SELECTIVE ACTIVATION OF MMP-2 AND MMP-9 BY METALLOTHIONEIN IN PROSTATE CANCER CELLS

Ibrahim O. Farah¹, Ali. Bajwa², Krishna C. Agrawal³, and Asim B. Abdel-Mageed²

¹Department of Biology, Jackson State University, Jackson, MS, 39217, USA
²Department of Urology, Tulane University Health Sciences Center, New Orleans, LA, 70112, USA
³Department of Pharmacology and Toxicology, Tulane University Health Sciences Center, New Orleans, LA, 70112, USA

Abstract: Metallothioneins (MT) are low molecular weight proteins that bind metals such as Zn, Cu, Cd, and Hg to cysteine residues of thionein. They are ubiquitously expressed by all human cells in response to metals, hormones, physical stimuli, and other physiological stresses. MTs have several physiologic roles in mammals including metal ion donors or acceptors, metal detoxification, or by acting as antioxidants. MTs have also been shown to be a factor in cancer development and therapeutic resistance. Among all isoforms, MT-IIa is overexpressed in human tumor cells, including breast, thyroid and prostate. We and others demonstrate that the increased expression of MTs in tumor cells increases the survival of cancer cells and accelerates growth via inactivation of p53 and/or activation of NF-κB. As proteolytic enzymes of extracellular matrix, matrix metalloproteinases (MMPs) have also been implicated in the early stages of cancer metastasis and in determining cancer prognosis. MMPs are subclassified as based on their structure and according to the specificity of their substrate into collagenases, gelatinases, stromelysins, and matrilysins. MMP-2 and MMP-9 (subclass gelatinase A and B respectively) are particularly important in cancer metastasis because they act on collagen IV, which is an essential component of the basement membrane. In this study we examined if MMPs are involved in MT-induced prostate tumor cell growth and metastasis in vitro. Prostate cancer (PCa) cells, PC-3, LNCaP, and C4-2b cells were stably transfected with hMT-IIa expression plasmid. The expression of MT-IIa was confirmed by PCR and western blot analysis in comparison to their respective controls. Overexpression of MT-IIa in PCa cells lead to upregulation of MMP-2 and MMP-9 transcripts in PC-3 and C4-2B cells, but not the LNCaP cells. The upregulation of gene expression was associated with increased secretion of MMP-2 and MMP-9 by PCa cells as evidenced by zymogram gel analysis. As zinc-based enzymes, MT-IIa may selectively regulate the expression and/or activity of MMPs in PCa cells via regulation of Zn homeostasis. Since MT-IIa has been shown to be upregulated in metastatic prostate cancer cells, activation of MMP-2 and MMP-9 can mediate MT-induced tumor cell growth progression and metastasis by enhancing the degradation of basement membranes in vivo. Taken together, our data demonstrates a role for MT-IIa in selectively inducing MMPs gene expression and secretion by PCa cells suggesting cross-talk between these factors in progression of PCa.

Keywords: Metallothioneins, MMPs, NFkB, p53, Stable transfects, PCa, hMT-IIa, metastasis.

Acknowledgements: We would like to thank Department of Urology and Tulane Cancer Center, Tulane University Health Sciences Center for support of the project. We also would like to acknowledge the JSU Center for University Scholars and the NIH-RCMI Program for technical support.