

FEATURES

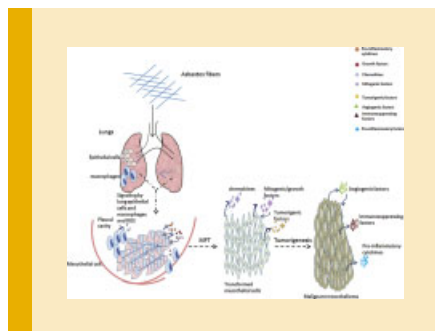
VOLUME 115 • NUMBER 1

Malignant Mesothelioma: Development to Therapy

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ACCEPTED MANUSCRIPT ONLINE 19 AUGUST 2013



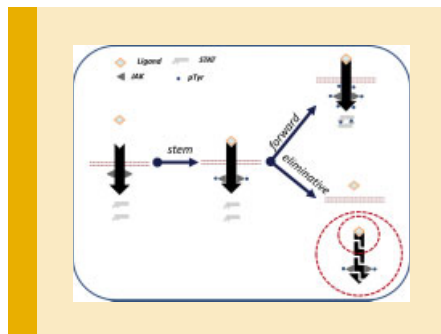
Malignant mesothelioma (MM) is an aggressive cancer of the mesothelium caused by asbestos. Asbestos use has been reduced but not completely stopped. In addition, natural or man-made disasters will continue to dislodge asbestos from old buildings into the atmosphere and as long as respirable asbestos is available, MM will continue to be a threat. Due to the long latency period of MM development, it will still take decades to eradicate the disease even if asbestos is completely removed. Therefore, there is a need for researchers and clinicians to work together to understand the deadly disease and find a solution for early diagnosis and treatment. The article focuses on developmental mechanisms as well as current therapies available for MM.

Eliminative Signaling by Janus Kinases: Role in the Downregulation of Associated Receptors

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ACCEPTED MANUSCRIPT ONLINE 19 AUGUST 2013



Activation of cytokine receptor-associated Janus kinases (JAKs) mediates most, if not all, of the cellular responses to peptide hormones and cytokines. Consequently, JAKs play a paramount role in homeostasis and immunity. Members of the family of tyrosine kinases control the cytokine/hormone-induced alterations in cell gene expression program. The function is largely mediated through an ability to signal toward activation of the signal transducer and activator of transcription proteins (STAT), as well as toward some other pathways. Importantly, JAKs are also instrumental in tightly controlling the expression of associated cytokine and hormone receptors, and, accordingly, in regulating the cell sensitivity to cytokines and hormones. The review highlights the enzymatic and non-enzymatic mechanisms of regulation. The importance of the ambidextrous nature of JAK as a key signaling node that integrates the combining functions of forward signaling and eliminative

signaling is discussed. Attention to the latter aspect of JAK function may contribute to emancipating current approaches to the pharmacological modulation of JAKs.

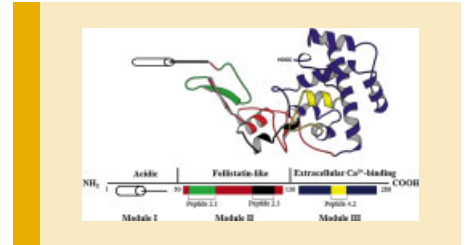
Role of SPARC in Bone Remodeling and Cancer-Related Bone Metastasis

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ACCEPTED MANUSCRIPT ONLINE 13 AUGUST 2013

There is a growing socioeconomic recognition that clinical bone diseases such as bone infections, bone tumors and osteoporotic bone loss mainly associated with ageing, are major issues in today's society. SPARC (secreted protein, acidic and rich in cysteine), a matricellular glycoprotein, may be a promising therapeutic target for preventing or treating bone-related diseases. In fact, SPARC is associated with tissue remodeling, repair, development, cell turnover, bone mineralization and may also participate in growth and progression of tumors, namely cancer-related bone metastasis. Yet, the function of SPARC in such biological processes is poorly understood and controversial. The main objective is to review the current knowledge related to the activity of SPARC in bone remodeling, tumorigenesis, and bone metastasis. Progress in understanding SPARC biology may provide novel strategies for bone regeneration and the development of anti-angiogenic, anti-proliferative, or counter-adhesive treatments specifically against bone metastasis.



Glucocorticoids Antagonize RUNX2 During Osteoblast Differentiation in Cultures of ST2 Pluripotent Mesenchymal Cells

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ACCEPTED MANUSCRIPT ONLINE 14 AUGUST 2013

The efficacy of glucocorticoids (GCs) in treating a wide range of autoimmune and inflammatory conditions is blemished by severe side effects, including osteoporosis. The chief mechanism leading to GC-induced osteoporosis is inhibition of bone formation, but the role of RUNX2, a master regulator of osteoblast differentiation and bone formation, has not been well studied. The effects of the synthetic GC dexamethasone (dex) on transcription of RUNX2-stimulated genes during the differentiation of mesenchymal pluripotent cells into osteoblasts are assessed. Dex inhibited a RUNX2 reporter gene and attenuated locus-dependently RUNX2-driven expression of several endogenous target genes. The anti-RUNX2 activity of dex was not attributable to decreased RUNX2 expression, but rather to physical interaction between RUNX2 and the GC receptor (GR), demonstrated by co-immunoprecipitation assays and co-immunofluorescence imaging. Investigation of the RUNX2/GR interaction may lead to the development of bone-sparing GC treatment modalities for the management of autoimmune and inflammatory diseases.

