
Maxsea-v10.3.5

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Due to the significance of metallothioneins in stress responses, and their role in human disease, there is an increasing interest in their mechanisms of action and gene regulation. Three related promoters have been found to influence the expression of Metallothioneins-1 and -2. While the two proximal promoters mediate responses to nickel and cadmium, the third, located 30 kb away, is specific for copper responses. I propose to continue the analysis of the copper-inducible promoter. I will define the response elements by deletion and mutational analysis, and define the region that confers constitutive expression. This should help in elucidating the function of the metal-responsive elements and hopefully identify additional transcription factors that interact with this region. Second, I will investigate the role of a specific homeobox gene that is expressed in response to copper and binds specifically to the region that mediates the copper response. This gene is important for mouse development and mutation of its coding region causes abnormalities in the nervous system and skeleton. Preliminary data indicates that the homeobox protein is a zinc finger containing DNA binding protein and is a paralogue of Pax2, which has been implicated in kidney development. I will characterize this gene and its role in development by defining its

expression pattern and performing in situ hybridization with whole-mount embryos as well as transgenic mice. Lastly, I will initiate studies on the role of metallothioneins in copper homeostasis. Since a tumor microenvironment has been found to exhibit increased expression of copper-inducible metallothioneins, I will assess the importance of these genes in tumorigenesis. I will determine whether metallothioneins participate in the enhancement of tumorigenicity by the addition of copper, and will assess the effect of these genes on tumor cell growth in nude mice.

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