THE REGULATION OF TBX2 IN RESPONSE TO PHOSPHORYLATION BY THE P38 MITOGEN-ACTIVATED PROTEIN (MAP) KINASE

Amaal Abrahams[1], Colin Goding[2], M. Iqbal Parker[1] and Sharon Prince[1,2]

[1]Division of Medical Biochemistry, Faculty of Health Sciences, University of Cape Town, Observatory, Cape Town, 7925, South Africa. [2]Signalling and Development Laboratory, Marie Curie Research Institute, The Chart, Oxted, Surrey, RH8 OT L, UK

T-box factors represent a conserved family of transcription factors that play an important role in the development of many tissues[1]. Tbx2, a member of this family, is expressed in cells of the melanocyte lineage and has been shown to be a direct target of the microphthalmia associated transcription factor[2]. Furthermore, Tbx2 represses the tyrosinase-related protein 1 (Tyrp1) promoter[3] but the precise role of Tbx2 in melanocytes is not clearly understood. To gain some insight into this role we have focused on identifying signal transduction pathways that regulate the activity of this transcription factor. Here we show, using western blot analysis, that Tbx2 is phosphorylated in response to UV irradiation. Phosphorylation was shown to be mediated specifically by the p38 mitogen-activated protein kinase, which is activated in response to stress-inducing agents. Furthermore, we have identified the p38 target sites using site-directed mutagenesis and have shown that these sites are phosphorylated both in vitro, by p38 kinase assays, and in vivo using western blotting. In addition, we have shown that Tbx2 mutants, which inhibit phosphorylation by the p38 kinase affects the stability of the protein in vivo. The results of this study suggest that in response to UV irradiation, Tbx2 is phosphorylated by the p38 MAP kinase and that this phosphorylation affects the stability of the Tbx2 protein. Future work is aimed at looking at the effect of p38 phosphorylation of Tbx2 on its ability to repress the Tyrp1 promoter.

1. Bollag, R. J., Siegried, Z., Cebra-Thomas, J.A., Garvay, N., Davison, E. M. and Silver, L.M. (1994). An ancient family of embryonically expressed mouse genes sharing a conserved protein motif with the T locus. Nature Genetics (7) 383-389.

2. Carreira, S., Liu, B. and Goding, C.R. (2000). The Gene Encoding the T-box Factor Tbx2 Is a Target for the Microphthalmia-associated Transcription Factor in Melanocytes. The Journal of Biological Chemsitry (275) 21920-21927.

3. Carreira, S., Dexter, T. J., Yavuzer, U., Easty, D. J. and Goding, C. R. (1998). Brachyury-Related Transcription Factor Tbx2 and Repression of the Melanocyte-Specific TRP-1 Promoter. Molecular and Cellular Biology (18) 5099-5108.