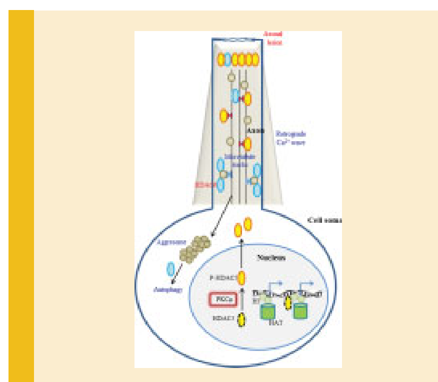
FEATURES

VOLUME 115 • NUMBER 7

Class II HDACs and Neuronal Regeneration 1225

Bor Luen Tang

ACCEPTED MANUSCRIPT ONLINE 7 MARCH 2014

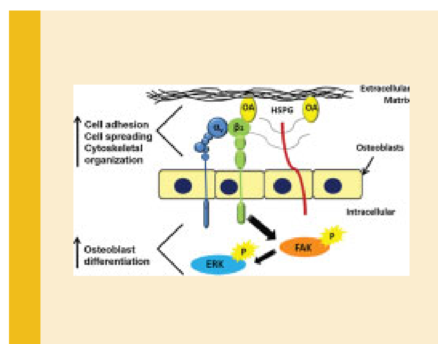


The vastly more superior regenerative capacity of the axons of peripheral nerves over central nervous system (CNS) neurons has been partly attributed to the former's intrinsic capacity to initiate and sustain the functionality of a new growth cone. Growth cone generation involves a myriad of processes that centers around the organization of microtubule bundles. Histone deacetylases (HDACs) modulate a wide range of key neuronal processes such as neural progenitor differentiation, learning and memory, neuronal death, and degeneration. HDAC inhibitors have been shown to be beneficial in attenuating neuronal death and promoting neurite outgrowth and axonal regeneration. Recent advances have provided insights on how manipulating HDAC activities, particularly the type II HDACs 5 and 6, which deacetylate tubulin, may benefit axonal regeneration.

Osteoactivin Promotes Osteoblast Adhesion Through HSPG and $\alpha v\beta 1$ Integrin 1243

Fouad M. Moussa, Israel Arango Hisijara, Gregory R. Sondag, Ethan M. Scott, Nagat Frara, Samir M. Abdelmagid, and Fayez F. Safadi

ACCEPTED MANUSCRIPT ONLINE 10 JANUARY 2014



Osteoactivin (OA), also known as glycoprotein nmb (gpmb) plays an important role in the regulation of osteoblast differentiation and function. Recent studies reported a role for OA in cell adhesion and integrin binding. The authors demonstrate that recombinant osteoactivin (rOA) as a matricellular protein stimulated adhesion, spreading and differentiation of MC3T3-E1 osteoblast-like cells through binding to $\alpha_v\beta_1$ integrins and heparan sulfated proteoglycans (HSPGs). MC3T3-E1 cell adhesion to rOA was blocked by neutralizing anti-OA or anti-α_v and β_1 integrin antibodies. rOA stimulated-cell adhesion was also inhibited by soluble heparin and sodium chlorate. Interestingly, rOA stimulated-cell adhesion promoted an increase in FAK and ERK activation, resulting in the formation of focal adhesions, cell spreading and enhanced actin cytoskeleton organization in MC3T3-E1 cells. In addition, differentiation of primary osteoblasts was augmented on rOA coated-wells marked by increased alkaline phosphatase staining and activity. Taken together, the data implicate OA as a matricellular protein that stimulates osteoblast adhesion through binding to $\alpha_v\beta_1$ integrin and cell surface HSPGs, resulting in increased cell spreading, actin reorganization, and osteoblast differentiation with emphasis on the positive role of OA in osteogenesis.

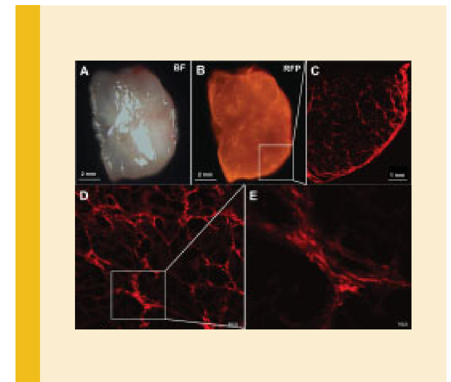
Journal of Cellular Biochemistry

Efficacy of *Salmonella typhimurium* A1-R Versus Chemotherapy on a Pancreatic Cancer Patient-Derived Orthotopic Xenograft (PDOX) 1254

Yukihiko Hiroshima, Ming Zhao, Ali Maawy, Yong Zhang, Matthew H.G. Katz, Jason B. Fleming, Fuminari Uehara, Shinji Miwa, Shuya Yano, Masashi Momiyama, Atsushi Suetsugu, Takashi Chishima, Kuniya Tanaka, Michael Bouvet, Itaru Endo, and Robert M. Hoffman

ACCEPTED MANUSCRIPT ONLINE 17 JANUARY 2013

The aim of the study is to determine the efficacy of tumor-targeting *Salmonella typhimurium* A1-R (A1-R) on a pancreatic cancer patient-derived orthotopic xenografts (PDOX). The PDOX model was originally established from a pancreatic cancer patient in SCID-NOD mice. The pancreatic cancer PDOX was subsequently transplanted by surgical orthotopic implantation (SOI) in transgenic nude red fluorescent protein (RFP) mice in order that the PDOX stably acquired red fluorescent protein (RFP)-expressing stroma for the purposes of imaging the tumor after passage to non-transgenic nude mice in order to visualize tumor growth and drug efficacy. The nude mice with human pancreatic PDOX were treated with A1-R or standard chemotherapy, including gemcitabine (GEM), which is first-line therapy for pancreatic cancer, for comparison of efficacy. A1-R treatment significantly reduced tumor weight, as well as tumor fluorescence area, compared to untreated control ($P = 0.011$), with comparable efficacy of GEM, CDDP, and 5-FU. Histopathological response to treatment was defined according to Evans's criteria and A1-R had increased efficacy compared to standard chemotherapy. The present report is the first to show that A1-R is effective against a very low-passage patient tumor, in this case, pancreatic cancer. The data suggest A1-1 will have clinical activity in pancreatic cancer, a highly lethal and treatment-resistant disease and may be most effectively used in combination with other agents.



Transcriptional Activation by NFκB Increases Perlecan/HSPG2 Expression in the Desmoplastic Prostate Tumor Microenvironment 1322

Curtis R. Warren, Brian J. Grindel, Lewis Francis, Daniel D. Carson, and Mary C. Farach-Carson

ACCEPTED MANUSCRIPT ONLINE 17 FEBRUARY 2014

Perlecan/HSPG2, a heparan sulfate proteoglycan typically found at tissue borders including those separating epithelia and connective tissue, increases near sites of invasion of primary prostatic tumors as previously shown for other proteins involved in desmoplastic tissue reaction. Studies of prostate cancer cells and stromal cells from both prostate and bone, the major site for prostate cancer metastasis, showed that cancer cells and a subset of stromal cells increased production of perlecan in response to cytokines present in the tumor microenvironment. In silico analysis of the *HSPG2* promoter revealed two conserved NFκB binding sites, in addition to the previously reported SMAD3 binding sites. By systematically transfecting cells with a variety of reporter constructs including sequences up to 2.6 kb from the start site of transcription, the investigators identified an active cis element in the distal region of the *HSPG2* promoter, and showed that it functions in regulating transcription of *HSPG2*. Treatment with TNF-α and/or TGFβ1 identified TNF-α as a major cytokine regulator of perlecan production. TNF-α treatment also triggered p65 nuclear translocation and binding to the *HSPG2* regulatory region in stromal cells and cancer cells. In addition to stromal induction of perlecan production in the prostate, the investigators identified a matrix-secreting bone marrow stromal cell type that may represent the source for increases in perlecan in the metastatic bone marrow environment.