On Chromatin Remodeling in Mammary Gland Differentiation and Breast Tumorigenesis

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The role of epigenetic programs, including DNA methylation, chromatin (histone) modification, and noncoding RNAs, in cellular differentiation and tumorigenesis is well established and, with recent technological improvements, increasingly well understood at the molecular level. Increasing evidence also implicates epigenetic alterations in mediating the long-term effects of environmental risk factors such as diet, exposure to allergens, and various chemicals in various human diseases, including cancer, asthma, and mental disorders (Heijmans et al. 2009; Feinberg 2010). DNA and histone modification patterns have been the most extensively studied in embryonic stem cells (ESCs) (Mikkelsen et al. 2007; Meissner et al. 2008; Lister et al. 2009), whereas the roles of epigenetic changes in mammary gland development and in the differentiation of mammary epithelial stem cells have not been analyzed in either humans or laboratory animals.

Huang and Esteller (2011) provide an overview of epigenetic modifications and the technologies developed for their characterization and profiling studies performed in normal mammary epithelial cells and breast cancer. The role of epigenetic programs in regulating human mammary epithelial cell differentiation has not been defined, largely owing to difficulties and controversies associated with the purification and functional characterization of various progenitor and differentiated cells. As

discussed by Borowsky (2011) and Visvader and Smith (2011), currently there is no consensus on the identity of bipotential human mammary epithelial stem cells and luminal and myoepithelial progenitors. Further hampering progress in this area are the lack of technologies suitable for the characterization of genome-wide DNA methylation and histone modification profiles of small numbers of cells that can be recovered from tissue samples. Advances in single-molecule sequencing platforms and their application to epigenetic studies will likely solve this problem as methods allowing genome-wide gene expression, DNA methylation, and histone methylation profiling of minute cell numbers have recently been described (Adli et al. 2010; Gu et al. 2010; Ozsolak et al. 2010). The lack of defined human mammary epithelial stem cell hierarchy also makes the interpretation of epigenetic alterations identified in breast cancer problematic, owing to uncertainties about what normal cell to use for comparison. This is especially problematic when using bulk tissue samples, which is the case in the majority of published studies. Numerous genes have been identified as being epigenetically altered in breast cancer and some of these are likely to reflect true malignancy-associated events, but many events may just reflect cell-type-specific differences between normal and cancer tissues. Although this issue does not influence the use of

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these markers for cancer diagnosis and prognostication, it complicates attempts to understand their potential role in tumorigenesis.

One of the most exciting areas of investigation is the role of epigenetic alterations in the long-term effects of various life events on breast cancer risk. For example, in utero exposure to chemicals such as bisphenols (BPA) may increase breast cancer risk by inducing epigenetic alterations in mammary epithelial stem and progenitor cells. Similarly, the reduced risk of postmenopausal breast cancer associated with full-term pregnancy in young adulthood may also be explained by epigenetic alterations in stem cells. The development of new technologies and improved understanding of human mammary epithelial cell types will assure rapid progress in these areas.

Finally, the most important question is how we can use the knowledge we have gained for the prevention and treatment of breast cancer. Drug discovery efforts aimed at the identification of inhibitors of specific DNA- (and histone) modifying enzymes will likely lead to the discovery of clinically useful agents. The number of studies published on these topics in the past few years and the number of pharmaceutical companies pursuing epigenetic targets guarantee that progress in these areas will be made soon.

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