FEATURES

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Rad9: Oncogene or Tumor Suppressor?

Constantinos G. Broustas and Howard B. Lieberman

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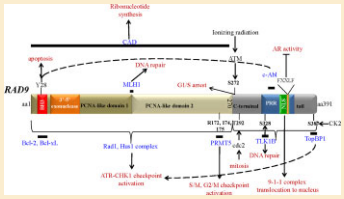

Rad9 protein is best known for its roles in cell cycle checkpoints and DNA repair as part of the Rad9-Hus1-Rad1 (9-1-1) complex, which has a critical function in maintaining genomic stability. Rad9, however, has additional roles unrelated to 9-1-1. Recent studies indicate that the protein can specifically transactivate a number of genes, including $p21^{waf1/Cip1}$, some of which are not known to participate in cell cycle control or DNA repair, thus suggesting novel functions for Rad9. Most importantly, Rad9 protein levels are regulated in various human cancers. This regulation is complex as Rad9 protein abundance is diminished in some cancers (e.g. skin and gastric cancer), whereas it is increased in others (e.g. breast and prostate cancer). The role of Rad9 in tumorigenesis appears to be tissue specific. Rad9 functions as a tumor suppressor in skin cancer, but as an oncogene in prostate cancer. In this review, Broustas and Lieberman provide a summary of the multiple functions of Rad9 and discuss the role of this protein in human tumorigenesis. Moreover, they offer possible mechanisms that could explain the role of Rad9 as a context specific tumor suppressor or promoter, in part using knowledge about other dual function genes.

HDACi Alters Pathways in Osteosarcoma

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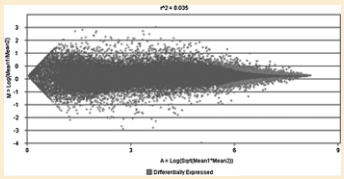

The utility of histone deacetylase inhibitors (HDACi) as targeted therapy for cancer has been well established for some tumor types; however, the molecular mechanisms by which they exert their anti-tumor effect in osteosarcoma are poorly understood. This study evaluates global gene expression changes in osteosarcoma cells exposed to clinically relevant doses of the HDACi valproic acid (VPA), with the additional step of placing all of the differentially expressed genes into functional pathways utilizing a novel data analysis pipeline. Results demonstrate that the oxidative phosphorylation pathway is the most significantly altered, with an overall upregulation in response to VPA. Additional pathways discovered through our analysis include cytoskeleton remodeling, cell cycle control, ubiquitin-proteasome, and ubiquinone metabolism. Wittenburg et al. demonstrate that the HDACi-mediated inhibition of the proteasome pathway leads to synergistic anti-proliferative activity when VPA is combined with a novel inhibitor of proteasome activity, and that upregulation of ubiquinone metabolism translates to an increase in cellular NQO1 activity and sensitization of OS cells to the NQO1 substrate drug mitomycin C. These results provide insight into the potential mechanisms of action of VPA in OS, and provide further rationale for combination therapies involving HDACi in the treatment of OS.

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Neonatal Cardiac Cell differentiation on a Polymeric Matrix

Clara Gallina, Serena Dolgetta, Giuseppe Alloatti, Renzo Levi, and Maria Pia Gallo

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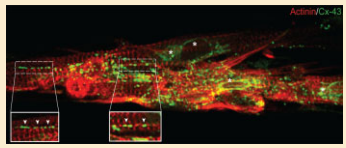

Tissue engineering is a promising emerging field requiring biological and technological approaches to prototype useful constructs. Myocardial reconstruction can be considered the philosopher's stone of tissue engineering in the field of reconstruction of non-regenerating organs. The report by Gallina et al. introduces two aspects of this complex issue: a) the biocompatibility of a hyaluronan-based mesh (HYALONECT®), a substrate currently available for medical practice, with cardiac cells; and b) its capability to sustain differentiation of neonatal cells toward a more mature functional state.

The latter issue is relevant as implanted myocardial cells cannot be autorhythmic, unless they are intended to replace pacemaker tissue. Neonatal tissue is a good model for this transition, as the cells obtained from dissociation dedifferentiate into spontaneously beating rounded cells, losing morphological and functional properties within minutes. The construct development is analyzed with immunofluorescence and calcium concentration measurement. The report shows that upon adhesion on the polymeric mesh, cells recuperate in 2 to 7 days with organized sarcomeric structure and Cx-43 based electrical connections, while spontaneous pacemaking ceases. This model could be applied as a tool to control the phenotype of implantable constructs based on other cardiac cell models such as those originating from stem cells.

Molecular Mechanism of hADSC Differentiation

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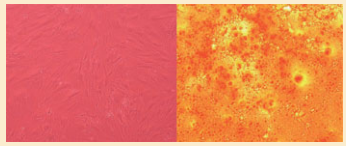

Human adipose-derived stem cells (hADSC) are capable of differentiating into an osteogenic lineage. It is believed that miRNAs play important roles in regulating this osteogenic differentiation of hADSC, although its molecular mechanism remains unclear. Zhang et al. comprehensively investigated the miRNA expression profile using microarray essay and assessed the roles of involved miRNAs during osteogenic differentiation of hADSCs, revealing that eight miRNAs were differently expressed pre-and post-osteogenic induction, among which four miRNAs (miR-17, miR-20a, miR-20b, and miR-106a) were up-regulated and four miRNAs (miR-31, miR-125a-5p, miR-125b, and miR-193a) were down-regulated. Predicted target genes of the differentially expressed miRNAs based on the overlap from three public prediction algorithms (MiRanda, TargetScan, and miRBase Target) have the known functions of regulating stem cell osteogenic differentiation, self-renewal, signal transduction, and cell cycle control. Zhang et al. identified a group of miRNAs that may play important roles in regulating hADSC cell differentiation toward an osteoblast lineage. Further study of these miRNAs may elucidate the mechanism of hADSC differentiation into adipose tissue, and thus provide basis for tissue engineering.