FEATURES

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Bisphosphonates and Osteoporosis Therapy

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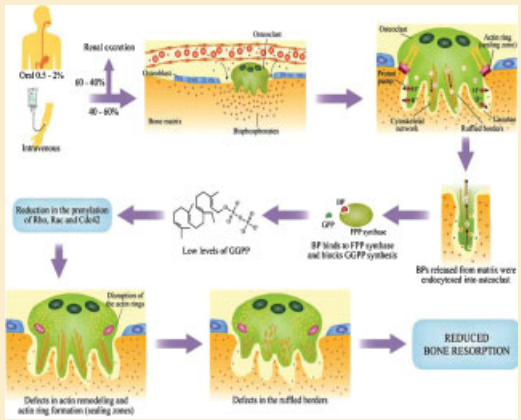

With about 50% of women and 25% of men affected worldwide, osteoporosis characterized by reduced bone density and increased risk of fractures has become a problem, especially in countries with an aging population. Probable causes for osteoporosis are mainly grouped into either an elevated bone resorption by osteoclasts or a decrease in osteoblastic activities. Current treatment thus far involves mainly the use of anti-resorptive drugs. Of particular interest, bisphosphonates, especially N-containing, have proven to be the most effective and with minimal adverse effects. Studies have shown that a newer generation of N-bisphosphonates have longer retention time in the bone and thus have longer efficacy even after treatment has stopped. Evidence from van Beek's group has demonstrated that the primary target for N-bisphosphonates is farnesyl PP synthase, which affects the generation of geranylgeranyl diphosphates that play a crucial role in the prenylation of Rho, Rac and Cdc42. This results in the disruption of the actin ring formation and eventually the ruffled borders, causing the detachment of osteoclasts from resorption sites. In view of the great bone-binding specificity of bisphosphonates, an attractive option might be to utilize the bone seeking property of bisphosphonates to introduce an anabolic drug. This could enhance bone formation in order to treat a wider spectrum of osteoporosis.

RUNX3 in GI Oncogenic Signaling

Kosei Ito

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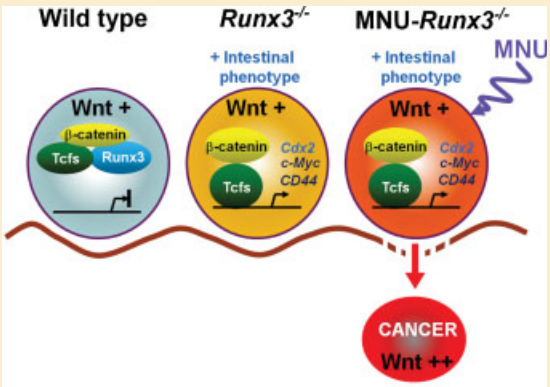

The reputation of RUNX3 as a strong candidate for a tumor suppressor originated from studies of gastric carcinogenesis using *Runx3*-deficient animal models and currently extends to a variety of other human cancers. Tumor suppressive TGFβ/BMPs and oncogenic Wnt signaling are known to regulate the function and development of adult epithelial stem cells and so-called cancer stem cells in the gastrointestinal epithelium. RUNX3 was found to function as a novel node of these major signaling pathways. Inactivation of RUNX3 is known to be caused by mutation, epigenetic gene silencing (promoter hypermethylation), or cytoplasmic protein mislocalization in more than 80% of gastric and 40% of colorectal cancers in humans. The phenotype of *Runx3*-deficient mice presented clearly suggests that RUNX3 is a gatekeeper and prompts exploration of the precise molecular mechanisms by which RUNX3 prevents oncogenesis in gastrointestinal and other human cancers.

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The Survivin Cell Cycle Network

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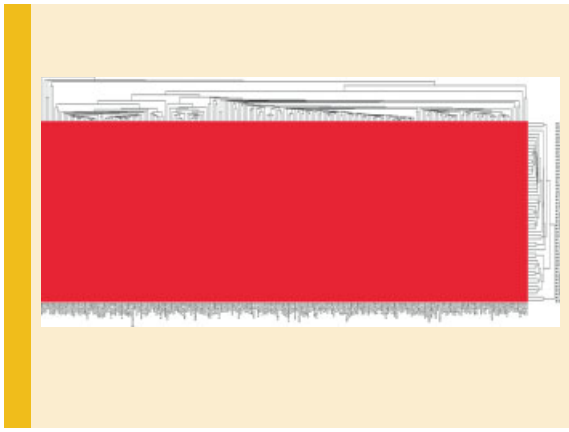

Survivin's (*BIRC5*) relationship with tumors is presented in several papers. However, understanding the molecular network and interpretation of the *BIRC5* cell cycle in "no-tumor" hepatitis/cirrhosis versus hepatocellular carcinoma (HCC) remains to be elucidated. Here, Wang et al construct and analyze the highly expressed *BIRC5* gene, within the context of both its activated and inhibited cell cycle network. Samples came from HCC versus "no-tumor" hepatitis/cirrhosis patients (viral infection HCV or HBV) from the GEO Dataset, by using a combination of gene regulatory network inference methods. Public databases used included Gene Ontology, KEGG, BioCarta, GenMapp, Intact, UniGene, and OMIM. By comparing different activated and inhibited *BIRC5* networks with GO analysis between "no-tumor" hepatitis/cirrhosis and HCC, results show that in the *BIRC5* cell cycle network, there is stronger nuclear protein binding but weaker cytoplasm protein binding in "no-tumor" hepatitis/cirrhosis, and stronger cytoplasm protein phosphatase binding but weaker ubiquitin-protein ligase activity in HCC. The authors infer that the *BIRC5* cell cycle induces more mitosis but less complex-dependent proteasomal ubiquitin-dependent protein catabolism as a result of increasing cell division (and therefore cell numbers) in "no-tumor" hepatitis/cirrhosis, and that there is more protein amino acid autophosphorylation but less negative regulation of ubiquitin ligase activity during the mitotic cell cycle as a result of increasing growth and cell volume in HCC.

Propagation of hESCs from Human Foreskin

Murali Krishna Mamidi, Rajarshi Pal, Nor Azah Binti Mori, Greetha Arumugam, Saratha Thevi Thrichelvam, Puteri J Noor, Hj. Mohamad Farouk Abdullah, Pawan Kumar Gupta, Anjan Kumar Das, Zubaidah Zakaria, and Ramesh Bhonde

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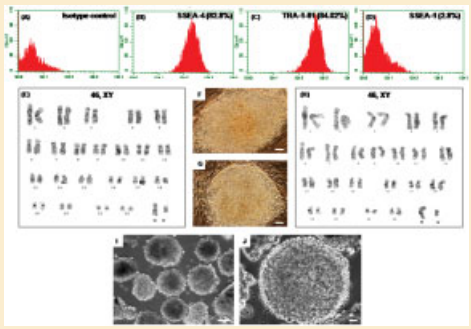

Since foreskin harbors a heterogeneous population of cells, Mamidi et al developed an elegant and innovative two step strategy to isolate pure populations of MSCs from the human foreskin. In the first stage, they separated cells positive for surface markers associated with MSCs (CD90, CD73 and CD166) by flow cytometry and cultured them *in vitro*. In the second step high glucose media (DMEM) was used to propagate those cells enabling them to preferentially grow the desired MSC population thereby withering out fibroblasts. Growth patterns, morphological features, gene profiling, cytoskeletal protein expression and tri-lineage differentiation potential of HF-MSCs confirmed their mesenchymal stromal cell status. Human feeders lay the foundation for eradication of animal-derived hESC culture system. Thus, Mamidi et al exploited the potential of human foreskin-derived mesenchymal-like stromal cells (HF-MSCs) to support self renewal and pluripotency of hESCs in a xeno-free setting. These novel feeders in the form of HF-MSCs were able to extend the undifferentiated state of the hESCs compared to that of traditional MEFs, perhaps via paracrine signaling. This co-culture system also improved formation of EBs giving rise to cell types representing all the three germ layers. Another interesting offshoot of this study is to demonstrate the differential susceptibility of HF-MSCs and fibroblasts to Mitimycin C as a simple and reliable criterion to distinguish between these two cell types. This may eliminate the need of CD marker analysis thus making this method economical. This culture system bears the potential to aid in the development of clinical-grade hESCs for regenerative medicine and drug screening. Foreskin can also serve as an additional alternative source of MSCs which is unconventional, noninvasive, and noncontroversial compared to bone marrow-derived MSCs and raises no ethical issues in terms of being biologically wasteful.