# FEATURES

VOLUME 111 • NUMBER 5

## Osteoblasts in the Tumor Microenvironment



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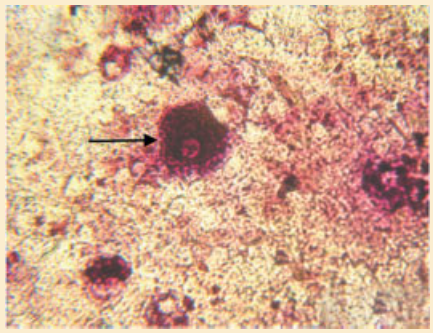
PUBLISHED ONLINE 3 AUGUST 2010

A major obstacle in bone metastatic breast cancer is that the precise mechanism for directional metastasis to the metaphyseal ends of long bones is unknown. Recent evidence suggests that cancer cells manipulate resident bone cells, such as the osteoblast, into facilitating tumor cell colonization and survival. Bussard et al. comprehensively investigate how osteoblast inflammatory cytokine production is altered in response to MDA-MB-231 metastatic breast cancer variants or their conditioned media. Results show that MC3T3-E1 murine osteoblasts treated with human metastatic breast cancer cell conditioned medium produce increased amounts of murine IL-6, VEGF, MIP-2 (human IL-8), KC (human GRO-α), and MCP-1. Human metastatic breast cancer cell variants produce a similar array of cytokines with one exception; they produce very small amounts of MCP-1. These same cytokines were detected *ex vivo* in the metaphyses of murine femurs bearing human metastatic bone metastases when compared to the diaphysis. Furthermore, concentrations of IL-6, VEGF, KC, MIP-2, and MCP-1 increase significantly in cancer-bearing versus non-cancer-bearing mice. Bussard et al. suggest that osteoblasts are an important source of cytokines, specifically MCP-1, in breast cancer bone metastasis. Evidence provided clearly implicates the bone microenvironment and cancer cell manipulation thereof in facilitating metastatic tumor cell colonization and survival.



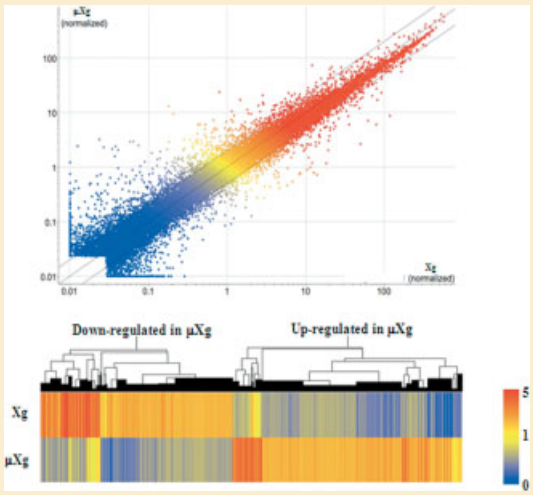
## Gene Expression During Osteoclast Differentiation in Modeled Microgravity



*Yuvaraj Sambandam, Jeremy J. Blanchard, Giffin Daughtridge, Robert J. Kolb, Srinivasan Shanmugarajan, Subramanya N.M. Pandruvada, Ted A. Bateman, and Sakamuri V. Reddy*

PUBLISHED ONLINE 17 AUGUST 2010

The National Aeronautics and Space Administration's (NASA) space exploration mission is challenged by microgravity (μXg) (weightlessness) conditions. Astronauts can lose 1–2% of entire bone mass per month in space. Studies have indicated that μXg affects normal bone homoeostasis through suppression of the bone forming ability of osteoblast cells and increased osteoclast bone resorption activity. However, the mechanism underlying μXg-induced osteoclast formation/bone resorption is unclear. Sambandam et al utilized the NASA-developed ground-based Rotating Wall Vessel Bioreactor (RWV), and the Rotary Cell Culture System (RCCS) model to simulate μXg conditions and performed large-scale microarray analysis to assess the gene expression patterns during osteoclast differentiation. The study revealed 11.4% of the genes were differentially regulated; of these 54% were upregulated and 45% were down regulated. Results identified increased expression of cytokines/growth factors, bone matrix degrading proteases, adhesion molecules and transcription factors, which play important roles in osteoclast differentiation and bone resorption activity. Further, μXg significantly down regulated negative regulators of osteoclastogenesis. Thus, modeled μXg regulated gene expression profiling during osteoclast differentiation provides new insights into molecular mechanisms and therapeutic targets of osteoclast differentiation/activity to prevent bone loss and fracture risk in astronauts during space flight missions.



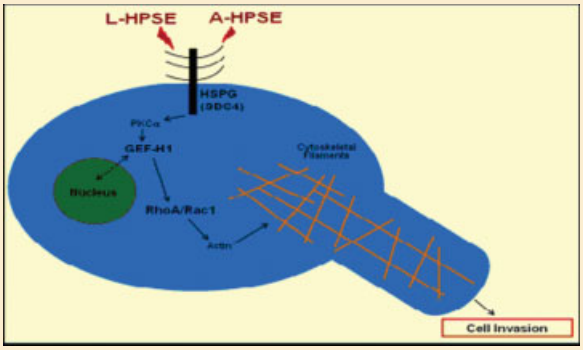
Journal of Cellular Biochemistry

## Heparanase as a Target For Therapy in Melanoma



*Lon D. Ridgway, Michael D. Wetzel, and Dario Marchetti*

PUBLISHED ONLINE 27 AUGUST 2010




Brain metastatic melanoma (BMM) is among the deadliest forms of cancer with significant associated morbidity and mortality. Despite this, BMM molecular mechanisms remain largely unknown. Highly invasive metastatic tumors express β-D-endoglucuronidase heparanase. Invasion and metastasis require cytoskeletal dynamics that are dependent upon the activity of the Rho family of small GTPases. Ridgway et al. hypothesized that exposure to heparanase could influence the activity of Rho small GTPases, perhaps independent of endoglucuronidase activity. This work demonstrates the differential expression of GEF-H1 between two isogenic melanoma cell lines that differ in brain metastatic ability. Ridgway et al provide evidence of an association between GEF-H1 and the carboxy terminal region of syndecan 4 (SDC4) providing a signaling pathway from heparanase through SDC4/GEF-H1 association to RhoA GTPase. The association of GEF-H1 with SDC4 CT provides the rationale for the hypothesis, which was tested by Rac1/RhoA GTPase activity assays. The biological endpoint of this article is the impact upon the invasive phenotype. The signaling links were verified by siRNA knockdown of GEF-H1, SDC1 and SDC4. These findings are relevant because they suggest distinct roles for active and latent heparanase, establishing new roles for this molecule. These findings may lead to novel heparanase-targeted BMM therapies.

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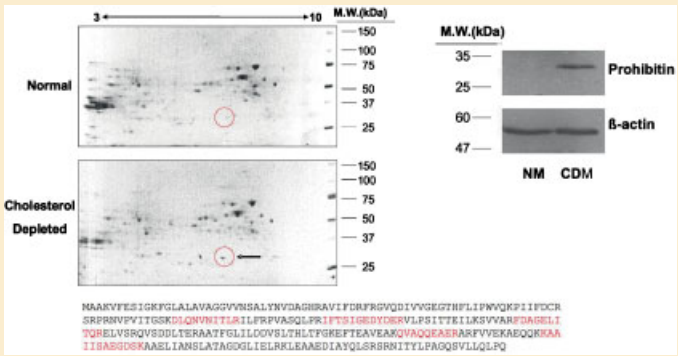
## Prohibitin in Cholesterol-Sensitive Cell Cycle Control



*Pei Dong, Jessica Flores, Kristine Pelton, and Keith R. Solomon*

PUBLISHED ONLINE 9 SEPTEMBER 2010




A critical problem for all animal cells is maintaining cholesterol homeostasis. Too much cholesterol causes cytotoxicity, while insufficient cholesterol impairs membrane synthesis and, consequently, cell proliferation. How cells coordinate cell cycle progression with cholesterol homeostasis, so that cell growth only occurs when cholesterol levels are sufficient, is not known. In the current issue Dong et al. use unbiased mass spectrometry-based proteomics and standard biochemistry to demonstrate that cholesterol insufficiency causes upregulation of prohibitin at both the mRNA and protein level. Prohibitin is an evolutionarily conserved, ubiquitously expressed, 30 kDa protein that is found in the cytoplasm, plasma membrane, nucleus, and mitochondria. Prohibitin has been shown to regulate cell cycle transit, has antiproliferative activity, regulates Ras-mediated MAP kinase pathway activation, and appears to be essential for cell survival. Dong et al. demonstrate that the prohibitin gene promoter contains a novel cholesterol-responsive element, GGTTCTAAGC (-118 to -109/reverse strand), which has moderate homology to known sterol response elements (SREs). They show that prohibitin protects cells from apoptosis caused by growth factors (EGF and PDGF) under conditions of cholesterol insufficiency. Collectively, these results suggest that cellular sensing of cholesterol concentration regulates cell cycle progression and that prohibitin is an important node in the cholesterol-sensitive network.