FEATURES

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SHIP2's Multiple Functions

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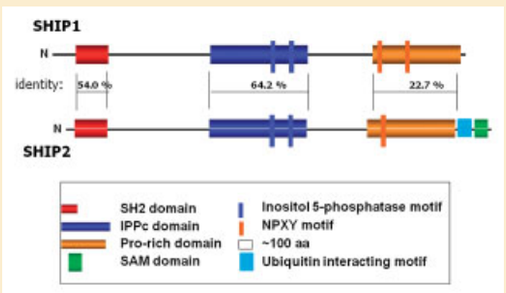
The SH2 domain containing inositol 5-phosphatases (SHIPs) are a subfamily of the mammalian inositol polyphosphate 5-phosphatases, a family of 10 isoenzymes in humans. cDNAs encoding SHIPs, i.e. SHIP1 and SHIP2, have been reported in 1996 and 1997. The two isoenzymes were soon reported to act on $PI(3,4,5)P_3$ as substrates to generate $PI(3,4)P_2$. Both molecules are implicated in signaling events in the recruitment of fundamental enzymes and adaptors such as PDK1 or PKB. SHIP2 does not only consist of a catalytic domain but shows the presence of multiple interacting domains such as the SH2 domain, proline rich sequences and the SAM domain. The protein can also be tyrosine phosphorylated on a NPXY motif, e.g. in response to growth factors such as EGF. SHIP2 interacting proteins are cytoskeletal proteins, adaptors, protein phosphatases and tyrosine kinase receptors. Because of the participation of these binding partners in diverse signaling pathways, SHIP2 has attracted wide interest. Erneux et al discuss the concept that SHIP2 function is a balance of catalytic and non catalytic mechanisms. Non catalytic properties have also been reported for other fundamental signaling enzymes such as $Ins(1,4,5)P_3$ 3-kinases, inositol phosphate multikinase (IPMK) and PTEN.



MicroRNA Regulation During Tumor Metastasis

G. Reshmi, Charles Sona, and M. Radhakrishna Pillai

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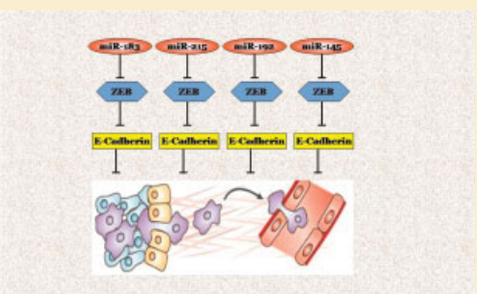
Genes involved in development, differentiation, homeostasis of cells and tissues, oncogenesis and senescence are effectively regulated by Transcription Factors; miRNA pairs. In spite of a large body of information about the upstream regulators of metastasis, the impact of regulatory microRNA patterns remains obscure. Reshmi et al explain a catalogue of mixed Feed Forward Loops (FFLs), Feed Back Loops (FBL) and Autoregulatory Loops in various stages of metastasis. The paper elaborates on the most significant patterns, which influence progression of epithelial to mesenchymal transitions, which is mostly accelerated by rewired regulation of a double positive FBL between ZEB1 -miR-200. Similarly the positive autoregulatory loop (PAR) formed by the self-regulating E2F transcription factor and mir-17–92 cluster appears to be critical since the E2F family plays a crucial role in control of the cell cycle. Reshmi et al have analyzed numerous feed forward combinatorial regulatory circuits that signify the aggressive progression of the complex multi-step process, metastasis. Further studies can be combined into functional network models, which can be engineered to identify potential therapeutic targets for drug development as well as to elucidate the systems-level mechanisms in gene regulation mediated by TFs and miRNAs.



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The Role of Lrp5/6 in Cardiac Valve Disease

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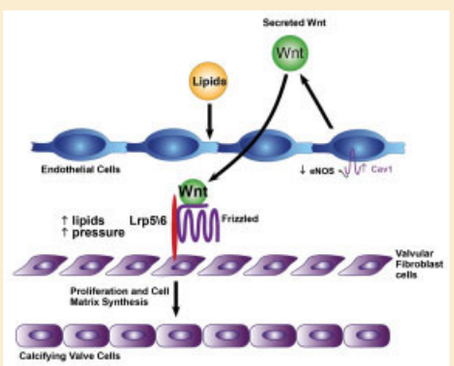

Our group has demonstrated that osteoblastogenesis and chondrogenesis are critical in calcific aortic valve disease (CAVD). The osteoblast phenotype in CAVD is secondary to the activation of the mesenchymal osteogenic gene pathway in the presence of lipids. Rajamannan demonstrates the role of Lrp5/Lrp6 in valve calcification in a series of knockout mouse models. This data is the first to demonstrate in genetic knock-out mice that an experimental cholesterol diet can upregulate Lrp5 and Lrp6 associated receptors with varying degrees of calcification in the aortic valve. The ApoE$^{-/-}$ demonstrates marked increase in lipids, Lrp5, Runx2 and calcification in the aortic valves. The Lrp5$^{-/-}$ single gene KO demonstrates no calcification or leaflet thickening as measured by MicroCT, Synchrotron MicroCT, despite a mild increase in lipids, Lrp6 and Runx2. The double knockout ApoE$^{-/-}$:Lrp5$^{-/-}$ develops severe elevated lipids, associated with mild increases in the Lrp6 receptor, Runx2 and mild calcification by MicroCT. These results demonstrate in a series of lipoprotein receptor knockout mouse models, that different levels of lipids can upregulate the Lrp5/6 coreceptor associated with varying degrees of calcification in the aortic valves. This series of lipoprotein receptor mouse models demonstrates the importance of hyperlipidemia and Lrp5/6 mechanical effects in the LDL-Density-Pressure Theory in CAVD.

Caspase 2 and Diabetes-Induced Osteoporosis

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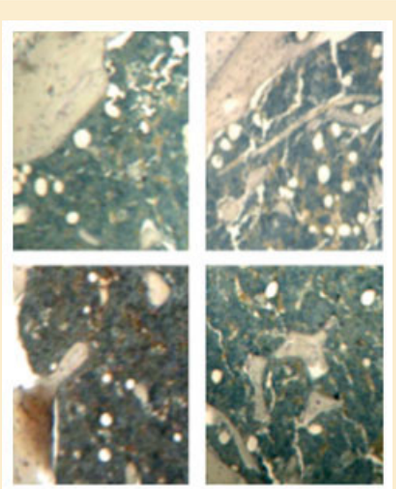

Identification of the molecular mechanisms accounting for diabetes induced bone loss is essential to developing effective therapeutic approaches. Clinical, experimental and epidemiological studies confirm that osteoporosis is a serious complication of type 1 (T1) diabetes. Type 1 diabetic bone loss occurs through suppression of osteoblast number and activity. Marrow adiposity is increased in diabetic mice. While the mechanism is unknown, the altered lineage selection (adipocytes over osteoblasts) does not cause the bone loss. Recent studies indicate reduced osteoblast viability during T1-diabetes onset in mice. Coe et al investigated the role of caspase-2, an initiator caspase involved in cell death, in diabetic bone pathology. Caspase-2 deficiency did not prevent diabetes-induced osteoblast death or bone loss. However, caspase-2 deficiency did prevent the 2-fold increase in marrow adiposity observed in wild type diabetic mice. These data indicate that caspase-2 is not required for diabetes induced osteoblast death. More importantly, the data suggest a novel role for caspase-2 in promoting marrow adiposity under stress or disease conditions.