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This Month in *AJP*

Alternative Lengthening of Telomeres in Human Cancer Subtypes

A minority of human cancers (10% to 15%) lack demonstrable telomerase activity, and of these, some maintain proper telomere lengths through a telomerase-independent mechanism termed alternative lengthening of telomeres (ALT). Heaphy et al (**Am J Pathol 2011, 179:1608–1615**) assessed the prevalence of ALT by comprehensively surveying the ALT phenotype in a broad range of human cancers. In total, tumors from 94 different cancer subtypes, 541 benign neoplasms, and 264 normal tissue samples were assessed by combined telomere-specific fluorescence *in situ* hybridization and immunofluorescence labeling for the transcription regulator promyelocytic leukemia (PML) protein. ALT was observed in nearly 4% of all tumor specimens and was not observed in benign neoplasms or normal tissues. This is the first description of ALT in multiple carcinomas and in multiple brain tumor types. Therefore, further studies are warranted to assess the potential prognostic significance and unique biology of ALT-positive tumors.

Differential Expression of Oncogenic miRNAs from the Same Gene Locus

The *C13orf25* gene is amplified in some human cancers, and six miRNAs, miR-17-92, are processed from the gene transcript. Ji et al (**Am J Pathol 2011, 179:1645–1656**) found that the amount of each miRNA varied relative to each other and to the primary transcript, with the promoter being regulated by multiple transcription factors. Mutation of putative SP1-binding sites greatly reduced promoter activity. Mutation of a putative MYC-binding site actually enhanced promoter activity, as the inhibitory MYC family member MXI1 normally binds to this region. Because these miRNAs are implicated in several cancers and target genes that control cell proliferation and survival, continued research is necessary to further clarify the transcriptional control of the *C13orf25* locus.

miRNAs Regulate Aquaporin-1 in Cirrhosis and Hepatic Fibrogenesis

The water channel aquaporin-1 is overexpressed in cirrhosis, and changes in vasculature are observed in hepatic fibrogenesis. Huebert et al (**Am J Pathol 2011, 179: 1851–1860**) tested the role of the water channel in both disease processes by generating aquaporin-1-knockout mice. After bile duct ligation, wild-type mice overexpressed aquaporin-1 whereas aquaporin-1 knockout mice demonstrated reduced angiogenesis, fibrosis, and portal hypertension. Expression of aquaporin-1 protein, but not mRNA, was increased by hyperosmolality *in vitro*, suggesting posttranscriptional regulation. In fact, miR-666 and miR-708 targeted aquaporin-1 mRNA and were decreased in cirrhosis and in cells exposed to hyperosmolality. Thus, these miRNAs mediate osmolar changes via aquaporin-1 and may prove useful targets to ameliorate fibrosis and portal hypertension.

JNK Science in Rheumatoid Arthritis

The roles of the c-jun N-terminal kinases (JNK) JNK1 and JNK2 in inflammatory arthritis have been previously investigated, but differences in models used and assays used have made direct comparisons of their roles difficult. Using JNK1- or JNK2-deficient mice in two models of arthritis, Denninger et al (**Am J Pathol 2011, 179:1884–1893**) found JNK1 deficiency results in arthritis protection, whereas JNK2 deficiency aggravates disease. This may be partly due to altered macrophage function affecting T cell–mediated immunity. The results may explain why modest beneficial effects are observed with broad-spectrum JNK inhibitors and suggest that future therapies should selectively target JNK1.

Sialylation Defects Characterize a Novel Form of Thrombocytopenia

Thrombocytopenia, which frequently leads to spontaneous bleeding, can arise from several different causes. Jones et al (**Am J Pathol 2011, 179:1969–1977**) observed a new variant characterized by the appearance of giant platelets and variable neutropenia. Platelets, neutrophils, and monocytes exhibited deficient α2,3-sialylation, resulting in greatly lessened sialyl–Lewis X but concomitantly increased Lewis X surface expression. Platelets from such patients bound to the asialoglycoprotein receptor (ASGP-R), a liver cell-surface protein essential for removing desialylated thrombocytes from the circulation. Thus, the lack of proper glycosylation effects cell removal, leading to functional thrombocytopenia.