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Review Article

The Effects of Obesity on Adipose-Derived Stromal Cells and Impact on Breast Cancer Tumorigenesis

Amy L Strong[1], Matthew E Burow[2], Jeffrey M Gimble[1,3] and Bruce A Bunnell[1,4]*

[1]*Center for Stem Cell Research and Regenerative Medicine, Tulane University School of Medicine, USA*
[2]*Department of Medicine, Tulane University Health Sciences Center, USA*
[3]*LaCell LLC, USA*
[4]*Department of Pharmacology, Tulane University School of Medicine, USA*

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***Corresponding author**

Bruce A Bunnell, Tulane University School of Medicine, 1430 Tulane Avenue, SL-99, New Orleans, Louisiana, USA, Tel: (504) 988-7711; Fax: (504) 988-7710; Email: bbunnell@tulane.edu

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Abstract

Obesity increases the incidence of many types of cancers, and as the incidence of obesity continues to rise, the frequency of obesity-associated cancers will likely increase. While obesity increases postmenopausal breast, endometrial, pancreatic, colorectal, and renal carcinomas, understanding the effects of obesity on postmenopausal breast cancer remains a priority, as it is the most commonly diagnosed cancer in women. Obesity is characterized by the expansion of adipose tissue, resulting in inflammation of the adipose tissue. This inflammatory environment may, in turn, alter the Adipose-derived Stromal Cells (ASCs) within adipose tissue, influencing their effects on breast cancer cells. Recent studies demonstrate that ASCs in obese patients traffic through the circulation and into the tumor more frequently compared to lean patients. Furthermore, once at the tumor site, ASCs have been shown to alter the gene expression profile of cancer cells, leading to the expansion and enhanced invasiveness of these cancer cells. Together, these results suggest that obesity alters the ASCs within the tumor stroma, which in turn alters the cancer cells and leads to the development of aggressive breast cancer. Future studies investigating the precise mechanisms by which ASCs isolated from obese patients enhance breast cancer cell growth and the development of new therapies to target these ASCs will decrease the morbidity and mortality of obesity-associated breast cancers.

ABBREVIATIONS

WAT: White Adipose Tissue; TNF-α: Tumor Necrosis Factor-alpha; IL-6: Interleukin-6; MCP-1: Monocyte Chemotactic Protein-1; MMP-2: Matrix Metalloproteinase-2; PAI-1: Plasminogen Activator Inhibitor-1; ASCs: Adipose-derived Stromal Cells

INTRODUCTION

Obesity is the excessive accumulation of adipose tissue, resulting in physical and psychological health impairments. The prevalence of obesity in the United States has tripled over the past decades, with more than one third of adults meeting the criteria for obesity [1,2]. Recently, the World Cancer Research Fund used a standardized approach to review the effects of obesity on cancer incidence and mortality [3]. This study determined that increased adiposity was associated with increased risk of multiple types of cancers, including postmenopausal breast, endometrial, pancreatic, colorectal, and renal cancers [4]. With regard to breast cancer, approximately 18-20% of postmenopausal breast cancer cases are attributable to obesity [5-7]. As postmenopausal breast cancer is the second leading cause of cancer-related deaths in women, understanding the influence of obesity on the development and progression of this disease remains a major healthcare concern.

Expansion of adipose tissue in obesity

The enlarged adipocytes, which is a hallmark of obesity results in increased distance between the adipocytes and the surrounding vasculature. Large adipocytes can grow an upwards of 100-200 μm in diameter often exceeding the normal diffusion distance of oxygen into tissue [8,9]. Studies have demonstrated that oxygen concentration is close to zero at 100 μm distance

from the vasculature [8]. Furthermore, studies have shown that despite the substantial expansion of adipose tissue in obese humans, neither cardiac output nor total blood flow to the adipose tissue is increased [10,11]. All of these factors lead to a hypoxic environment in the adipose tissue [12-15]. Moreover, in obese mice, reduced blood perfusion and hypoxia appeared to be particularly pronounced in the White Adipose Tissue (WAT) [16]. The hypoxic environment in WAT triggers an inflammatory response in an attempt to increase blood flow and stimulate angiogenesis. However, it is insufficient to compensate for the expanding adipocytes, consequently resulting in chronic low-grade inflammation [17-19]. This chronic inflammation induces the secretion of several pro-inflammatory cytokines (tumor necrosis factor-α and IL-6), chemokines (MCP-1), proteases (MMP2), and protease inhibitor (PAI-1) by immune cells and endothelial cells, which conditions the cells within the Stromal Vascular Fraction (SVF) of adipose tissue and ultimately results in adipose tissue dysfunction [20,21].

Alterations to ASCs in Obesity

The SVF of adipose tissue is composed of ASCs, preadipocytes, endothelial progenitor cells, and immune cells. As the major component of the stromal layer of tumors, ASCs have drawn significant attention. Recent studies have reported that hypoxia induced by obesity is sufficient to increase the frequency of ASCs in circulation. Obese mice demonstrated an increased circulation of ASCs isolated from WAT compared to lean mice [22]. Furthermore, Bellows et al. demonstrated that patients who were obese displayed increased mobilization of ASCs in the circulation [23]. Moreover, ASCs isolated from subcutaneous WAT of the abdomen of obese women were found to be more migratory towards breast cancer conditioned media than the ASCs from lean women of the same adipose depot site [24]. Furthermore, the mechanism by which the trafficking of these ASCs was enhanced was attributed to increases in MMP and calpain expression [24]. Together, these studies support conditioning of ASCs by the local environment, resulting in robust alterations to ASCs with respect to their ability to circulate and home to cancer cells.

ASCs altered by obesity and breast cancer

Recently studies have focused on understanding the potential implications of this enhanced migratory ability of ASCs on the tumor and tumor stroma. Studies have shown that once recruited to the tumor site, ASCs increase the proliferation of breast cancer cells and enhance the invasion and metastasis of cancer cells [25]. Utilizing ASCs isolated from the breast and from abdominal adipose tissue, Walter et al. demonstrated that the secretion of IL-6 from ASCs enhanced the migration and invasion of breast cancer cells [26]. Additionally, studies have shown that ASCs isolated from obese subjects further enhanced breast cancer cell proliferation and tumor volume through altered gene expression [27]. Genes involved in cell cycle regulation and apoptosis were over expressed following co-culture with ASCs from obese patients [27]. Furthermore, ASCs isolated from obese patients were found to enhance the expression of angiogenic and metastatic genes in breast cancer cells [27]. Collectively, these studies suggest that ASCs isolated from obese patients increase the aggressiveness of breast cancer cells and lead to the diagnosis of more advance staged breast cancer in obese women.

CONCLUSION

Multiple independent studies have demonstrated that obesity is directly linked to an increased risk of developing postmenopausal breast cancer. ASCs derived from adipose tissue of obese subjects possess novel biologic properties and these altered ASCs influence the gene expression profile of breast cancer cells, contributing to enhanced tumorigenesis. In order to reduce the incidence of obesity-associated postmenopausal breast cancers, additional studies are necessary to investigate the precise mechanism(s) by which obesity alters the ASCs within the tumor stroma. By identifying the alterations in the ASCs, it may be possible to utilize these ASCs for targeted cancer therapies in obese women. Furthermore, by targeting the complex interaction between cancer cells and ASCs, it will be possible to reduce the morbidity and mortality caused by obesity-associated breast cancer.

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Conflict of Interest

J.M.G. is co-founder and chief scientific officer for LaCell LLC.

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