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The prognostic value of TIMP-1 in multiple myeloma

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Keywords

Multiple myeloma; TIMP-1

Tissue inhibitor of metalloproteinases (TIMP)-1 is an extracellular matrix protein with multifunctional properties. High levels of TIMP-1 in the serum of patients diagnosed with various types of carcinomas have been shown to correlate with disease progression and treatment outcome, thus making TIMP-1 an important clinical marker for these solid tumors [1–4]. However, unlike carcinomas, information on the expression of TIMP-1 in patients with hematological tumors has not been as forthcoming. In this issue, Terpos et al. [5] report the first clinical observations of TIMP-1 expression in a plasma cell dyscrasia. These authors demonstrate the correlation of high TIMP-1 level in serum of patients with multiple myeloma (MM) with advanced disease and poor survival. Most importantly, serum TIMP-1 levels are associated with the pivotal clinical parameters in MM, such as the status of bone lytic disease, the most devastating feature of this disease. Therefore, these clinical findings strongly support the prognostic value of TIMP-1 in multiple myeloma. Osteolysis is the hallmark of advancing MM and determines the therapeutic response of MM patients [6]. Moreover, recent clinical and experimental data reveal that lytic bone disease is key for MM progression [7,8]. Of the various biomarkers identified in MM and validated in the malignant plasma cells, very few stand out as useful and consistent predictors of lytic bone disease [9]. This makes it important that the design of future experimental and clinical studies leading to the identification and validation of MM markers follow the example of Terpos et al. [5].

Tissue inhibitor of metalloproteinases (TIMP-1) is a member of a family of four proteins (TIMP 1–4) characterized by a conserved structure and by their inhibition of matrix metalloproteinases (MMP) [10,11]. Prior to its description as MMP inhibitor, TIMP-1 was first identified for its erythroid-potentiating activity [12,13]. TIMP-1 has been shown to induce cell proliferation and inhibit apoptosis of a wide range of cell types *in vitro* [11,14–16]. In addition, animal models of carcinogenesis also demonstrated that TIMP-1 expression is associated with susceptibility to HPV-16-induced carcinogenesis [17], promotion of angiogenesis [18,19], and modulation of inflammation [20]. TIMP-1 effects on B-cells *in vitro* indicate that it drives plasmablastic differentiation of germinal center B-cells, and

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allows, in an autocrine fashion, the survival of plasma cells by a T-cell-independent mechanism [21]. Although the underlying mechanisms are still poorly understood, the examination of primary B-cell tumors revealed that unlike follicular lymphoma and Burkitt's lymphomas, plasmablastic and plasmacytic tumors are strongly positive for both cytoplasmatic and secreted TIMP-1 [21]. High levels of TIMP-1 are also associated with changes in the transcription factors controlling plasma cell differentiation. These include the repression of the major germinal center factors, and upregulation of post-germinal center transcription factors [21]. Moreover, this effect of TIMP-1 on the transcriptional machinery of B-cells is carried out even in the presence of deregulated c-Myc. The resulting cell phenotype is consistent with an apoptosis resistant/long lived plasma cell (CD138+/CD44+) with cyclin D2 overexpression and STAT-3 activation. These experimental observations are in agreement with markers commonly altered in multiple myeloma, e.g. overexpression of CD44 and CD138 by plasma cells in the bone marrow of MM patients. Cyclin D2 has been associated in MM with secondary translocations involving c-Maf and FGRFR3 genes and other cell cycle regulators [22]. In addition, secreted TIMP-1 is capable of upregulating cytokines such as IL-6 and IL-10 [20,23], important for the survival and differentiation of B-cells. Interestingly, these cytokines are also equally important for the control of inflammation [20]. Therefore, one could hypothesize that the role of TIMP-1 in MM is a direct effect on the tumor cell survival and cell differentiation as well as through modification of the tumor microenvironment, promoting inflammation and angiogenesis, both processes that are required for osteolysis [24]. This is in part supported by the effective therapeutic response of MM to treatment with thalidomide, a very well-known anti-angiogenic agent [25].

In summary these clinical observations of Terpos et al. [5] provide new insights and offer grounds for interpretation of prior experimental studies, as well as advancing our understanding of the role of TIMP-1 in the complex biology of multiple myeloma. Better biomarkers are urgently needed to improve diagnosis and monitor effective targeted therapies in MM; TIMP-1 has the potential to be one of these biomarkers.

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