point of interest in the study by Meeths et al is the observation of a 9-fold reduction in the transcription of the mutated UNCI3D allele relative to the wild-type in lymphocytes. The relative frequency of the transcript from the mutated allele in CD4+, CD8+, and CD56- cells was significantly less than that observed in CD14+ cells, suggesting a role for the intronic mutation in cell-specific transcription of the UNCI3D gene. One could argue that in the future the search for protein expression or gene transcription has to be performed only in the presumed sick cell to be informative. In light of these considerations, going back to the functional assessment as the key point of the diagnostic procedure for PIDs might prove to be the more appropriate strategy.

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

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Adipokines in MM: time to trim the fat

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In this issue of Blood, Fowler et al provide new evidence that the adipokine adiponectin may be a therapeutic target in myeloma and myeloma-associated bone disease.1

The global epidemic of obesity has been linked to several diseases such as metabolic syndrome, atherosclerosis, and several cancers including myeloma (MM).2 Several studies have now clearly shown that the accumulating fat does not simply serve as an inert storage site, but as a dynamic endocrine organ secreting hormones called adipokines.3 Adipokines play a key role in regulating energy homeostasis as well as inflammation. Adiponectin was initially identified in mid-1990s as an adipocyte-derived protein similar to complement 1q, and later shown to have anti-inflammatory properties.3,4 Several adipokines, particularly leptin and adiponectin, have also been implicated in regulating the risk of developing cancers.2

The initial identification of adiponectin as a potential target in myeloma was based on gene array analysis of the marrow microenvironment between KaLwRij mice that permit growth of murine 5T1 myeloma cells, versus nonpermissive but closely related G57Bl6 mice. Adiponectin was one of several genes in this analysis and the role of other differentially expressed genes may well be equally relevant and deserve further study. Nonetheless, increased tumor burden and MM bone disease were clearly observed in adiponectin-deficient mice and pharmacologic induction of adiponectin using an apolipoprotein peptide mimetic L-4F led to the reduction of tumor growth and prevention of MM bone disease in this model. L-4F can in principle also impact other targets, but the antitumor activity of L-4F seems to require adiponectin as they were lacking in adiponectin-deficient mice. These findings suggest the need for further study to better understand the mechanism(s) by which host adiponectin expression might regulate MM growth. Adiponectin seems to have direct effect on both MM cells and bone cells. However, the effects of adiponectin in promoting an MM-permissive microenvironment may be multifactorial and additionally include effects on the recruitment of innate immune cells, such as macrophages.5 These elegant studies suggest a novel concept that the expression of adipokines such as adiponectin in the tumor microenvironment may regulate the permissive state of the marrow microenvironment to MM growth.

What are the potential clinical implications of this work? Detection of low adiponectin levels may suggest an increased risk for MM.6,7 While adiponectin levels are inversely related to obesity (a known risk factor for MM),8,9 the authors were careful in their use of controls matched for body mass index. Patients with monoclonal gammopathy of undetermined significance (MGUS) who progressed to MM in this small sample had lower levels of serum adiponectin compared with those that did not progress. However, this risk was restricted largely to females and the reasons behind this apparent sex bias are not readily evident at present. Nonetheless, further systematic investigation of this biomarker in ongoing prospective studies of monoclonal gammopathies may yield further insight.

The concept that the permissive state of tumor microenvironment for MM growth may be altered by adipokines such as adiponectin has important implications for preventing clinical MM. While the outlook for clinical MM has improved considerably in the past decade, the net gains in improving mortality have been much more modest compared with tumors, wherein early detection and prevention have instead been emphasized.10 The current studies set the stage for future investigations targeting obesity or pharmacologic manipulation of adipokines (such as adiponectin) as an attractive strategy for the prevention of clinical MM in selected cohorts. It is certainly now time to trim the fat.

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Early CTCL diagnosis, a (miR)age no more?

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Early and accurate diagnosis of cutaneous T-cell lymphoma (CTCL) has long been an elusive target for clinicians, pathologists, and patients alike. In this issue of Blood, Ralfkiaer and colleagues show that microRNAs (miRNAs), a family of single-stranded regulatory RNA molecules, are a powerful new tool for distinguishing CTCL from benign dermatoses.1

CTCL is a heterogeneous family of primary extranodal T-cell non-Hodgkin lymphomas whose incidence and prevalence rates appear to have increased over the past few decades but are likely still underestimated because of insensitive diagnostic criteria.2 The most common types (~70%) are Mycosis Fungoides (MF), initially characterized by erythematous patches and thick scaly plaques in non–sun-exposed areas of the skin, and Sezary syndrome (SS), a less common but more aggressive leukemic T-cell disorder associated with generalized erythroderma and lymphadenopathy.3 Although other less common types of CTCL exist, CTCL is often used interchangeably with MF/SS.

Early skin lesions in CTCL are nonspecific and result from cell-cell interactions and cytokine cross-talk between neoplastic CD4+ T cells and the cutaneous microenvironment. At this stage, the neoplastic CD4+ T cells are outnumbered by reactive CD8+ T cells and by skin-resident innate effector cells, leading to a nonspecific inflammatory infiltrate, which is very difficult to distinguish from benign dermatitis. With progression, the CD4+ T-cell infiltrate becomes heavier and more atypical, and gradually acquires a vertical growth pattern, leading to the classic tumoral (fungating) lesions described by Alibert in 1806.3 When tumor lesions, large cell transformation, and extracutaneous dissemination occur, in advanced stage CTCL, the diagnosis is obvious, but the horse is out of the barn.4

Most patients with early-stage CTCL discover what ailment afflicts them only after endless doctors’ visits and multiple skin biopsies. Having generally applied some form of over-the-counter topical steroid by the time they present to the doctor’s office, they are typically told to stop, hang on, and come back in 2 to 3 weeks for a biopsy, which too often returns inconclusive (the dreaded atypical T-cell infiltrate). The journey to diagnosis takes on average 5 to 6 years. While a delayed diagnosis of CTCL may not negatively affect survival, there are times when it certainly does. It is always inefficient, unnecessarily postpones counseling, and frustrates patients.

Currently, the diagnosis of early CTCL relies primarily on the triad of histopathology, immunophenotype, and T-cell receptor (TCR) gene rearrangement analysis, in the presence of compatible skin lesions.1,3 When epidermotropism, atypia, a high CD4:CD8 ratio, and clear loss of pan T-cell markers, such as CD7 and CD26, are all present, the diagnosis of CTCL is easy, especially if buttressed by a monoclonal TCR gene rearrangement. In most cases, however, findings are vague, diagnosis is deferred, and patients bounce from office to office, befuddled and discouraged. Therefore, the identification of biomarkers that accurately predict the difference between CTCL and benign inflammatory skin diseases (BDs) has a significant impact.

Here, Ralfkiaer et al describe how, using a relatively large sample, they identified a specific and consistent microRNA (miR) signature in the lesional skin of patients with CTCL. Recent studies have suggested several miR signatures in the diagnosis and prognosis of CTCL.6–8 To date, however, findings have been inconsistent and there is not a single genetic marker or method capable of diagnosing CTCL in clinically overlapping subgroups.

Ralfkiaer and colleagues used 63 patients with CTCL and 83 patients with BDs (psoriasis, dermatitis) or healthy individuals. Conventional, formalin-fixed, paraffin-embedded (FFPE) samples were used to perform miR microarray analysis and identify the most induced or repressed miRs in CTCL compared with the control group. Through systematic statistical analysis of the 27 most deregulated miRs, the authors further identified the 3 most up-regulated (miR-326, miR-663b and miR-711) and the 2 most down-regulated miRs (miR-203 and miR-205) as successful candidates for further testing. They then confirmed the robustness of the signature by performing expression analysis on both the training and validation sample sets. Intriguingly, they also demonstrated that the 5 miR classifiers were effective in separating inflammatory skin disease from peripheral T-cell lymphoma (PTCL) secondarily affecting the skin. However, in the absence of more detailed clinical and pathologic data on the PTCL cohort, it is difficult to draw any conclusions about the general validity of the classifier beyond CTCL.

The highlight of this study is the unexpected observation that the 5-miRNA classifiers not only discriminated benign from malignant samples in skin xenografts on laboratory mice, but that the majority of the miRNAs were not affected by drug treatment. If confirmed, this would be excellent news for
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