FEATURES

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The Balance Mediated by miRNAs and the Heme Oxygenase 1 Feedback Loop Contributes to Biological Effects

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Ning Ma, Ying Xiang, Yanfen Zhang, Xia Zhao, Lingyun Zhou, and Xu Gao

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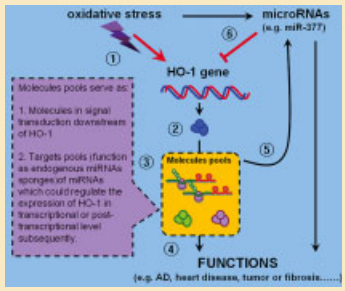

Heme oxygenase-1 (HMOX1) is a ubiquitously expressed inducible enzyme that degrades heme to carbon monoxide, biliverdin, and free iron ions. Since 1950, many studies have revealed the role of HMOX1 in reducing the impact of oxidative stress in many types of diseases, such as Alzheimer's disease, heart disease, and the development of tumors. These effects arise as a result of the removal of heme, the biological activities of the products of HMOX1 and the activity of HMOX1 itself. However, HMOX1 has some contradictory effects. The discovery of microRNAs (miRNAs) and their relationship with HMOX1 has provided a new direction for research in this field. Here, the role of a potential regulatory feedback loop between HMOX1 and miRNAs in pathological processes based on recently published data is discussed. The hope is to describe a new mechanism for HMOX1 function based on miRNAs to address the contradictory results reported in the literature.

MicroRNA-212 Inhibits Proliferation of Gastric Cancer by Directly Repressing Retinoblastoma Binding Protein 2

2666

Zeng Jiping, Fang Ming, Wang Lixiang, Liang Xiuming, Shen Yuqun, Yu Han, Liu Zhifang, Sun Yundong, Liu Shili, Chen Chunyan, and Jia Jihui

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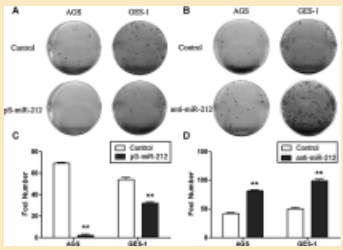

Retinoblastoma binding protein 2 (RBP2), a newly found histone demethylase, is over-expressed in gastric cancer. We examined the upstream regulatory mechanism of RBP2 at the microRNA (miRNA) level and the role in gastric carcinogenesis. Bioinformatics is used to predict that microRNA-212 (miR-212) might be a direct upstream regulator of RBP2 and verified the regulation in gastric epithelial-derived cell lines. Overexpression of miR-212 significantly inhibited the expression levels of RBP2, whereas knockdown of miR-212 promoted RBP2 expression. Furthermore, the putative miR-212 targeting sequence in the RBP2 3′ UTR by luciferase assay is identified. MiR-212 inhibited the colony formation ability of cells by repressing RBP2 expression and increasing that of $P21^{CIP1}$ and $P27^{kip1}$, both critical in cell cycle arrest. In addition, the expression of RBP2 and miR-212 in tumor tissue and matched normal tissue from 18 patients further supported the results in vivo. MiR-212 directly regulates the expression of RBP2 and inhibits cell growth in gastric cancer, which may provide new clues to treatment.

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MicroRNA-23a Modulates Tumor Necrosis Factor-Alpha-Induced Osteoblasts Apoptosis by Directly Targeting Fas

2738

Jun Dong, Xingang Cui, Zhensong Jiang, and Jianmin Sun

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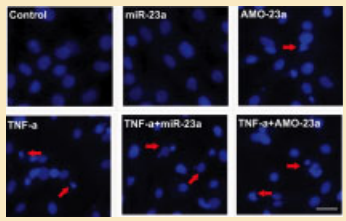

Tumor necrosis factor (TNF)-alpha is a key cytokine regulator of bone and mediates inflammatory bone loss. The molecular signaling that regulates bone loss downstream of TNF-alpha is poorly defined. Recent studies implicated an important role of microRNAs (miRNAs) in TNFalpha-mediated bone metabolism, including osteoblasts differentiation, osteoclasts differentiation and apoptosis. However, there are very few studies on the complex regulation of miRNAs during TNF-alpha-induced osteoblasts apoptosis. In the present study, the clonal murine osteoblastic cell line, MC3T3-E1, was used. We screened for differentially expressed miRNAs during TNF-alpha induced MC3T3-E1 cell apoptosis and identified microRNA-23a as a potential inhibitor of apoptosis. To delineate the role of microRNA-23a in apoptosis, we respectively silenced and overexpressed microRNA-23a in MC3T3-E1 cells. We found that microRNA-23a depletion significantly enhances TNF-alpha-induced MC3T3-E1 cell apoptosis and over-expressing microRNA-23a remarkably attenuates this phenomenon. Mechanistic studies showed that microRNA-23a inhibits Fas expression through a microRNA-23a-binding site within the 3′-untranslational region of Fas. The posttranscriptional repression of Fas was further confirmed by luciferase reporter assay. These results showed that microRNA-23a, an important protecting factor, plays a significant role in the process of TNF-alpha induced MC3T3-E1 cell apoptosis, by regulating Fas expression.

Comparative Proteomics of Glioma Stem Cells and Differentiated Tumor Cells Identifies S100A9 as a Potential Therapeutic Target

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Song Chen, Hongxin Zhao, Jinmu Deng, Peng Liao, Zhongye Xu, and Yuan Cheng

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Recent studies have suggested the existence of a small subset of cancer cells called cancer stem cells (CSCs), which possess the ability to initiate malignancies, promote tumor formation, drive metastasis, and evade conventional chemotherapies. Elucidation of the specific signaling pathway and mechanism underlying the action of CSCs might improve the efficacy of cancer treatments. In this study, we analyzed differentially expressed proteins between glioma stem cells and differentiated tumor cells isolated from the human glioma cell line, U251, via iTRAQ-tagging combined with two dimensional liquid chromatography tandem MS analysis to identify proteins correlated with specific features of CSCs. Out of a total data set of 559 identified proteins, 29 proteins were up-regulated in the glioma stem cells when compared with the differentiated cells. Interestingly, The expression level of S100A9 was five fold higher in glioma stem cells than differentiated cells. Similar results were also observed in glioma stem cells derived from other glioma cells. More importantly, knockdown of S100A9 by RNA interference suppressed the proliferation of glioma stem cell line and decreased the growth of xenograft tumors in vivo. Taken together, these results indicate that the tumorigenesis potential of CSCs arises from highly expressed S100A9.