Environmental Epigenetics and Stem/Progenitor Cell Injury

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Environmental exposure to endocrine-disrupting agents, or xenoestrogens, can increase the risk of developing breast cancer. Animal and population studies indicate an imprinting phenomenon whereby early exposure of xenoestrogen may lead to tumorigenesis later in life. However, the molecular mechanism by which these environmental stressors transform breast genomes is not well understood. We suggest that epigenetic alteration, in the form of CpG island hypermethylation, transmits this imprinted information. Immature cells located in the stem/progenitor compartment of the human breast are prime targets of this environmental insult. For this U01 project, primary breast stem/progenitor cells will be exposed to xenoestrogens. Global analysis is expected to identify altered methylation status in human CpG islands being queried. These epigenetic events may be the direct results of exposing stem/progenitor cells to xenoestrogens. We will functionally determine whether the prolonged exposure of xenoestrogens to stem/progenitor cells disrupt the homeostasis of estrogen signaling and triggers an epigenetic perturbation cascade in its downstream targets. Polycomb repressors may be recruited to promoter CpG islands thereby attracting DNA methyltransferases to these promoters. Acquired DNA methylation, as a result of increased local methyltransferase activities, marks the heritable gene silencing. This CpG island hypermethylation induced by xenoestrogen exposure may be observed in clinical samples. The presence of these molecular alterations in primary breast tumors may constitute a xenoestrogen epigenotype(s). In this regard, patients exhibiting the epigenotype are likely exposed to xenoestrogens in their early years. In addition, low levels of these methylation changes may exist in normal looking mammary epithelial, leaving a field of cancerization in the human breast. These loci are future biomarkers for early breast cancer detection and are putative biosensors to environmental estrogens.