokine molecule led to direct apoptosis of lymphoma cells, including those that were resistant to IL-21 treatment alone. Furthermore, they found that the fusokine enhanced NK cell activation, resulting in increased cytokine production by effector cells and greater antibody-dependent cytotoxicity. These findings strongly suggest that local action of IL-21 rather than systemic administration may clearly provide a significant therapeutic advantage.

Unique molecules such as the anti-CD20-IL-21 fusokine provide a proof of principle that local delivery of a cytokine such as IL-21 in the context of antibody binding to the malignant cell may have profound therapeutic advantages, and may be better than administering these components systemically. Clearly, additional studies will be necessary to assess whether the agent is safe and effective, and clinical trials are planned. However, these early preclinical studies suggest that a fusokine molecule such as this may be highly effective in treating lymphoma. The addition of IL-21 to an anti-CD20 antibody in this fashion is truly a case of “the tail wagging the dog.”

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MYELOID NEOPLASIA

Comment on Tesi et al, page 2266

I am SAMD9L: 7q regulator I am

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The SAMD9L gene and its paralog SAMD9, sitting head to tail on chromosome 7q, are among the notable absences in −7/7q− myelodysplastic syndromes (MDSs). As with many other genes harboring somatic mutation in neoplasia, germ line variants often provide critical insights into the mechanisms of dysfunction. In this issue of Blood, Tesi et al provide tantalizing new details to the story of SAMD9L mutation and familial −7/7q− syndromes.1 This widely expressed protein normally functions to inhibit proliferation and is therefore a potential tumor suppressor gene. The authors find 2 novel gain-of-function (GoF) variants that are associated with cytopenias, immunodeficiency, and neurological dysfunction and show how these can be ameliorated by coinheritance of loss-of-function alleles, or by somatic reversion of the mutated alleles in the bone marrow. When the progenitor ecosystem fails to select benign revertant clones,
Anti-CD20-IL-21 fusokine: the tail wags the dog

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