What Is the Biological Significance of Circulating Blood Levels of Metalloproteinases?

To the Editor: Nikkola et al. (1), examining pretreatment serum levels of matrix metalloproteinase 9 (MMP)-9 in 71 patients and MMP-1 and MMP-13 in 48 patients with advanced melanoma, showed that MMP-1, MMP-9, and MMP-13 “play important roles at different phases of metastatic melanoma spread and that serum MMP-9, in particular, could have clinical value in identifying patients at high risk for melanoma progression.” In the editorial accompanying this paper, Zucker et al. (2) asserts that, according to previous reports in breast cancer (3), the measurement of circulating blood levels of MMP-9 may be useful in predicting prognosis in advanced melanoma, although serious technical issues concerning the details of plasma specimen collection must be addressed before drawing any conclusion: serum MMP-9 is unstable, widely variable in the population, and could reflect release of proteases by leukocytes during the clotting process in the blood collection tube. In addition, there is no correlation between MMP-9 levels in serum and plasma (4).

Also worth noting is that, as far as studies showing correlation, a correlation in serum/plasma concentrations of proteases does not necessarily mean correlation of tissue activity; these must be shown separately using proper methods. It could be an oversimplification to conclude anything otherwise. The authors conclude that “studies with serum samples obtained at different phases of melanoma progression could further elucidate the role of MMPs in growth and metastasis of melanoma.” By contrast, the MMPs serum levels could be progressively under the influence of administered drugs. We have shown previously that, in 18 consecutive breast cancer patients with bone metastases, zoledronic acid could exert a transient reduction of MMP-2 circulating level measured just before and 2 and 7 days after infusion (5). Moreover, collecting serum samples before initiating chemoimmunotherapy does not take into account the long-term genetic variation that results after prolonged tumor growth or prolonged exposure to antineoplastic drugs. Thus, at this time, the significance of these findings remains unknown.

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References
In Response: We thank Dr. Ferretti and coworkers for their valuable comments on our article “High serum levels of matrix metalloproteinase (MMP)-9 and MMP-1 are associated with rapid progression in patients with metastatic melanoma” (1). Dr. Ferretti is correct in saying that MMP levels can be altered due to cancer therapy and thus their use in the evaluation of disease progression might be difficult. This is evident in patients with breast cancer, in whom the authors have seen transient reduction of serum MMP-2 levels after therapy with zoledronic acid (2). Zoledronic acid belongs to the group of bisphosphonates (3), of which the important mechanism of action is inhibition of MMPs. Thus, it is possible that drugs of this group might reduce MMP levels and activity in serum and tissue. Other drugs, such as β-IFN, are also known to reduce serum MMP-9 levels (4).

The effect of cytotoxic drugs on MMP levels has not been widely studied and it is therefore difficult to determine whether changes in serum levels of MMPs are due to the effects of chemotherapeutic agents or due to lack of response. In our study, we examined only pretreatment samples and did not repeat the analysis during the therapy cycles. Interestingly, our previous studies with melanoma metastases have shown that tumor tissue MMP-1 levels are associated with favorable chemoimmunotherapy response (5). It would be interesting to study the expression levels of MMPs in different time points during therapy to see whether any relationship to outcome can be seen.

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