Structural Overview Of Mammalian Zinc Metalloproteinases

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ABSTRACT

Matrix metalloproteinases (MMP) are crucial for homeostasis (tissue remodelling and repair, bone growth, wound healing, etc.) and pathology (metastasis, angiogenesis, aneurysm rupture, etc.). Upregulated MMPs from macrophages are thus a two-edged sword, playing both defensive and aggressive roles. The related family of ADAMs (a disintegrin and a metalloproteinase) is sometimes overlooked because of classification peculiarities. The best-studied ADAM-17, tumor necrosis factor a convertase (TNF-a), is a membrane-bound “shedase” that releases a membrane-bound cytokine, tumor necrosis factor a (TACE). Many of the ADAMs have remarkable structural and mechanistic and inhibitor proclivities similar to the MMPs; the potential for inhibitor side reactions and drug toxicities abounds. Over the past 10 years the crystallographic study of proMMPs, MMPs, and ADAMs in free and complexed forms has revealed the mechanistic and structural nature of these macromolecules to atomic resolution. These results will be reviewed and indications for future work will be presented. Special attention will be given to visualization tools to assist with the conceptualization of complex molecular interactions. (Support provided by the Robert A. Welch Foundation, the US National Science Foundation, and the R.W. Johnson Pharmaceutical Research Institute)

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