Stem and progenitor cells play important roles in organogenesis during development and in tissue homeostasis and response to injury postnatally. As the regenerative capacity of many human tissues is limited, cell replacement therapies hold great promise for human disease management. Pluripotent stem cells such as embryonic stem (ES) cells and induced pluripotent stem (iPS) cells are prime candidates for the derivation of unlimited quantities of clinically relevant cell types through development of directed differentiation protocols, that is, the recapitulation of developmental milestones in in vitro cell culture. Tissue-specific progenitors, including progenitors of endodermal origin, are important intermediates in such protocols since they give rise to all mature parenchymal cells. The authors focus on the in vivo biology of embryonic endodermal progenitors in terms of key transcription factors and signaling pathways. The aim is to apply the basic knowledge to achieve efficient and reproducible in vitro derivation of endodermal progenitors such as pancreas, liver and lung precursor cells.
HIGHLIGHTS

ARTEM PLISS, ANDREW J. FRITZ, BRANISLAV STOJKOVIC, HU DING, LOPAMUDRA MUKHERJEE, SAMBIT BHATTACHARYA, JINHUI XU, AND RONALD BEREZNEY

427 Non-Random Patterns in the Distribution of NOR-Bearing Chromosome Territories in Human Fibroblasts: A Network Model of Interactions
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The authors present a 3-D mapping in WI38 human diploid fibroblast cells of chromosome territories (CT) 13, 14, 15, 21, and 22, which contain the nucleolar organizing regions (NOR) and participate in the formation of nucleoli. The nuclear radial positioning of NOR-CT correlated with the size of chromosomes with smaller CT more interior. A high frequency of pairwise associations between NOR-CT ranging from 52% (CT13–21) to 82% (CT15–21) was detected as well as a triplet arrangement of CT15–21–22 (72%). The associations of homologous CT were significantly lower (24–36%). Moreover, singular contacts between CT13–14 or CT13–22 were found in the majority of cells, while CT13–15 or CT13–21 predominantly exhibited multiple interactions. In cells with multiple nucleoli, one of the nucleoli (termed "dominant") always associated with a higher number of CT. Moreover, certain CT pairs more frequently contributed to the same nucleolus than to others. The nonrandom pattern suggests that a large number of the NOR-chromosomes are poised in close proximity during the postmitotic nucleolar recovery and through their NORs may contribute to the formation of the same nucleolus. A global data mining program termed the chromatic median determined the most probable interchromosomal arrangement of the entire NOR-CT population. The interactive network model was significantly above randomized simulation and was composed of 13 connections among the NOR-CT. In conclusion, the NOR-CT form a global interactive network in the cell nucleus that may be a fundamental feature for the regulation of nucleolar and other genomic functions.

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KIMBERLY T. LEBLANC, MARIE E. WALCOTT, TRIPTI GAUR, SHANNON L. O'CONNELL, KIRTI BASIL, CHRISTINA P. TADIRI, APRIL MASON-SAVAS, JASON A. SILVA, ANDRE J. VAN WIJNEN, JANET L. STEIN, GARY S. STEIN, DAVID C. AYERS, JANE B. LIAN, AND PAUL J. FANNING

440 Runx1 Activities in Superficial Zone Chondrocytes, Osteoarthritic Chondrocyte Clones and Response to Mechanical Loading
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The authors addressed Runx1 functions, by examining expression in cartilage during mouse and human osteoarthritis (OA) progression and in response to mechanical loading. Spared and diseased compartments in knees of OA patients and in mice with surgical destabilization of the medial meniscus were examined for changes in expression of Runx1 mRNA (Q-PCR) and protein (immunoblot, immunohistochemistry). Runx1 levels were quantified in response to static mechanical compression of bovine articular cartilage. Runx1 function was assessed by cell proliferation (Ki67, PCNA) and cell type phenotypic markers. Increasing loading conditions in bovine cartilage revealed a positive correlation with a significant elevation of Runx1. Runx1 becomes highly expressed at the periphery of mouse OA lesions and in human OA chondrocyte clones’ where Runx1 colocalizes with Vcam1, the mesenchymal stem cell (MSC) marker and lubricin (Prg4), a cartilage chondroprotective protein. The OA induced cells represent a proliferative cell population, Runx1 depletion in MPCs decreases cell growth, supporting Runx1 contribution to cell expansion. The highest Runx1 levels in SZC of normal cartilage suggest a function that supports the unique phenotype of articular chondrocytes, reflected by upregulation under conditions of compression. The authors propose Runx1 co-expression with Vcam1 and lubricin in murine cell clusters and human clones of OA cartilage, participate in a cooperative mechanism for a compensatory anabolic function.

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