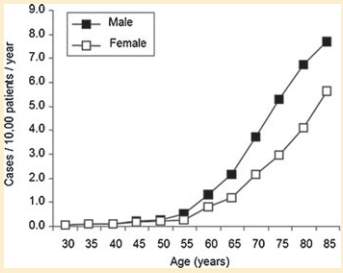
FEATURES

VOLUME 117 • NUMBER 2

Journal of Cellular Biochemistry

ACCEPTED MANUSCRIPT ONLINE 24 JULY 2015

Paget's disease of bone (PDB) is a common skeletal disorder characterized by increased and disorganized bone remodeling affecting one or more skeletal sites. Although some patients are asymptomatic others develop complications such as bone pain, deformity, nerve compression syndromes, and fragility fractures. Genetic factors play an important role in the pathogenesis of PDB and there is strong evidence that susceptibility is determined by variants within or close to genes that regulate osteoclast function. Environmental factors also play a key role but the nature of the environmental triggers is less clear. Bisphosphonates are a highly effective treatment for the elevations in bone turnover that are characteristic of PDB but it is unclear at present if they alter the natural history of the disease. Here, we review the epidemiology, clinical, cellular, and molecular abnormalities in PDB as well as environmental and genetic triggers, and current available treatment options.



ACCEPTED MANUSCRIPT ONLINE 24 JULY 2015

The amount, timing, and location of bone morphogenetic protein 2 (BMP2) synthesis influences the differentiation of pluripotent mesenchymal cells in embryos and adults. The BMP2 3′untranslated region (3′UTR) contains a highly conserved AU-rich element (ARE) embedded in a sequence that commonly represses gene expression in mesenchymal cells. Computational analyses indicate that this site also may bind several microRNAs (miRNAs). Although miRNAs frequently target AU-rich regions, this ARE is unusual because the miRNAs directly span the ARE. We began to characterize the factors that may regulate Bmp2 expression via this complex site. The activating protein HuR (Hu antigen R, ELAVL1, HGNC:3312) directly binds this ARE and can activate gene expression. An miRNA was demonstrated to reverse HuR-mediated activation. Mutational and RNA-interference evidence also supports an AUF1 (AU-factor-1, HNRNPD, HGNC:5036) contribution to the observed repressive activity of the 3′UTR in mesenchymal cells. A limited number of studies describe how miRNAs interact with ARE-binding proteins that bind adjacent sites. This study is among the first to describe protein/miRNA interactions at the same site.