FEATURES

VOLUME 110 • NUMBER 1

Role of FGFs in Embryonic Stem Cell Differentiation

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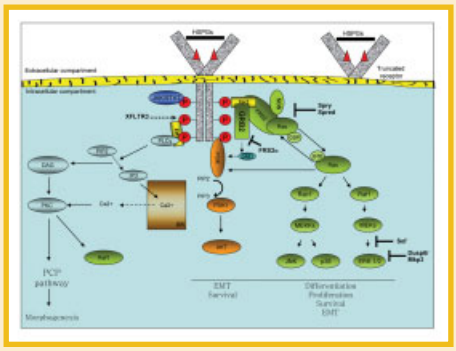
PUBLISHED ONLINE 24 MARCH 2010



Fibroblast growth factors (FGFs) and their receptors regulate a diverse range of biological processes. As a result, this pathway acts in different ways at multiple points in embryonic development. Thus, while the study of FGF signaling in development has come under intense scrutiny the activities of this pathway often appear contradictory. In this issue Villegas et al. explore the role of FGF signaling as a regulator of embryonic transitions in multiple lineages using Embryonic Stem (ES) cells as a model. They use data from the literature and their own laboratory to resolve the means by which this pathway regulates the decision between self-renewal, early steps in ES cell differentiation and embryos. Substantial evidence now available from work in ES cells is brought to bear on the role of this pathway as a regulator of pluripotency and an inducer of differentiation. As FGF signaling is also known as a major mediator of morphogenetic movements its roles during early lineage specification have been difficult to resolve. Villegas et al build a case for a direct role for this pathway in mediating transitions in differentiation toward all the major lineages of the mammalian embryo and ES cell differentiation.

Replication Initiation and DNA Topology: The Twisted Life of the Origin

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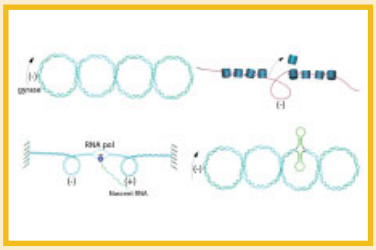
PUBLISHED ONLINE 8 MARCH 2010



Although the *cis*- and *trans*- elements that control genomic duplication have diverged during evolution, replication initiation in both prokaryotes and eukaryotes involves the same basic aspects, including recognition of replication origins, multi-protein complex assembly, helicase activation and loading of the replication machinery. Recent studies have shown that regulation of DNA topology is an important parameter during initiation of DNA replication in a variety of organisms. Here, Rampakakis et al. undertake an evolutionary approach, examining the role of DNA topology in the recognition and activation of replication origins across species and, interestingly, identify certain conserved features between bacteria, viruses, lower- and higher-eukaryotes. Furthermore, the implications of the participation of DNA topoisomerases in replication initiation in clinical matters such as cancer treatment and nuclear-transfer experiments are also discussed. Finally, the authors describe newly-developed, high-resolution techniques for the study of the function of DNA topoisomerases, which should facilitate obtaining the answers to existing and new biological questions.

Journal of Cellular Biochemistry

Role of RUNX2 Mutation in Cleidocranial Dysplasia

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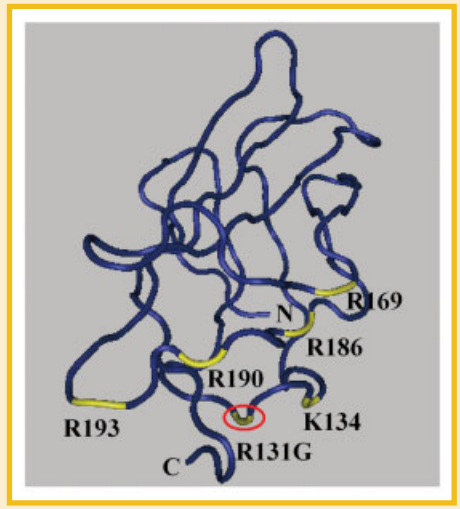
PUBLISHED ONLINE 11 MARCH 2010

Cleidocranial dysplasia (CCD) is caused by haploinsufficiency in *RUNX2* function. Many mutations of *RUNX2* have been identified. However, there are very few functional analyses. Han et al show the structure-function analyses of CCD caused by RUNX2 R131G missense mutation (RUNX2 ^{R131G}) with respect to the DNA binding activity, nuclear localization, heterodimerization with core binding factor-β (CBF-β), and target gene transactivation function. Results demonstrate that RUNX2^{R131G} has no DNA binding activity and target gene transactivation function. However, it contains functions of nuclear localization and heterodimerization with CBF-β. Han et al. provide a clear structure-function relationship of the single point mutation of RUNX2^{R131G} causing CCD in the context of full length *RUNX2*. Evidence provided indicates that retention of specific functions including nuclear localization and binding to CBF-β of the RUNX2^{R131G} mutation may render the mutant protein an effective competitor that interferes with wild type function.



T-Ag, Molecular Networks, and Medulloblastoma

Valentina Caracciolo, Marcella Macaluso, Luca D'Agostino, Micaela Montanari, Jonathan Scheff, Krzysztof Reiss, Kamel Khalili, and Antonio Giordano

PUBLISHED ONLINE 24 MARCH 2010

To date, the mechanisms underlying the biology of medulloblastoma (MB) remain unclear. Although somatic inactivation of the pRb/p105 retinoblastoma protein in combination with somatic or a germ-line TP53 inactivation leads to MB in a mouse model, there is no specific evidence of pathway alterations for the other two members of the retinoblastoma family, pRb2/p130 and/or p107 in MB. The human polyomavirus JCV is highly oncogenic when injected into the brain of experimental animals but there is no firm evidence that this virus plays a causal role in human neoplasia. Several studies relate the oncogenic properties of JCV mainly to its early protein large T-antigen, which is able to bind and inactivate both TP53 and Rb family proteins. Caracciolo et al. compared the protein expression profiles of p53, p73, pRb family proteins, and PCNA in different cell lines of mouse primitive neuroectodermal tumors, T-Ag-positive or T-Ag-negative, and in human MB cell lines. Evidence provided reveals that both in mouse PNET cells and human medulloblastoma cells the protein expression pattern and/or cellular distribution of pRb family, p53, p73 and PCNA may be altered by T-Ag presence and suggests that alterations of these tumor suppressor pathways cooperate in tumorigenesis in a cell type-specific manner.