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A novel CAPER⍰-MLL1 epigenetic complex functions high in the transcriptional hierarchy of breast cancer cells and its disruption restricts cancer phenotype - Pavan Kumar Puvvula - Weis Center for Research

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Abstract

Breast cancer is a constellation of diseases, with different molecular etiologies and signatures that determine cell behaviors and risk of metastasis and death. Despite significant progress in defining molecular signatures of different types of breast cancer, there are major gaps in understanding the mechanisms that regulate them. Nearly half of all cancer driver mutations are in genes encoding chromatin modifiers. The resulting epigenetic changes promote cancer cell hallmarks: Hence the ability to disrupt the function of epigenome regulators might hold a key to develop effective epigenetic therapies. We previously showed that CAPER⍰ (Coactivator of AP1 and Estrogen Receptor) prevents senescence of primary cells by regulating epigenetic marks. Since CAPER⍰⍰ is overexpressed in many cancers and interacts with other oncoproteins, we investigated its functions and partners in breast cancer. We discovered a novel complex between CAPER⍰ and the histone methyltransferase MLL1 (CAP/MLL1). The CAP/MLL1 complex is present in human luminal and basal breast cancers and BC cell lines, but not present in normal breast cells, primary mammary epithelial cells, nor is it detected in any of the other normal human tissues we have tested (brain, lung, liver, bone marrow, intestine). CAP/ MLL1 occupies and regulates thousands of targets genes and functions high in the hierarchy controlling transcription by regulating chromatin marks and expression of critical cell cycle genes in both luminal (ER+) and basal-like (ER-) BCs. Remarkably, we found that CAP/MLL1 occupies and regulates ~ 30 % of the 137 cancer “driver genes”3 in BCCs. Further, we have determined that the RRM3 domain of CAPER⍰ is critical for CAP/MLL1 complex formation and can function as a dominant-negative to disrupt MLL1 occupancy and H3K4 trimethylation of target genes, decrease expression of pro-proliferation and cancer progression genes, all of which result in decreased BC cell growth. An RRM3-derived cell penetrating peptide restricted the growth of BC cells but does not perturb the growth of primary cells, demonstrating cancer-specific therapeutic potential for CAP/MLL1 complex disruption in BC.

Compelling evidence have demonstrated that bulk tumors can arise from a unique subset of cells commonly termed “cancer stem cells” that has been proposed to be a strong driving force of tumorigenesis and a key mechanism of therapeutic resistance. Recent advances in epigenomics have illuminated key mechanisms by which epigenetic regulation contribute to cancer progression. In this review, we present a discussion of how deregulation of various epigenetic pathways can contribute to cancer initiation and tumorigenesis, particularly with respect to maintenance and survival of cancer stem cells. This information, together with several promising clinical and preclinical trials of epigenetic modulating drugs, offer new possibilities for targeting cancer stem cells as well as improving cancer therapy overall.

Cancer stem cells (CSCs) define a small, unique subset of cells with self-renewal ability and the capacity to generate the different cell types that constitute the whole tumor [1]. These cells are termed CSCs because of their “stem-like” properties commonly shared with normal tissue stem cells. Such properties include extensive self-renewal ability (symmetrical and asymmetrical) and differentiation capacity. It should be noted that a general capacity to differentiate is not a mandatory feature of CSCs and that the ability of CSCs to differentiate and repopulate the cell types found in the original tumor is of greater significance. More importantly, CSCs should demonstrate potent tumor-initiation capacity. This property is usually demonstrated by injecting limited number of CSCs into an orthotopic in vivo environment to generate the bulk tumor. Nevertheless, the concept of CSC is of significant importance as it highlights the need to eradicate the CSC populations to achieve an effective cure.

Epigenetic mechanisms have emerged as key players in cancer development which affect cellular states at multiple stages of the disease. During carcinogenesis, alterations in chromatin and DNA methylation resulting from genetic lesions unleash cellular plasticity and favor oncogenic cellular reprogramming. At later stages, during cancer growth and progression, additional epigenetic changes triggered by interaction with the microenvironment modulate cancer cell phenotypes and properties, and shape tumor architecture. We review here recent advances highlighting the interplay between epigenetics, genetics, and cell-to-cell signaling in cancer, with particular emphasis on mechanisms relevant for cancer stem cell formation (CSC) and function.

Breast cancer is the most common malignancy in women worldwide. The risk of breast cancer in women increases with age, and this is partly attributable to the accumulation of genetic lesions. Growing evidence demonstrates the role played by epigenetic modifiers and the tumor microenvironment in contributing to the increased risk of breast cancer. This chapter provides a comprehensive overview of the epigenetic regulatory signatures that impact the well-studied signaling pathways in breast tissues. Additionally, we will also delve into the therapeutic and diagnostic potential of noncoding RNAs in breast cancer. Tumorigenesis is a multistep process that involves accumulation of genetic mutations which confer a selective growth advantage to the cancer cells. However, an emerging area of research suggests that epigenetic changes complement these genetic mutation events and direct the cancer cells towards a full blown malignancy. Epigenetic changes refer to the modifications that do not occur on the primary nucleotide sequence of DNA (genetic mutations) but rather affect chromatin structure and function and are reversible in nature. Epigenetic changes involve histone modifications by enzymes that can “write” marks on histone tails such as acetyl and methyl transferases, enzymes that can “erase” these marks such as demethylases and deacetylases and a group of proteins that can “read” the chromatin marks and recruit other proteins to alter gene expression.