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Role of mammary gland stem/progenitor cells in tumorigenesis

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Aging is a major risk fact for breast cancer. Recent research implicated that adult mammary stem cells (MaSCs) might be responsible for the initiation and progression of certain types of breast cancer. In this study, MaSC-enriched basal cells were utilized for the evaluation of MaSC frequency and function during aging by *in vitro* mammosphere formation and 3D-ECM sphere differentiation assays and by *in vivo* cleared mammary fat pad transplantation (IVT) as we reported recently. We found that the basal-to-luminal cell ratios analyzed with flow cytometry and the frequency of MaSCs analyzed with the *in vitro* assays increased steadily with increasing age in various strains of mice. Subsequent IVT using mammosphere or 3D-ECM structures formed by young (2-4 months) or old (25-32 months) MaSCs derived from C57BL/6 mice showed that the regenerated glands from old MaSCs had significantly higher number of spontaneous atypical ductal hyperplastic lesions than those from young MaSCs. These findings indicate that aged MaSCs can serve as the cell of origin for early neoplastic transformation in breast tissue. Subsequent whole genome transcriptome analysis with the second generation sequencing revealed age-associated differential expression of genes involved in immune, inflammatory, and wounding responses in both mammosphere-forming cells and stromal cells suggesting that these may be the main cellular processes contributing to the dysfunctional MaSC phenotypes. Consistently, short-term (5-10 days) treatment of old C57BL/6 mice with rapamycin, an anti-inflammation drug, reversed phenotypic changes associated with aged mammary gland. Histological analysis of regenerated glands by aged MaSCs derived from control and rapamycin-treated mice showed a significant decrease of early neoplastic lesions in rapamycin-treated group. In conclusion, our findings suggest that aging causes MaSC to form early neoplastic lesions, which can be inhibited by rapamycin treatment.

Biography

LuZhe Sun has received his PhD in Physiology from Rutgers University and UMDNJ-Robert Wood Johnson Medical School in 1990 and obtained his Postdoctoral training in Baylor College of Medicine in the US. He is currently Professor, Dielmann Endowed Chair in Oncology, and Associate Director for Basic Research at NCI-Designated Cancer Center. His research is focused on investigating molecular mechanisms of tumorigenesis and metastasis, and novel experimental therapeutics in various models of carcinomas. His research has been supported with multi-million dollar grants from NIH, DOD, CPRIT and other private foundations. He is an elected AAAS Fellow.

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