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## **APRIL showers cause CLL and myeloma to flower**

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the  $\alpha$ FG helix. They also noted that the structure of the loop between  $\beta$ 2 and  $\beta$ 3 is distinct and creates a pocket in the posterior on the N-lobe. The authors predict, based on primary structure, that these features may be conserved in other vertebrate Jaks. This is of interest, as we know from several lines of evidence that pseudokinase and FERM domains have essential regulatory functions with respect to catalytic activity. Mutations in the Jak3 pseudokinase domain result in SCID, whereas mutations in the Jak2 pseudokinase domain have recently been shown to underlie polycythemia vera and related disorders.<sup>7</sup>

In summary, the study by Boggon and colleagues is an important advance that should facilitate the development of Jak inhibitors. Exploiting the unique aspects of Jak3 structure can hopefully help in the generation of more selective inhibitors. Among the Jaks, Jak3 is most closely related to Jak2, which is important for erythropoietin and thrombopoietin signaling. Minimizing the effect of a Jak3 inhibitor on Jak2 could be of clinical benefit. Conversely, this information might be helpful in generating selective inhibitors of other Jaks. For instance, Tyk2, which is critical for IL-12 signaling, may be a useful target in diseases characterized by T-helper 1 (Th1)-mediated pathology, whereas targeting mutant Jak2

molecules could be of use in the treatment of myeloproliferative disorders. While the solution of the structures of the individual Jak domains is important, defining the structure of an intact Jak molecule will ultimately be needed to understand how these critical kinases are regulated. Understanding precisely how the pseudokinase domain regulates catalytic activity might offer unique opportunities for intervention. ■

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now reported that APRIL and BAFF levels are elevated in the sera of patients with CLL and myeloma and that both autocrine and paracrine APRIL and BAFF signaling exists in these related malignancies.<sup>1-5</sup> The 2 papers in this issue focus on the role of accessory cells and paracrine signaling in these diseases. Burger et al originally reported that blood-derived nurse-like cells (NLCs) protect CLL cells from spontaneous apoptosis through stromal cell-derived factor-1 (SDF-1).<sup>6</sup> This same group has now discovered that NLCs express BAFF and APRIL and that these molecules can promote CLL cell survival via a paracrine pathway that is distinct from that of SDF-1. Nishio and colleagues discovered that NLCs expressed significantly higher levels of BAFF and APRIL than monocytes and B-CLL cells. The viability of CLL B cells cultured with NLCs was significantly reduced when cultured with a decoy receptor of BCMA, which binds APRIL, and BAFF, but not BAFF-R:Fc, which only binds BAFF. Importantly, the effect of these molecules on survival was additive and distinct from that of SDF-1 $\alpha$ , which may be explained by differences in activation of downstream signaling cascades. An important finding is that CLL cells likely use multiple nonoverlapping survival signaling pathways as a means to escape death. It will be interesting to see which other factors NLC produce to promote CLL growth and survival.

In the second report, the Klein laboratory expands on previous work in which they showed that BAFF and APRIL can protect myeloma cells from apoptosis induced by IL-6 deprivation and/or dexamethasone.<sup>5</sup> In the current study, Moreaux and colleagues show that the main site of BAFF and APRIL production is in the bone marrow and that, not unexpectedly, this is derived mainly from osteoclasts. Obviously this is of great relevance given that osteoclast numbers are increased in myeloma bone marrow. They also showed that *TACI* expression varied dramatically in malignant plasma cells. Using supervised hierarchical clustering of global gene expression profiles from 65 primary myeloma samples, they demonstrated that differences in *TACI* expression could distinguish tumors with a microenvironment-interacting signature versus a plasmablastic signature, suggesting that myeloma expressing high levels of *TACI* are microenvironment dependent. As with the plasmablastic gene expression signature, patients with the

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Comment on Moreaux et al, page 1021, and Nishio et al, page 1012

## APRIL showers cause CLL and myeloma to flower

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There is growing evidence that tumor cell growth and survival are intimately associated with signals derived from the microenvironment and, as such, these signals represent therapeutic targets.

Two studies in this issue of *Blood* expand on this concept by providing evidence that dysregulated B cell-activating factor of the tumor necrosis factor (TNF) family/a proliferation-inducing ligand BAFF/APRIL signaling exists in B-chronic lymphocytic leukemia (B-CLL) and multiple myeloma (MM). B-lymphocyte stimulator (BlyS)/BAFF and APRIL are members of the tumor necrosis family of membrane-bound ligands expressed

by cells of the monocyte lineage that bind B-cell-specific receptors BAFF-R, B-cell maturation antigen (BCMA), and transmembrane activator and calcium modulator and cyclophilin ligand interactor (TACI) to control B-cell maturation and proliferation. A clear link between APRIL signaling and B-cell malignancies came from the observation that mice transgenic for *APRIL* develop B-1 cell-associated neoplasms.<sup>1</sup> Multiple studies have

*TACI*<sup>low</sup> signature also had clinical parameters associated with poor prognosis. We eagerly await evidence that survival is indeed different in these two groups.

Although these studies provide us with new and powerful information, they also raise new questions. It will be important to determine if the *TACI*<sup>low</sup> gene expression signature is reflective of a de novo form of the disease or whether all myelomas are *TACI*<sup>high</sup> and that expression of this gene is lost during disease progression. Longitudinal studies of patients that present with *TACI*<sup>high</sup> at diagnosis will help answer this question. If this is true, it will be important to understand the genetic mechanisms that compensate for its loss. Will we find activating mutations in downstream signaling components in these cases? Like myeloma, will we find a subset of CLL that are *TACI/BCMA/BAFF-R*–high and –low expressers? Will we see that there is heterogeneity of *APRIL/BAFF* responsive and nonresponsive cells in a given CLL or myeloma case? If so, will the degree of heterogeneity be indicative of the stage of disease? Will targeting this signaling system as a therapeutic approach simply select out those cells that are not

responsive? Time will tell, but it certainly appears that *APRIL* “showers” prime the “soil” and promote the “seeds” of CLL and myeloma to “flower.” With new therapeutic measures to interfere with this signaling network on the horizon, the question is, can anybody stop the rain? ■

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#### CLINICAL OBSERVATIONS

Comment on Rajkumar et al, page 812

## Determining the undetermined

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Although a limited proportion of patients with monoclonal gammopathy of undetermined significance (MGUS) progress to multiple myeloma and related disorders, inability to distinguish those who progress has required life-long follow-up of all patients. In this issue of *Blood*, Rajkumar and colleagues have determined that a subgroup of patients with MGUS (non-immunoglobulin G [IgG] isotype, abnormal serum free light chain [FLC] ratio, and serum M protein level less than 15 g/L) have a 58% chance of progression, while patients without these features have only a 5% chance of progression at 20 years.

**M**onoclonal gammopathy of undetermined significance (MGUS) affects up to 2% of persons older than 50 years, and since its description in 1978 it has remained an enigma in regards to its natural history and relationship to myeloma. In a previous report, cumulative probability of progression of MGUS to overt myeloma and related disorders was 30% over 25 years.<sup>1</sup> The majority of patients with MGUS have an uncomplicated clinical course during their lifetime, and at-

tempts at identifying factors predictive of progression have so far failed to recognize subpopulations with a significantly different clinical course or prognosis. Cytogenetic and fluorescence in situ hybridization (FISH) analysis have identified aneuploidy as well as frequent immunoglobulin heavy-chain translocations, including t(11:14)(q13;q32) and deletion of chromosome 13 in MGUS.<sup>2</sup> However, these abnormalities have not been clearly associated with progression to multiple my-

eloma (MM). In this issue of *Blood*, Rajkumar and colleagues report use of a new assay measuring serum free light chains<sup>3</sup> to develop a risk stratification model for MGUS. The model specifically identifies a subgroup of MGUS, with IgG subtype, serum M protein less than 15 g/L, and normal free light chain ratio, with a 5% chance of progression to MM over 20 years. This group may therefore be followed less stringently and reassured of a great likelihood of a benign course. In contrast, patients with non-IgG subtype, serum M protein of 15 g/L or greater, and abnormal free light chain ratio have a 58% chance of progression and may be ideal candidates, not only for close follow-up, but also for consideration of preventative therapy. Besides the clinical significance of this result, the study also raises biologically important questions that may eventually lead to improved understanding of the disease process. Expression of an excess amount of light chain suggests dissociation of heavy- and light-chain biosynthesis by plasma cells indicative of an underlying molecular abnormality or mutation. It is unclear whether the higher light-chain production precedes the transformed phenotype or whether transformed cells acquire this change. The high-risk subgroup identified in this study will form the basis for further molecular characterization of MGUS and its progression to MM. Already we have begun to gain insight into the multistep transformation of MGUS to MM using gene expression profiling.<sup>4</sup> The next level of prognostic classification of MGUS will depend on the results of such expression-profiling studies. Until such time that the underlying molecular defects responsible for the transformation are understood, the current study provides a clinically meaningful way to categorize patients with significantly different biological behavior.

The serum free light chain measurement used by Rajkumar and colleagues for prognostication is also the first major validation of serum free light chain measurement for evaluation of disease activity and burden in plasma cell dyscrasias. The test has potential utility in patients with renal failure, amyloidosis, light chain–only disease, and oligosecretory or nonsecretory MM.<sup>5</sup> However, it is important to remember that this test does not identify monoclonal protein, and absolute levels of free light chain need to be interpreted carefully, taking into consideration the  $\kappa/\gamma$  ratio. The extent of change in free light chain or its ratio