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Biological function of TIMP-2 is regulated by the composition of the tissue microenvironment

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The activity of mammalian matrix metalloproteinases (MMPs) is regulated by a family of four endogenous inhibitors known as the tissue inhibitor of metalloproteinases (TIMPs). Since their original discovery and characterization several additional physiological functions have been ascribed to TIMP family members, including MMP-independent biological functions, such as regulation of cell growth and migration. TIMP-2 is abundantly expressed in normal tissues with low levels of MMP expression and demonstrates broad spectrum inhibition of MMPs, binding to and inhibiting all 23 members of this family and ADAM12 with varying affinities. In addition, TIMP-2 has been shown to interact with several membrane proteins including MMP14, insulin-like growth factor-1 receptor (IGF-I-R), low density lipoprotein receptor-related protein 1 (LRP1) and alpha3 beta1 integrin (a3b1). Recent studies in our lab have shown that TIMP-2 is a promising candidate for biological cancer therapy. However, the role of TIMP-2 in tumorigenesis has been subject to debate with varying accounts purporting both anti- and pro-tumor effects. In addition, TIMP-2 and its putative receptors have been shown to exhibit multiple interactions with components of the tissue microenvironment. Using various cell-lines we demonstrate that TIMP-2 cellular binding, signaling and uptake in tumor cells can be differentially regulated by components of the tissue microenvironment resulting in opposing effects on cell behavior, such as intracellular kinase activity in response to growth factors. Our goal is to understand the regulatory factors/conditions that influence the different cellular responses to TIMP-2 in order to effectively target the aberrant extracellular environment that is associated with many human diseases.