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Involvement of p38 Mitogen-Activated Protein Kinase in the Cell Growth Inhibition by Sodium Arsenite

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It is well known that p38 mitogen-activated protein kinase (p38MAPK) participates in cellular responses to mitogenic stimuli, environmental and genotoxic stresses, and apoptotic agents. Although there are several reports on p38MAPK in relation to cell growth and apoptosis, the exact mechanism of p38MAPK-mediated cell growth regulation remains obscure. Here, we examined possible roles of p38MAPK in the sodium arsenite-induced cell growth inhibition in NIH3T3 cells. Sodium arsenite induced transient cell growth delay with marked activation of p38MAPK. In addition, arsenite induced CDK inhibitor p21CIP1/WAF1 and enhanced its binding to the CDK2, which resulted in inhibition of CDK2 activity. The levels of cyclin D1 expression and the CDK4 kinase activity were also significantly reduced. pRB was hypophosphorylated by sodium arsenite. SB203580, a specific inhibitor of p38MAPK, blocked arsenite-induced growth inhibition as well as the arsenite-induced p21CIP1/WAF1 expression. Expression of dominant negative p38MAPK also blocked arsenite-induced p21CIP1/WAF1 expression. Inhibited-CDK2 activity was also completely reversed by SB203580 or expression of dominant negative p38MAPK, while the decreased-cyclin D1 protein by the compound was not restored. These data demonstrate a possible link between the activation of p38MAPK and induction of p21CIP1/WIF1, suggesting that the activation of p38MAPK is, at least in part, related to the cell growth inhibition by sodium arsenite.