FEATURES

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Rho GTPase Signaling in Colorectal Cancer Development and Progression

2549

Fernanda Leve and José A. Morgado-Díaz

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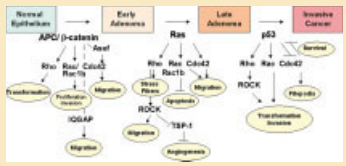

Colorectal cancer is the second most lethal neoplasia worldwide. However, the molecular mechanisms leading to tumor progression and acquisition of a metastatic phenotype are highly complex and therefore only partially understood. Accumulating evidence supports the concept that Rho GTPases play important roles in both tumor development and cancer progression. Moreover, expression and activity of Rho GTPases and their regulators are commonly altered in colon cancer. As a result, Rho GTPases are attracting considerable interest as potential targets for cancer therapy. In this Prospect article, Leve and Morgado-Diaz discuss the regulation and role that the three well characterized members of Rho family, Rho, Rac and Cdc42, play in this cancer type, as well as the molecular mechanisms that mediate Rho-dependent cell transformation. The authors point out the crosstalk between Rho GTPases and the most important genes for colon cancer development, Ras, Apc and p53, as well as the influence of this GTPase on the cellular functions related with cancer progression, such as cell-cell adhesion loss, proliferation, migration and invasion. The understanding of these and other molecular events highlights the relevance of targeting Rho signaling as novel tumor therapeutic strategy which may benefit colorectal cancer patients.

A Systematic and Comprehensive Analysis of Structure and Function of AGO Proteins

2576

Kai-Fa Wei, Ling-Juan Wu, Juan Chen, Yan-feng Chen, and Dao-xin Xie

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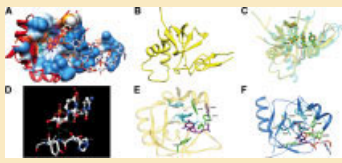

AGO proteins are key components of the RNAi process and are involved in diverse biological functions and pathogenesis of diseases. A need has arisen for molecular evolutionary analyses of AGO proteins in a large number and wide range of species, to help us understand how evolutionary stresses modified the functional role of AGO proteins and solve major issues including the host defense mechanism against virus infection and the molecular basis of disease. In this study, Wei et al. chose 135 full-length AGO protein sequences derived from 36 species covering prokaryote, archaea and eukaryote. Bacteria and archaeal AGO proteins are clustered in the same clade and there exist multiple AGO proteins in most eukaryotic species. The emergence of the PAZ domain in AGO proteins is a unique evolutionary event. The analysis of MID-nucleotide contaction shows that either the position of sulphate I bond in Nc_QDE2 or the site of phosphate I bond in Hs_AGO2 represents the 5'nucleotide binding site of miRNA. H334, T335 and Y336 of Hs_AGO1 can form hydrogen bonds with 3'overhanging ends of miRNAs. The same situation exists in Hs_AGO2, Hs_AGO3, Hs_AGO4, Dm_AGO1 and Ce_Alg1. Some PIWI domains containing conserved DDH motif have no slicer activity, and post-translational modifications may be associated with the endonucleolytic activities of AGOs.

Journal of Cellular Biochemistry

Gene Regulation in Nuclear Space: What Keeps Inactive genes in Place? 2607

Joscha S. Muck, Karthikeyan Kandasamy, Andreas Englmann, Martin Günther, and Daniele Zink

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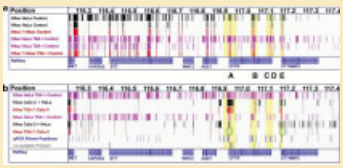

Mammalian genomes display a radial organization in the nucleus, and inactive loci are more peripheral than active loci. It is not understood how the spatial organization of genomes is determined and how the mechanisms involved could be linked to the regulation of gene activity. Zink and colleagues had shown previously that the human cystic fibrosis gene (CFTR) shuttles between peripheral and interior positions depending on its state of activity. This was now further investigated by Muck *et al.* and the results reveal that an active histone deacetylase (HDAC) at a CTCF binding site close to the CFTR promoter, CTCF as well as A-type lamins are essential for the perinuclear positioning of CFTR. Hyperacetylation of histone H3 at the CTCF site and CFTR repositioning were induced within 20 minutes of treatment with the HDAC inhibitor trichostatin A (TSA), and knockdown of CTCF had similar effects on CFTR positioning as TSA treatment. The results suggest CTCF, A-type lamins and a histone deacetylase form a complex with the inactive CFTR promoter at the nuclear periphery, which disintegrates when the HDAC is inactive. The findings point to a central role of HDACs in linking gene regulation with spatial genome organization.

Three miRNAs Linked to hMSC Differentiation 2687

Salla K. Laine, Jessica J. Alm, Sanna P. Virtanen, Hannu T. Aro, and Tiina K. Laitala-Leinonen

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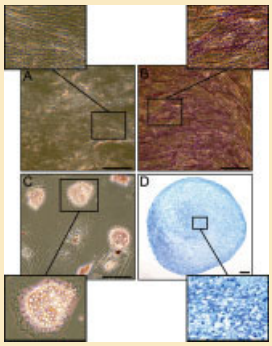

Human mesenchymal stem/stromal cells (hMSCs) are able to differentiate into e.g. osteoblasts and chondrocytes and thus offer a great promise for clinical stem cell therapy of different skeletal conditions. Increasing evidence suggests that the proliferation and differentiation of hMSCs are regulated by small non-coding microRNAs. Previous studies by Laine *et al.* showed altered miRNA expression patterns during osteogenic and chondrogenic differentiation of mouse bone marrow stem cells. In the present study, Laine *et al.* characterize the expression of three most differentially expressed miRNAs, miR-96, miR-124 and miR-199a, during osteogenic, adipogenic and chondrogenic differentiation of hMSCs. The results show an increased expression of miR-96 in all three differentiation processes whereas miR-124 expression was demonstrated only upon adipogenic differentiation. On the other hand, miR-199a was found to be upregulated in osteoblasts and chondrocytes while its expression in adipocytes remained at the baseline level. Based on further studies with synthetic miRNA precursors and inhibitors, these miRNAs may play important roles in hMSCs through modulating the expression of genes involved in hMSC differentiation or function.