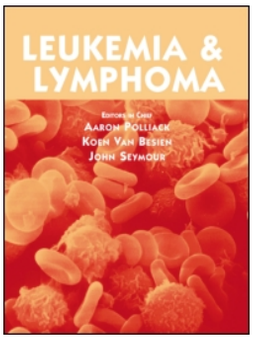

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COMMENTARY

The role of phosphatase and tensin homolog deleted on chromosome 10 and focal adhesion kinase in aggressive multiple myeloma

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Mutation, deletion or down-regulation of PTEN (phosphatase and tensin homolog deleted on chromosome 10) has been reported in a number of solid tumors and some hematologic malignancies, and may be found in early tumorigenesis as well as advanced cancer [1,2]. As an intracellular tumor suppressor protein, PTEN is an important regulator of the PI-3K (phosphatidylinositol-3-kinase) pathway. It regulates tumor cell proliferation by antagonizing activation of Akt and its downstream mTOR (mammalian target of rapamycin) targets through dephosphorylation of PIP3 (phosphatidylinositol-3, 4,5-triphosphate) to PIP2 (phosphatidylinositol-4,5-biphosphate). It regulates VEGF (vascular endothelial growth factor) expression and angiogenesis by destabilizing and inhibiting transcription activities of HIF1 (hypoxia-inducible factor). It regulates cell interaction with extracellular matrix and migration by reducing the tyrosine phosphorylation of FAK (focal adhesion kinase) [3].

In this issue of ***Leukemia and Lymphoma*,** Wang and colleagues examined PTEN and FAK expression in multiple myeloma [4]. They showed that, compared to patients with iron deficiency anemia who served as controls, PTEN mRNA and protein levels were decreased in plasma cells of patients with myeloma. They found that decreased PTEN mRNA levels correlated with increased FAK mRNA expression. More interestingly, they found that patients with Durie–Salmon stage I–II disease had normal levels of PTEN whereas those with stage III disease had significantly decreased PTEN levels. Similarly they report that the highest levels of FAK mRNA expression and phosphorylated FAK proteins are seen in stage III disease and with extramedullary involvement.

While this study is limited by the small sample size and the lack of clinical correlation with cytogenetic prognostic markers, it nevertheless provides relevant information from primary patient samples on these potentially important protein regulators in myeloma. This study supports a previous report by Chang and colleagues in which they found PTEN deletion/mutation to be uncommon in myeloma but that it appears to be associated with Durie–Salmon stage III disease and high-risk cytogenetic changes [5].

Extramedullary myeloma involvement is a more aggressive clinical entity as evidenced by resistance to therapy, early relapse and decreased survival. Its incidence has appeared to be rising in the recent era of novel treatment [6,7]. While this may be due to natural progression of disease as patients are now living longer with myeloma, there is concern that the increased incidence of extramedullary disease may reflect the selection of more aggressive malignant clones by novel therapy, particularly with thalidomide and allogeneic stem cell transplant. In addition, extramedullary disease appears to be resistant to treatment with thalidomide. One hypothesized mechanism of action for increased incidence with these treatments is the disruption of malignant plasma cells' adhesion and interaction with the bone marrow microenvironment. Understanding the pathogenesis of extramedullary disease can lend insight to improve treatment strategies.

Evidence of abnormal PTEN and FAK expression supports further study of the mechanistic interaction of PTEN and FAK in extramedullary myeloma. It is worth noting that technical limitations did not allow the investigators to compare PTEN and FAK expression in myeloma plasma cells versus normal plasma cells, but rather versus bone marrow mononuclear cells of controls. In addition, comparison between plasma cells in the bone marrow and the extramedullary site would be warranted. Other studies have suggested that plasma cells in extramedullary sites may be more plasmablastic in nature and have undergone a light escape, changing their production from previously intact immunoglobulin to only free light chain [8]. Animal models may allow further examination of a potential causal relationship between PTEN and FAK in the development of extramedullary disease *in vivo*.

In mouse models, restoration of PTEN expression by gene therapy does mitigate myeloma disease, although study of this effect has focused on Akt and its downstream mTOR targets rather than its effect on FAK [9]. Unfortunately at present, we do not have a targeted agent that can induce PTEN expression for cancer treatment. Akt and mTOR inhibitors are being tested as other inhibitors of the PI3K pathways [10,11]. Early phase trials suggest a potential role for these

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agents in the relapsed or refractory setting. Preclinical development of agents directly targeting PTEN may be useful in malignancies with abnormal PTEN expression by providing either synergistic therapy with Akt and mTOR inhibitors or alternative intervention when a tumor develops resistance to these other agents.

Finally, while studies of PTEN modulation have focused on its effect on Akt and downstream targets, there is growing evidence that FAK may be another therapeutic target. Patients with extramedullary myeloma disease have responded to bortezomib-based therapy [12,13]. Studies *in vitro* suggest that bortezomib may be active in this setting via the inhibition of FAK expression through the NFκB (nuclear factor κB) pathway [14]. Development of targeted agents to FAK may augment the treatment of advanced, aggressive myeloma. If indeed this may be a mechanism of action for bortezomib and other proteosome inhibitors, correlative testing should be considered for PTEN and FAK expression levels in prospective studies. The ability to use PTEN and/or FAK expression as a biomarker for the prediction of response to specific targeted treatment will allow truly personalized treatment of disease.

Potential conflict of interest: Disclosure forms provided by the authors are available with the full text of this article at www.informahealthcare.com/lal.

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