FEATURES

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Progenitor Cells in Proximal Airway Epithelial Development and Regeneration

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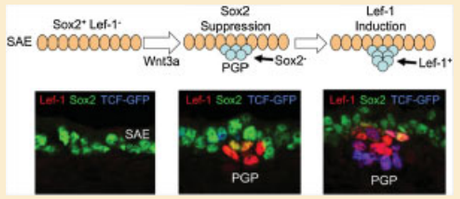
Several progenitor cell populations in the proximal airway have been identified to reside in confined microenvironmental niches including the submucosal glands (SMGs), which are embedded in the tracheal connective tissue between the surface epithelium and cartilage, and basal cells that reside within the surface airway epithelium (SAE). Current research suggests that regulatory pathways that coordinate development of the proximal airway and establishment of progenitor cell niches may overlap with pathways that control progenitor cell responses during airway regeneration following injury. SMGs have been shown to harbor epithelial progenitor cells, and this niche is dysregulated in diseases such as cystic fibrosis. However, mechanisms that regulate progenitor cell proliferation and maintenance within this glandular niche are not completely understood. The authors discuss glandular progenitor cells during development and regeneration of the proximal airway and compare properties of glandular progenitors to those of basal cell progenitors in the SAE. Further investigation into glandular progenitor cell control will provide a direction for interrogating therapeutic interventions to correct aberrant conditions affecting the SMGs in diseases such as cystic fibrosis, chronic bronchitis, and asthma.



The "Connexin" Between Bone Cells and Skeletal Functions

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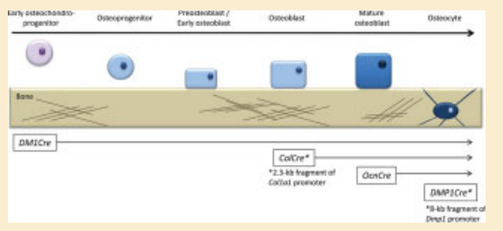
The processes of bone modeling and remodeling are crucial in the skeleton's functions as a supportive and protective structure, a mineral reservoir, and an endocrine organ. The coordination between bone cell activities (bone formation and bone resorption), necessary to maintain the integrity of the skeleton during these processes, is mediated at least in part by cell–cell and cell–environment interactions across gap junctions and hemichannels. The increasing number of genetically engineered Connexin 43 (Cx43) knockout and missense mouse models have provided insight into the complex and critical roles of Cx43-containing gap junctions and hemichannels in the development and turnover of the skeleton, in differentiation, activity and survival of the bone cell lineages, and in the cellular and molecular mechanisms by which Cx43 functions and assists in mediating cellular responses to stimuli in bone. Cx43 may be a potential therapeutic target in the future.



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Hepatocyte Nuclear Factor 4α (HNF4α) in Coordination With Retinoic Acid Receptors Increases *all-trans*-Retinoic Acid-Dependent CYP26A1 Gene Expression in HepG2 Human Hepatocytes

Reza Zolfaghari and A. Catharine Ross

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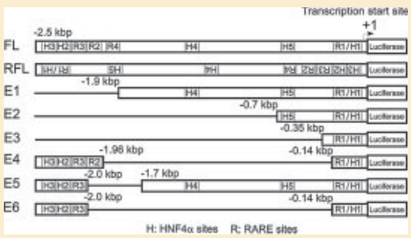

CYP26A1 expression is very highly induced by retinoic acid (RA) in the liver, compared to most other tissues, suggesting that a liver-enriched factor may be required for its physiological transcriptional response. HNF4α is a highly conserved liver-specific/enriched member of nuclear receptor superfamily. The authors hypothesized that HNF4α and RARs may cooperate in an RA-dependent manner to induce a high level of CYP26A1 expression in liver cells. Partial inhibition of endogenous HNF4α by siRNA reduced the level of RA-induced CYP26A1 mRNA in HepG2 cells. Cotransfection of HNF4α, with or without RARs, demonstrated RA-dependent activation of a human CYP26A1 promoter-luciferase construct. Analysis of a 2.5-kbp putative CYP26A1 promoter sequence identified five potential HNF4α DNA response elements: H1 located in a proximal region overlapping with an RAR element-1 (RARE1 or R1); H2 and H3 in the distal region, close to RARE2 (R2) and RARE3 (R3); and H4 and H5 in intermediary regions. In EMSA and ChIP analyses HNF4α and RARs binding in the proximal and distal CYP26A1 promoter regions was significantly higher in RA-treated cells. Mutational analysis of the individual HNF4α DNA-response elements identified H1 as the major site for HNF4α binding because mutation of H1 inhibited the promoter activity by ~90%, followed by H2 mutation with less than 40% inhibition. The results indicate that HNF4α coordinates with RARs in an RA-dependent manner to strongly induce CYP26A1 gene expression in the liver, which may explain the high level of response to RA observed in vivo.

MCP-1 as a Potential Target to Inhibit the Bone Invasion by Oral Squamous Cell Carcinoma

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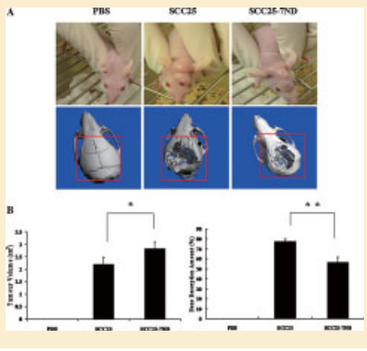

Bone invasion is a common complication of oral squamous cell carcinoma (OSCC), and the following study sought to explore whether suppressed expression of monocyte chemotactic protein-1 (MCP-1) can be used to inhibit the bone invasion by OSCC. Strong staining of MCP-1 protein was observed from 10 archival blocks of OSCC by immunohistochemistry (IHC). Real-time PCR showed MCP-1 mRNA was highly expressed by OSCC cell lines (SCC25, HN5, and Tca8113), and SCC25 cells had the highest expression. An expression construct of a dominant negative variant of MCP-1 with 7 amino acids truncated (7ND), in the vector pcDNA was used to transfect SCC25 cells, and resultant stabilized SCC25 cells (SCC25-7ND) were generated by antibiotic selection. 10% conditioned media (CM, supernatant) of SCC25-7ND cells efficiently inhibited the formation of human osteoclasts grown from $CD14^+$ monocyte subpopulation, comparing with 10% CM of SCC25 cells. Further, cells of SCC25 or SCC25-7ND were injected onto the surface of calvariae of nude mice to establish an animal model of bone invasion by OSCC. H&E staining showed well-differentiated OSCC was formed in both groups, tumour cells invading the bone while osteoclasts locating in typical resorption lacunae. TRAP staining indicated significantly fewer osteoclasts were found in calvariae with cells of SCC25-7ND in comparison to cells of SCC25. The data shows the relevance of MCP-1 to research on bone invasion by OSCC, and suggests the potential value of MCP-1 as a target to inhibit the common complication of oral cancer.