

FEATURES

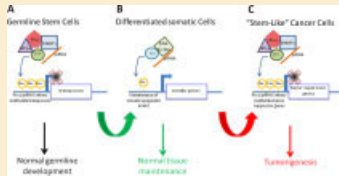
VOLUME 113 • NUMBER 2

piRNAs and Piwis in Cancer Epigenetics

Sara Siddiqi and Igor Matushansky

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PUBLISHED ONLINE 16 SEPTEMBER 2011

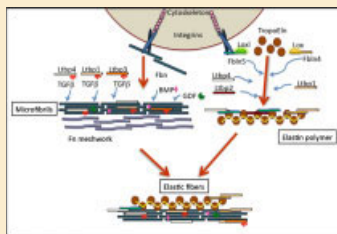


Piwi proteins are known to be critical for stem cell maintenance during development, especially in the germline, where they associate exclusively with a class of small RNAs called piwi-interacting RNAs (piRNA). Together, Piwi and piRNAs maintain genomic integrity by silencing transposon repeats through DNA methylation. Recently several groups have uncovered that Piwi family members and piRNAs are expressed in human cancers. The exact role that Piwis and piRNAs might play in tumorigenesis remains undetermined, however the importance of epigenetic regulation has been well studied in cancers and DNA methylation remains an important epigenetic regulatory mechanism that is perturbed during the tumorigenic process. This review provides a context for the recent studies that have identified Piwis and piRNAs outside the germline and in a cancer context. Moreover, this review offers a potential model by which Piwi expression may contribute to tumorigenesis.

LTBPs: Master Regulators of TGF- β

Vesna Todorovic and Daniel B. Rifkin

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TGF- β is an extraordinarily potent cytokine that regulates processes as varied as cell cycle progression, T cell differentiation and extracellular matrix maintenance. Abnormalities in TGF- β action affect development and tissue homeostasis, causing numerous pathologies including cancer, fibrosis and autoimmune disease. Thus, TGF- β action must be tightly controlled at many levels, including secretion and storage in the extracellular space. Mature TGF- β is secreted as part of a latent complex consisting of the growth factor, its propeptide and a separate gene product covalently bound to the propeptide called the latent TGF- β binding protein (LTBP). Todorovic and Rifkin have reviewed the published work describing the central role of LTBPs in modulating TGF- β functions, starting from the cytokine's folding and secretion, through its extracellular targeting and activation. The authors additionally describe how loss of individual LTBP isoforms (LTBP1-4) affects development and function of different organs in mice and humans. As expected, most of these phenotypes are the result of altered TGF- β activity. However, some LTBP-related pathologies stem from processes not directly dependent on TGF- β action, such as elastogenesis. Recent advancements in understanding of LTBP biology, as described in this review, have revealed the multifaceted nature of these proteins as they have been promoted from TGF- β chaperones to master regulators of this complex cytokine.

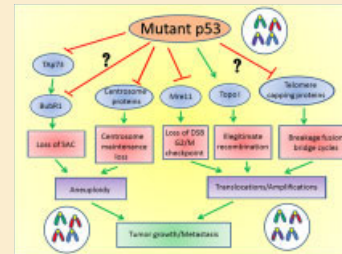
Mutant p53 and Genomic Instability

Walter Hanel and Ute M. Moll

433

PUBLISHED ONLINE 17 OCTOBER 2011

The tumor suppressor p53 is widely regarded as the most commonly mutated protein in human cancer. p53 commonly acquires missense mutation during tumor development or progression, with retention of the mutated protein inside the abnormal cells. The mutant p53 gain-of-function(GOF) field has made significant advances in recent years in elucidating novel mechanisms whereby p53 mutants, present in high amounts in tumor cells, exert additional pro-tumorigenic functions above and beyond the ones commonly associated with absence of p53. Numerous past studies have indicated that the presence of p53 mutants leads to higher levels of genomic instability by increasing aneuploidy, chromosomal translocations, and amplifications of genomic segments. Perturbation of interactions of key checkpoint proteins, including mre11, BubR1, p63 and p73, seems to account for these additional genome-destabilizing functions of p53 mutants. Evidence suggesting the nature of these interactions and their functional significance is presented. Novel mechanisms possibly contributing to mutant p53 induced genomic instability is also explored.



ERβ expression in ERα Negative Breast Cancer

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PUBLISHED ONLINE 17 NOVEMBER 2011

The role of estrogen receptor alpha (ERα) in breast cancer has been studied extensively and its expression is the most important predictive factor for benefit from endocrine therapy. However, the value of ERα's most closely related family member, estrogen receptor beta (ERβ), as a prognostic and predictive factor in breast cancer remains highly controversial due to the publication of conflicting reports. In this manuscript, Wu et al have demonstrated that much of this controversy likely results from the use of non-specific and/or insensitive ERβ antibodies. They also describe the development and characterization of a novel ERβ monoclonal antibody that recognizes not only full-length ERβ, but also its four splice variant forms. In addition, they identified a commercially available antibody that is highly specific and sensitive for only full-length ERβ. Of significant interest is their identification of ERβ expression in ERα negative breast tumors. The ability to accurately distinguish such tumors would allow for the identification of a new sub-group of patients who would potentially respond to endocrine therapy.

