plasma cell score, albeit using a markedly different technique, was not a significant risk if the GEP-70 score was included in the model. Greater than 1 lesion on surveillance MRI was a very strong predictor of progression, despite the fact that it was a very rare event in the SWOG (formerly the Southwest Oncology Group) cohort, with only 6% tested patients having >1 focal lesion in their spines.

Should all patients with MGUS and SMM have GEP-70 scores generated? Before these data can be used for more than hypothesis generation, validation will be required. Time to progression for the S0120 MGUS population tracked well with the published literature; however, the rates for time to MM requiring therapy in the SMM group did not. In the SWOG series, nearly 20% of SMM patients were deemed to have progressed at 1 year, and during the subsequent 3 years, the rate of progression was only approximately 3% per year. This contrasts markedly with the 10% per year rate of progression seen over the first 5 years seen in other series, highlighting 2 potential problems with observational studies, prospective or otherwise: (1) despite clear definitions of smoldering myeloma, in real-world practice, patients with newly diagnosed SMM are not infrequently siphoned off for active treatment; and (2) the decision to consider progression from SMM to MM requiring treatment can be subjective, thereby affecting estimates of time to progression.

The data from S0120 reinforce that the landscape of definitions for and treatments of plasma cell disorders is in flux. The MGUS, SMM, and MM constructs have served us well for decades, but it is clear that current definitions are imperfect (see figure). It is intuitive that a combination of clinical and genomic parameters should better define those patients with an active malignancy from those who have a premalignant condition. GEP added little prognostic information to the MGUS group, at least with the current follow-up and small sample size, with a 4-year time to progression in the presence and absence of high-risk GEP-70 was 3.5% and 0%, respectively. In contrast, the respective rates for the SMM group were 51% and 12%. S0120 alone is not sufficient to change definitions, but it brings us a step closer, especially if its findings can be validated in other MGUS and SMM cohorts. Only then might there be value for GEP to be done outside the research setting in patients with MGUS and SMM, but even then, clinical trials will be required to ascertain whether earlier intervention in patients with high-risk SMM should be treated preemptively and/or reclassified as active myeloma.

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

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 Comment on Jiang and Aguiar, page 86

Novel face of microRNA-155

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In this issue of Blood, Jiang and Aguiar1 present a novel mechanism in diffuse large B-cell lymphoma (DLBCL) cell lines by which microRNA (miR)-155 deregulate the crucial retinoblastoma protein (RB)/E2F cascade by repressing SMAD5. The resulting hyperphosphorylated RB is inactive and mediates unrestricted cell-cycle progression. Conversely, they demonstrate in mature B lymphocytes from miR-155 knockout (KO) mice elevated SMAD5 levels accompanied by a hypophosphorylated RB state and a more pronounced cell-cycle arrest. This might contribute to the reduced numbers of germinal center B cells and impaired T cell–dependent antibody response found in these mice.1

Despite recent advances in the understanding of the molecular pathogenesis of lymphomas, clinical parameters are still used to identify patients at risk receiving immunochemotherapy. A major step in deciphering molecular events in lymphomagenesis was the discovery of microRNAs (miRNA) and their causal involvement in multiple cancerous processes and tumor types. miRNA are small noncoding RNAs that posttranscriptionally regulate expression of target RNAs by reducing their stability. Mature miRNA are single-stranded molecules of 20-23 nucleotides in length that regulate gene expression in many physiological and pathological processes. In cancer, including lymphomas, miRNA dysregulation is a ubiquitous phenomenon; however, their exact functional role in lymphomagenesis has not been thoroughly investigated in many instances.2 Dysregulation of a single miR-155 in transgenic mice was the first report to prove that
miRNA can cause cancer. Overexpression of miR-155 was sufficient to develop polyclonal lymphoid proliferation followed by frank B-cell malignancies. More recently, the underlying mechanisms for the transforming events have been described: the Src homology 2 domain-containing inositol-5-phophatase (SHIP) and the CCAAT enhancer–binding protein β (C/EBPβ) are 2 important direct targets of miR-155. By downregulating C/EBPβ and SHIP, the interleukin-6 pathway is liberated, which in turn generates a block in the B-cell differentiation and favors the accumulation of proliferating apoptosis-resistant pre-B lymphocytes. Another publication reported that the ectopic expression of miR-155 in hematopoietic stem cells by retroviral infection causes a myeloproliferative disorder, corroborating the profound oncogenic role of miR-155 in hematopoietic tissues. Subsequently, miR-155 has also been shown to play a key role in lymphocyte biology and function of the immune system. miR-155–deficient mice are immunocompromised and B cells generate reduced immunoglobulin levels following antibody treatment. Furthermore, total numbers of germinal center-B (GC-B) cells are also significantly reduced. Finally, higher expression of miR-155 in aggressive lymphomas is associated with an adverse outcome.

The article by Jiang and Aguilar is a continuation of previous observations by the same group identifying the transcription factor SMAD5 as a direct target of miR-155 and defining a novel mechanism adopted by lymphoma cells to escape transforming growth factor-β (TGF-β) growth inhibitory effects. In their actual work, the authors precisely dissect the molecular events of miR-155–mediated disruption of the TGF-β–SMAD5 pathway in normal and malignant B lymphocytes. TGF-β exerts tumor suppressive effects in normal and malignant B lymphocytes predominantly through upregulation of the cyclin–dependent kinase inhibitors p15 (CDKN2B) and p21 (CDKN1A) and subsequent cell-cycle arrest. In stably expressed miR-155 DLBCL cell lines, the authors detected lower levels of SMAD5 and showed that stable expression of miR-155 could limit the TGF-β–induced G0/G1 arrest in a SMAD5-dependent fashion. Also, after TGF-β stimulation, they found increased RB phosphorylation and a significantly higher amount of free E2F1 in miR-155–expressing lymphoma cells compared with their empty vector control cells. As a consequence, the effects exerted by TGF-β exposure (ie, enhanced pRB-E2F1 complex formation and a hypophosphorylated RB state leading to cell-cycle arrest) are antagonized by miR-155. By an RNA interference (RNAi) strategy, the authors demonstrated that a specific SMAD5 knockdown following TGF-β signaling phenocopies miR-155 expression in DLBCL, underscoring the crucial role of this transcription factor in mediating TGF-β signals. Subsequently, in an RNAi experiment targeting the downstream mediators p15 and p21 in miR-155 overexpressing DLBCL cells exposed to TGF-β, p15 and p21 downregulation significantly reduced the TGF-β effects on RB phosphorylation. Together, these results support a model in which miR-155 attenuates the tumor suppressive properties of TGF-β by inhibiting SMAD5, resulting in a diminished transcriptional induction of p15/p21 and limited inhibition of the CDK–cyclin complex–mediated RB phosphorylation. The resulting hyperphosphorylated (inactive) RB allows tumor cells to progress through the cell cycle irrespective of prohibitive extracellular TGF-β signals instructing G0/G1 arrest. Mature B cells lacking miR-155 (B). In this instance, elevated SMAD5 expression sensitizes the cells to TGF-β–mediated induction of p15/p21. The high expression of these CDK inhibitors blocks the CDK–cyclin complex and the hypophosphorylated (active) RB promotes cell-cycle arrest. This scenario may explain the defective germinal center B-cell development found in miR-155 null mice. In this diagram, stimulatory interactions are indicated with →; inhibitory interactions with …. Professional illustration by Marie Dauenheimer.
Transplantation

Comment on Lindemans et al, page 126

ATG for cord blood transplant: yes or no?

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In this issue of Blood, Lindemans et al report on the impact of thymoglobulin (antithymocyte globulin [ATG]) during the preparative regimen for pediatric unrelated umbilical cord blood transplantation (UCBT). Survival and chronic graft-versus-host disease (GVHD) were similar whether or not patients received ATG. The patients who did not receive ATG had a lower rate of viral infections but an increased rate of acute GVHD.1

This year, 2013, marks the 25th anniversary of the first UCBT, performed by Gluckman et al2 in France in 1988 for a child with Fanconi anemia. More than 600 000 UCB units have been donated for public use worldwide, and more than 30 000 UCBTs have been performed. Multiple retrospective comparisons have indicated similar survival among children or adult patients receiving UCBT or a standard unrelated donor hematopoietic stem cell transplant (HSCT).3,4 The results of UCBT in children with acute leukemia and myelodysplasia have improved over time from an overall survival (OS) of 37% in 1996–1999 to 56% in 2006–2011. Likewise, adult OS has improved from 22% in 1996–1999 to 37% in 2006–2011.3 Despite these advances, infection and immune reconstitution remain significant causes of morbidity and mortality after UCBT. Are these issues with immunity related to inherent properties of the UCB product or to the use of ATG added into the conditioning regimen to prevent graft rejection?

References


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