HO-01 Activation of MAPK signaling pathway is essential for Id-1 induced serum independent prostate cancer cell growth

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Id proteins are a group of helix-loop-helix (HLH) transcription factors that lack the DNA binding domain. These proteins act as dominant inhibitors of basic HLH transcription factors by heterodimerization. The HLH protein Id-1 has been suggested to play a positive role in cell proliferation and tumorigenesis of many types of human cancers. However, little is known about the molecular mechanism involved in the function of Id-1. We have shown in an earlier study that Id-1 may stimulate cell proliferation by inactivation the function of $p16^{INK4a}$/pRb pathway (Carcinogenesis 23: 721, 2002). In this study, using four stable Id-1 transfectant clones, we investigated the involvement of MAPK signaling pathway in the Id-1 induced serum independent prostate cancer cell growth. Our results demonstrated that ectopic Id-1 expression in prostate cancer cell line, LNCaP, led to the activation of Raf/MEK1/2 signaling pathway. In addition, inhibition of MEK1/2 phosphorylation by one of its inhibitors, PD98059, resulted in the decreased cell cycle S phase fraction and cell growth rate, suggest that activation of MAPK signaling pathway is essential for Id-1 induced prostate cancer cell proliferation. Furthermore, treatment with antisense oligonucleotide complementary to Id-1 mRNA in PC-3 and DU-145 prostate cancer cells resulted in a decreased Id-1 expression which was accompanied by decreased Egr-1 protein, one of the downstream effectors of the Raf/MEK1/2 pathway. Our results suggest for the first time that the function of Id-1 is associated with MAPK signaling pathway activation and indicate a possible mechanism in which Id-1 regulates prostate cancer cell growth and tumorigenesis. (Supported by RGC grants to YCW [HKU7186/99M and HKU7314/01M] and Area of Excellence Scheme, UGC of HKSAR, China [Project No. AoE/P-10/01]).

HO-02 Significance of MAD2 expression in mitotic checkpoint control and cellular sensitivity in nasopharyngeal carcinoma cells

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Introduction: Nasopharyngeal carcinoma (NPC) occurs with a high incidence in Hong Kong. Chromosomal abnormalities have been commonly found in NPC, but the underlying mechanism is not well understood. MAD2 (mitotic arrest deficient 2) protein is the key factor controlling the mitotic checkpoint and down-regulation of MAD2 has been found in several types of human cancer.
Methods: Western blotting, DAPI staining, flow cytometry and BrdU staining techniques were used to study the mitotic checkpoint control on 5 NPC cell lines. Expression of MAD2 was achieved in one of the NPC cell lines using an inducible expression vector, and the effect of MAD2 expression on chemodrug sensitivity were determined by PI staining and colony forming assay.
Results: We found that the mitotic checkpoint was defective in two out of five (40%) of the tested NPC cell lines which was associated with reduced expression of MAD2. Ectopic expression of MAD2 in NPC cells conferred cellular sensitivity to one of the mitotic targeting drugs, vincristine.
Conclusion: Our findings support a new model of nasopharyngeal carcinogenesis in which a defective mitotic checkpoint characterized by the reduced expression of MAD2 contributes to chromosomal instability. And expression of MAD2 in NPC cells can lead to sensitization of NPC cells to certain anticancer drugs.