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Macrophage inhibitory cytokine-1 increases HIF-1α accumulation by the activation of mTOR pathways in human gastric cancer cells

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We previously reported that macrophage inhibitory cytokine-1 (MIC-1), a member of the transforming growth factor-β superfamily, is overexpressed in human gastric tumor tissues and plays an important role in the malignant progression of gastric cancer cells through the up-regulation of the uPA activation system. Here, we demonstrate that MIC-1 induces the expression of HIF-1α protein by the activation of mTOR signaling pathways. Stimulation of human gastric cancer cells with rMIC-1 strongly induces the phosphorylation of the mammalian target of rapamycin (mTOR) and its downstream substrates such as p70S6K and 4E-BP1. The rMIC-1-induced phosphorylation of these kinases was significantly suppressed by PI3K inhibitor wormanin, tyrosine kinase inhibitor genistein, or mTOR inhibitor rapamycin. Further analysis revealed that ErbB3, an EGFR family, could play a critical role in MIC-1-induced activation of mTOR. Taken together, these results indicate that MIC-1 may contribute to the malignant progression of human gastric cancer cells through mTOR signaling pathway by the activation of ErbB3 tyrosine kinase.

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Modulation of β-catenin functions by XIAP (X-linked inhibitor of apoptosis protein) induced NF-kB activation

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XIAP is an anti-apoptotic protein that inhibits capsase activity. Such an anti-apoptotic function is likely to be regulated by XIAP induced NF-kB transcription factor, therefore activating cell survival pathway in normal cells. β-catenin is an important regulator of Wnt signaling that might be involved in regulation of death, survival and proliferation of the cells. However, transcriptional activation by the oncogenic β-catenin protein complex is responsible for carcinogenesis of various cancer cells. Recently, we have made an interesting observation that transiently transfected XIAP significantly suppressed transcriptional activity of β-catenin in 293 cells but in less extent in colon cancer cells. We also observed that protein levels of XIAP was very low when β-catenin level was high in colon cancer cells. Since nuclear translocation of β-catenin was not regulated by XIAP, we tested how XIAP regulated nuclear transcriptional function of β-catenin. In this study, we have shown that XIAP activates NF-kB and nuclear translocated p65 subunit competes for p300 co-activator protein with nuclear β-catenin. Further characterization of protein interaction network would help to understand complex cellular signaling in normal cells as well as in cancer cells.

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Molecular Mechanism of osteopontin in angiogenesis of human hepatocellular carcinoma

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Osteopontin(OPN) is overexpressed by many transformed cell line and this excesss expression is correlated with metastatic potential of various tumors including gastric carcinoma. But the functions of osteopontin in human hepatocellular carcinoma are less clear. In highly hypervascular condition in hepatocellular carcrinogenesis, osteopontin may act potent angiogenic role under the tumor hypoxia. In our experiment, osteopontin expression is increased in hepatocellular carcinoma during hypoxia. We confirm that the expression level of osteopontin in HCC is markedly reduced when HIF-1α expression is suppressed both in normoxia and hypoxia, suggesting that the osteopontin is regulated by HIF-1α. Another factors acting in HCC development through stabilizing HIF-1α, such as IGF-II and HBx seem to regulate osteopontin expreesion in HCC. In conclusion, molecular function of osteopontin in human hepatocellular carcinogenesis may be processed through HIF-1α. And with the coupled action of IGF-II and HBx, osteopontin may promote angiogenesis in developing HCC. Finding the interaction between these hypoxia-regulatory proteins including osteopontin can provide new insights into hepatocarcinogenesis and potential therapeutic target of hepatocellular carcinogenesis.

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NF-KappaB inhibition increases chemosensitivity to trichostatin a-induced cell death of ki-ras-transformed human prostate epithelial cells

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In many tumor cells, the chemotherapeutics elicit NF-&;B activation, enhancing the chemoresistance, one of the major problems in cancer therapy. We previously reported the increased radiosensitivity of 267B1/K-ras human prostate epithelial cells by NF-&;B inhibition. In the present study, 267B1/K-ras cells were found to show enhanced NF-&;B activation and resistance to cell death by trichostatin A, an inhibitor of histone deacetylase. However, both the NF-&;B activation and chemoresistance were reduced by pretreatment with proteasome inhibitor-I (ProI), accompanied by accumulations of cytoplasmic I&;Bα and p65/RelA (but not p50/NF-&;B1). Clonogenic cell survival and soft agar assays further confirmed the increased chemosensitivity of 267B1/K-ras cells by ProI treatment. Moreover, dominant negative mutant of IKKβ, I&;Bα and p65 enhanced the chemosensitization, too. Unexpectedly, however, LY294002 and PD98059, specific inhibitors of phosphatidylinositol-3-kinase and mitogen-activated protein kinase, respectively, enhanced the TSA-chemosensitization, although these compounds had showed no effect on radiosensitization in the cells. On the other hand, activations of caspase-8 and caspase-3 by TSA and ProI were noticed, suggesting the involvement of apoptotic process in chemosensitization of 267B1/K-ras cells. Altogether, these results suggest an application of blocking NF-&;B activation pathway to the development of anticancer therapeutics in Ki-Ras-overexpressing cancer cells.