Avoiding spam in the proteolytic internet: future strategies for anti-metastatic MMP inhibition.

Abstract: Phase III clinical trials with cancer patients with the first generation of synthetic MMP inhibitors (MMPIs) failed due to inefficacy and adverse side effects. These results were unexpected, given the wealth of pre-clinical data implicating MMPs as cancer targets, but are attributable to the broad-spectrum activity of these early MMPIs and the limited knowledge of the variety of biological functions of MMPs at the time they were deployed. These experiences stimulated the development of a variety of highly specific synthetic MMPIs. However, the bottle-neck is the identification of true target-MMPs. Functional genetic approaches are being complicated by the existence of the 'protease web,' i.e., the dynamic interconnectivity of MMPs and other proteases, their inhibitors, and substrates that collectively establish homeostasis in signaling in healthy and disease-afflicted tissue. Therefore, even specific MMP inhibition can result in seemingly unpredictable induction of systemic protease web-associated modulations (spam), which can comprise metastasis-promoting molecules such as other proteases and cytokines. Such undesired information in local proteolytic networks or relayed systemically in the organism via the proteolytic internet needs to be understood and defined in order to design specific metastasis therapies employing highly specific MMPIs in combination with spam-filtering agents.