Age is the number one risk factor for breast cancer, with only 5% of all breast cancers occurring in women under 40 years old. Age-specific incidence of invasive breast cancer increases from less than 1.5% at age 40, to about 3% at age 50 and over 4% by age 70 in American women. More recently, new research findings have related more malignant invasive breast cancers to a cell origin of more basal or stem-like sources. To identify how aged stem/progenitor cells might serve as the cells of origin of various types of breast cancer, understanding the normal aging process of the breast tissue is an important prerequisite, yet no study has examined the effects of aging on mammary stem cells or their niches. This proposed study will involve the use of the mouse model to examine the changes in mammary stem/progenitor cell function and stem cell niche with age. Findings from this project will help identify the underlying mechanisms for the regulation of mammary stem cell self-renewal, proliferation, and differentiation during the normal aging process, enhance our understanding of the mechanisms of adult stem cell aging, and provide critical new insight into other normal and pathologic processes associated with aging stem cells.

Aim 1 – To determine the effect of aging on mammary stem/progenitor cell function. Our preliminary data have demonstrated that the fraction of the stem cell enriched population increased with age while the fraction of the progenitor compartment decreased with age in mammary glands from the C57BL/6 mice (e.g., compare 4 to 28-month-old animals). In this aim, we will further investigate the function of stem/progenitor cells during progressive aging in mammary epithelial cells of various age groups with our newly developed in vitro mammosphere assay and 2D or 3D colony formation differentiation assay, and in an in vivo single mammosphere transplantation assay in cleared mammary fat pads, to measure the self-renewal function of mammary stem and progenitor cells as a function of age. We will also determine the levels of steroid hormone receptors and DNA double strand break repair capacity in each compartment of the mammary stem/progenitor cells during progressive aging to elucidate how aging may alter hormone receptor expression and DNA repair function. The outcomes will shed light on age-associated cellular and molecular alterations in mammary stem/progenitor cells that may play key roles in mammary tumorigenesis.

Aim 2 – To determine the effect of aging on the stem cell niche and how the niche interacts with stem cell function. It is highly likely that the dysfunctional self-renewal and differentiation capacities of aging stem/progenitor cells may in part result from deregulated signals of the aged niche. In fact, studies with muscle satellite cells (the muscle stem cells) have shown that their regenerative capability is severely affected by the aging of their local niches. Thus in this aim we will examine the changes of frequency and differentiation capabilities in adipose-derived mammary stromal cells (also called mammary stromal stem cells or preadipocytes) with age. We will also test
how the aged niche affects stem cell function using the in vivo cleared mammary fat pad transplantation assay with reconstituted old mammary stroma.

Aim 3 – To determine the effect of genotoxin in combination with aging on mammary stem cell function and transformation. Since age is the number one risk factor for breast cancer, this aim will thus test the hypothesis that age-related increase in breast cancer incidence is intimately connected to the increased susceptibility of aging mammary stem/progenitor cells to transformation by genotoxin in comparison to young mammary stem/progenitors. Our preliminary studies have shown increased in vitro mammosphere formation and dysplastic mammary ductal formation in vivo by mammary stem cells from old mice treated with N-Methyl-N-Nitrosourea (MNU). In this aim, we will further examine how in vivo treatment with carcinogens, including irradiation, affects stem/progenitor cell proliferation and self-renewal in young and old mammary glands, and whether the old mammary stem cell is more susceptible to neoplastic transformation upon genotoxin induction (through epithelial and/or stromal components) when transplanted into young or old stroma reconstituted cleared mammary fat pads.

BD FACS™ sorting constitutes a significant part of our project, and we thus will use many antibodies from BD Biosciences.

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