FEATURES

VOLUME 115 • NUMBER 4

Emerging Role of MicroRNAs in Cancer and Cancer Stem Cells 605

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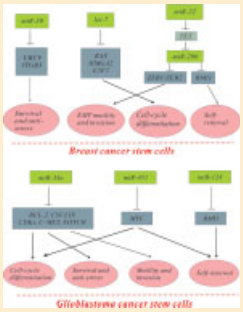
ACCEPTED MANUSCRIPT ONLINE 26 OCTOBER 2013

Cancer stem cells (CSCs), or cancer cells with stem cell properties, represent a small fraction of tumor bulk and are thought to be responsible for tumor formation and metastasis. However, the mechanisms of how CSCs are generated and regulated at the molecular level are poorly understood. Recent progress has highlighted the significance of microRNAs (miRNAs) in cancer progression and CSC function. The function and dysfunction of miRNAs in the development of cancer and CSCs have become a burgeoning area of intense research. A new finding has elucidated a mechanism of antagonistic miRNA crosstalk whereby one miRNA can inhibit another miRNA in regulating CSCs. The short review summarizes the current understanding of the regulatory mechanisms of miRNAs in cancer, CSCs and discusses the implications of targeting CSCs for cancer therapeutics.



Prospects on Strategies for Therapeutically Targeting Oncogenic Regulatory Factors by Small-Molecule Agents 611

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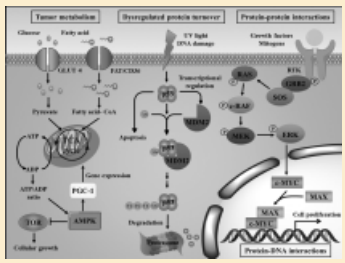
ACCEPTED MANUSCRIPT ONLINE 25 OCTOBER 2013

Although the Human Genome Project has raised much hope for the identification of druggable genetic targets for cancer and other diseases, the genetic target-based approach has not improved productivity in drug discovery over the traditional approach. In the prospect article, the authors provide an overview of potential drug targets related to the following four emerging areas: (1) tumor metabolism (the Warburg effect), (2) dysregulated protein turnover (E3 ubiquitin ligases), (3) protein-protein interactions, and (4) unique DNA high-order structures and protein-DNA interactions. Nonetheless, considering the genetic and phenotypic heterogeneities that characterize cancer cells, the development of drug resistance in cancer cells by adapting signaling circuitry to take advantage of redundant pathways or feedback/crosstalk systems is possible. The “phenotypic adaptation” underlies the rationale of using therapeutic combinations of targeted agents with cytotoxic drugs.



Journal of Cellular Biochemistry

Wnt Pathway in Osteosarcoma, from Oncogenic to Therapeutic

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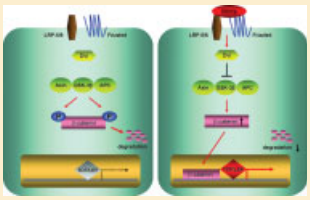
Yu Cai, Tiange Cai, and Yan Chen

ACCEPTED MANUSCRIPT ONLINE 5 NOVEMBER 2013



Osteosarcoma is the most common malignant bone tumor in children and adolescents. Although pathologic characteristics of this disease are clear and well established, much remains to be understood about this tumor, particularly at the molecular signaling level. Secreted signaling molecules of the Wnt family have been widely investigated and found to play a central role in controlling embryonic bone development, bone mass and postnatal bone regeneration. A variety of studies also suggest that the Wnt signaling pathway is closely associated with bone malignancies, including breast or prostate cancer induced bone metastasis, multiple myeloma, as well as osteosarcoma. The authors provide an overview of the role of the Wnt signaling pathway in osteosarcoma development and progression, highlighting the aberrant activation of the Wnt pathway in this bone malignancy. There is also discussion of the potential therapeutic applications for the treatment of osteosarcoma targeting the Wnt pathway.

Apoptosis Regulation at the Mitochondrial Outer Membrane

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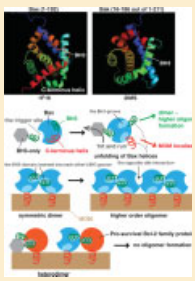
ACCEPTED MANUSCRIPT ONLINE 7 NOVEMBER 2013



Mitochondria play a critical role in apoptosis, or programmed cell death, by releasing apoptogenic factors from the intermembrane space. This process, known as mitochondrial outer membrane permeabilization (MOMP), is tightly regulated by the Bcl-2 family proteins. Pro-apoptotic Bcl-2 family members, Bax and Bak, change their conformation when activated by BH3 domain-only proteins in the family and permeabilize the MOM, whereas pro-survival members inhibit permeabilization. The precise nature of the apoptotic pore in the MOM is unknown, but is probably lipidic. Furthermore, it has been realized that there is another layer of MOMP regulation by a protein factor termed the catalyst in the MOM in order for Bax/Bak to achieve efficient and complete membrane permeabilization. Mitochondrial dynamics do not affect MOMP directly, but seem closely coordinated with MOMP for swift protein efflux from mitochondria. The review presents current views on the molecular mechanisms, the regulation of MOMP, and concludes with recent developments in clinical applications.