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Editorial

Mammary stem cell number as a determinate of breast cancer risk

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See related research article by Savarese *et al.*, <http://breast-cancer-research.com/content/9/3/R29>

Abstract

The 'cancer stem cell hypothesis' posits that cancers, including breast cancer, arise in tissue stem or progenitor cells. If this is the case, then it follows that the risk for developing breast cancer may be determined in part by the number of breast stem/progenitor cells that can serve as targets for transformation. Stem cell number may be set during critical windows of development, including *in utero*, adolescence, and pregnancy. The growth hormone/insulin-like growth factor-1 axis may play an important role in regulating breast stem cell number during these developmental windows, suggesting an important link between this signaling pathway and breast cancer risk.

In the previous issue of the journal, Savarese and coworkers [1] propose that there is a relationship between breast stem cell number *in utero* and subsequent risk for breast cancer development. They also suggest that assessing the number of hematopoietic stem/progenitor cells may provide a surrogate measure of this risk.

Recent evidence has provided support for the 'cancer stem cell hypothesis', which holds that cancers originate in tissue, stem, or progenitor cells; hence, carcinogenesis is driven by a small group of cells that retain stem cell properties [2]. These properties include self-renewal as well as differentiation. It follows that the risk for cancer development might be directly related to the size of the stem cell pool and its mitotic activity. Development of the mammary gland in both humans and rodents is regulated at three critical stages of development: during embryogenesis, puberty, and pregnancy. During embryonic development a rudimentary mammary gland is formed under the influence of maternal and placental hormones. Full mammary development is achieved during puberty, with further morphogenetic modifications occurring during pregnancy, lactation, and involution. Changes in the hormonal milieu during each of these stages of development may regulate the size of the breast stem cell pool, and so they may influence the development of carcinogenesis.

Both epidemiologic and experimental evidence has supported the hypothesis that the *in utero* environment influences cancer risk in offspring later in life. A number of studies have demonstrated a strong link between birth weight and breast cancer risk in offspring, as well as a strong association of maternal levels of insulin-like growth factor (IGF)-1 and birth weight [3]. This has led to the hypothesis, first articulated by Trichocopoulos [4], that levels of hormones such as IGF-1 and steroid hormones *in utero* may influence subsequent breast cancer risk by regulating the number of mammary stem cells. Indirect support for this stem cell based hypothesis was provided in a pilot study of 40 umbilical cord blood samples, which demonstrated a strong positive link between maternal levels of IGF-1 and steroid hormones and the number of hematopoietic stem cells in cord blood.

The study conducted by Savarese and coworkers [1] reported in this journal confirms and extends these studies by demonstrating a strong correlation of cord blood plasma levels of both IGF-1 and estradiol with the number of hematopoietic stem and progenitor cells. Because previous studies have demonstrated a strong link of both birth weight and IGF-1 levels *in utero* with subsequent risk for breast cancer, the authors propose that this link occurs through regulation of breast stem cell numbers by these hormones. This conclusion is based on the assumption that common mechanisms regulate the number of hematopoietic and breast stem cells.

Although no direct evidence for such linkage is provided in the report or elsewhere, it is plausible to posit common regulatory mechanisms for adult stem cells in different tissues. Indeed, there is evidence that the growth hormone/IGF-1 axis may serve as a master regulator, coordinating stem cell numbers in multiple organs. Growth hormone is an anabolic pulsatile hormone that is secreted by the pituitary gland. Growth hormone is the major regulator of IGF-1

IGF = insulin-like growth factor.

synthesis and secretion by the liver as well as by peripheral tissues. In addition to the indirect effects of growth hormone on cell proliferation mediated by IGF-1, it also acts directly on cells that express the growth hormone receptor through stimulation of JAK/STAT (Janus kinase/signal transducer and activator of transcription) pathway signaling [5]. Furthermore, recent evidence suggests a role for growth hormone in regulation of the hematopoietic system [6]. Interestingly, we previously reported that growth hormone receptor is over-expressed in human mammary epithelial stem/progenitor cells grown in mammospheres as compared with cells induced to differentiate by attachment to a collagen substratum [7].

The role played by growth hormone in mammary development is demonstrated by the rudimentary breast development seen in growth hormone receptor knockout mice [8] and by the observation that acromegalic patients who have increased growth hormone levels exhibit increased risk for cancers, including breast cancer [9]. Furthermore, it has recently been demonstrated that breast cancer risk correlates strongly with height at puberty, a characteristic that is strongly correlated with growth hormone levels [10]. In addition to growth hormone secretion by the pituitary gland, there is evidence for production of growth hormone by differentiated mammary epithelial cells in dogs, rats, and women [11]. Furthermore, this local growth hormone production is regulated by high levels of progesterone, which occur during pregnancy. Breast tissue growth hormone production may thus contribute to the high levels of this hormone observed during the third trimester of pregnancy.

The report by Savarese and coworkers [1], together with other epidemiologic studies, suggests a unifying hypothesis for breast cancer risk related to stem cell number, which is regulated by the growth hormone/IGF-1 axis. This signaling network may play a role in regulating mammary stem cell number and proliferation during key windows of mammary development, including *in utero*, adolescence, and pregnancy. Furthermore, if breast cancers originate in mammary stem/progenitor cells, then it follows that interventions aimed at regulating mammary stem cell number or proliferation represent a rational strategy for breast cancer prevention.

Competing interests

The authors declare that they have no competing interests.

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