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Does epigenetic drift contribute to age-related increases in breast cancer risk?

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Breast cancer is a major public health problem among US women, for whom it is the most commonly diagnosed cancer, accounting for an estimated 232,670 new cases each year, and second leading cause of cancer-related mortality, with an estimated 40,000 deaths per year [1]. While some women, particularly those with predisposing genetic mutations, may develop breast cancer at a relatively early age, there is a nonlinear increase in breast cancer risk with age, with the vast majority of patients being diagnosed beyond their 50th birthday [2].

Epigenetic dysregulation, which can impact gene expression and result in loss of genomic stability, has long been recognized as a major component of the carcinogenic process for most solid tumor types, including breast cancer [3]. In fact, promoter hypermethylation, an event associated with transcriptional silencing, may even play a larger role in tumor

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suppressor gene inactivation than do somatic mutations; conversely, aberrant hypomethylation of a promoter region can reinstate transcriptional activity, offering a potential avenue for oncogene activation. With respect to cancer development, the mode of occurrence for these epigenetic manifestations has historically been viewed in the context of the somatic mutation paradigm: that is, that promoter hyper- or hypomethylation is an acutely occurring event that, when conferring a selective advantage, can lead to an expansion of damaged clones. As it turns out, however, at least some of these changes in promoter methylation status may be the result of a chronic accumulation of small departures from the norm rather than an acute event. It has been suggested that these small changes may stem from a more gradual process through a phenomenon termed 'epigenetic drift' [4], in which DNA methylation departs from baseline levels through random errors during the transfer of epigenetic marks to the daughter strand following DNA replication. Although the postmitotic setting of DNA methylation marks occurs with high fidelity (~95–99% precision) [5], the process is still imperfect and errors do happen. Rapidly proliferating cells, such as precancerous lesions, and/or dysregulated, rapid self-renewal in stem/progenitor cells may be particularly susceptible to such events due to an increased rate of mitotic divisions and weaker fidelity in transferring the methylation marks. When these random errors, even those that are selectively neutral (i.e. do not confer an immediate growth or survival advantage), arise in stem cells with unlimited replicative potential, they can be continuously propagated to all subsequent progeny of that stem cell, giving rise to epigenetic variability in the associated tissue(s). It has been proposed that such variability is an adaptive remnant from early simple organisms [6], predating the advent of meiosis, which worked to hedge against environmental influences by creating epigenetic diversity that allowed for selective adaptation. However, in contemporary complex eukaryotic organisms, such as humans, this random variation can result in epigenetic field defects if growth or survival advantages are realized. While a single erroneous methyl group attached to (or lost from) a cytosine in a gene promoter may not exert an obvious effect on gene expression, the random accumulation (or loss) of several such marks over time within the same promoter region in any given stem cell may. When such gradual accumulation of methylation occurs to the point of affecting gene expression, this could lead to stochastic selection if the resultant change confers a survival advantage, giving rise to clonal expansion of the altered cells. As such, it has been suggested that this process may contribute to the age-associated increased risk for development of breast cancer through random inactivation of key tumor suppressor genes or, in the case of hypomethylation, activation of oncogenes.

Of course other types of epigenetic marks can also fluctuate with age. For example, certain global histone modifications have been associated with aging in humans, such as alterations in trimethylation of H3K9, H3K4 and H4K20 [7]. However, as post-translational histone modifications tend to be relatively less stable and more challenging to interpret, with less direct evidence connecting age-related changes to driver epigenetic modifications in breast cancer, the focus of this commentary will remain on age-related drift of DNA methylation in the context of breast cancer risk.

The rate of epigenetic drift can vary by cell type and between individuals and is likely impacted by both endogenous and exogenous factors [7]. The extent to which these factors can affect this rate is presently unknown, although a sentinel paper by Fraga and colleagues

has offered strong evidence of an environmental influence on epigenetic variation [8]. The authors showed that epigenetic profiles in various tissues taken from identical twins were similar at a young age and became more divergent in older twins, and further, that these differences were most pronounced in older identical twins that had spent more time apart. Evidence has also begun to emerge that indicates that epigenetic control of certain genes, known as estrogen responsive genes, can be influenced by interactions between estrogen and estrogen receptor α (ER α) [9], which may suggest a possible hormonal influence on age-associated epigenetic changes. Adding an additional layer of complexity, the impact of these exogenous and endogenous factors may largely depend upon the cell type and underlying genomic context of the locus [10–12]. To this latter point, it has been observed that methylation of imprinted genes is more protected (although not exempt) from age-related changes [13], while loss of methylation is more likely to occur at repeat regions.

Based on the concept of gradual epigenetic changes over time, investigators have developed and validated methodologies for estimating cellular age using on DNA methylation patterns that work across human tissue types [14,15]. When these techniques are applied to breast cancer cells, tumor DNA appears to have a high degree of epigenetic age acceleration [14]. Moreover, estrogen and progesterone receptor (ER/PR)-positive breast cancers exhibit a much higher degree of age acceleration compared with that of ER/PR-negative tumors. This is not wholly surprising given that estrogen may influence methylation profiles, and also since these hormones can stimulate proliferation in these tumors, as it has been previously proposed that methylation marks, in a sense, may represent a sort of replicative clock given that the chance for errors increases with cellular proliferation [16].

Indeed, substantive evidence has begun to emerge beyond the solely theoretical conception that epigenetic drift across the life course could impact cancer risk. It has previously been observed that promoter methylation of colorectal-cancer-related genes gradually increase with age in benign colonic epithelium [17]. More recently, Brock Christensen's laboratory used two independent publicly available Infinium HumanMethylation27 BeadArray data sets for non-pathologic breast tissue to identify age-related methylation loci [18]. In doing so, they identified 204 age-related CpG loci that were associated with age and directionally consistent in both data sets and found that these loci were enriched for those residing within a CpG island (which were more likely to exhibit a gain in DNA methylation) and polycomb gene targets, which is consistent with the observations of others [19]. Importantly, 24 of these loci were differentially methylated in malignant breast tumors in a direction that was consistent with the age-related changes, albeit to a greater extent than in the non-pathologic tissue. In further support of a role of epigenetic drift and subsequent stochastic selection in the genesis of breast cancer, there are indications stemming from studies of fine needle aspiration biopsies that the degree of methylation in the promoter regions of tumor suppressor genes that are commonly hypermethylated in breast cancer (including *BRCA1*) steadily increase with age in benign breast epithelium [16,20].

The emerging evidence seems to suggest that we need to modify our way of thinking about the accumulation of epigenetic insults in the context of cancer development, and consider that some such aberrations may in fact arise through a slow, chronic process, where a gradual and random accumulation (or possibly loss) of DNA methylation can eventually

impact gene expression and give rise to stochastic clonal selection. To be clear, we are by no means proposing that all age-related increases in cancer risk can be attributed to epigenetic drift. It is crucial to note that the impact of aging on cancer risk likely stems from a very complex combination of contributing factors (e.g. genetic programming, cumulative environmental exposures, change in hormonal milieu, accumulation of somatic mutations, telomere shortening, loss of fidelity of key cellular processes etc.). Further, the relative importance of different exogenous and endogenous factors varies by cancer type, which is highlighted by the differing age-specific incidence trajectories for various solid tumors. While there is clearly much more work to be done on the subject, the recent literature seems to support the notion that epigenetic drift may explain at least a portion of the observed nonlinear age-related increases in breast cancer risk. Of particular interest from a cancer-prevention standpoint is the extent to which potentially modifiable environmental and behavioral factors contribute to the pace of epigenetic drift. Such information could provide new avenues for development of breast cancer prevention strategies that could help to mitigate the impact of this devastating disease.

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Biography

Scott M Langevin

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