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Obesity and Triple-Negative Breast Cancer: Untangling the Connection

Brusi Kola, Sooraj Kakkat, Prabhat Suman, Sarah Atterberry, Aris Richter, Kennedy Sawrie, Rishi Gupta, Adhvika Mahadevan, Cindy Nelson, Debanjan Chakroborty, Chandrani Sarkar
Mitchell Cancer Institute, University of South Alabama, Mobile, Alabama

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Introduction

Breast cancer (BC) is the most commonly diagnosed cancer and the second leading cause of cancer-related mortality among women in the US. Obesity, defined by excessive and abnormal accumulation of body fat, is a well-established risk factor for hormone receptor–positive BC, particularly in postmenopausal women. However, the relationship between obesity and triple-negative breast cancer (TNBC)-a highly aggressive and therapeutically challenging molecular subtype of BC-remains poorly understood. To address this gap, we analyzed clinical and experimental data to investigate how obesity influences TNBC biology. Using patient data, we found that obesity is more prevalent among younger (<50 years) than older (≥50 years) women with TNBC. Furthermore, tumors from obese TNBC patients exhibited significantly higher Ki-67 levels compared to those from grade-matched normal-weight patients. Consistent with these clinical observations, our mouse model of diet-induced obesity demonstrated that obese mice develop tumors with shorter latency and accelerated growth compared to lean controls. Immunohistochemical analysis further revealed that tumors from obese mice display markedly elevated proliferative capacity, along with angiogenesis and lymphangiogenesis, relative to those from lean mice. Future investigations focusing on identifying the factors within the tumor microenvironment that drive accelerated and aggressive tumor progression in obese mice may uncover novel therapeutic opportunities for obesity-associated TNBC.

Methods and Materials

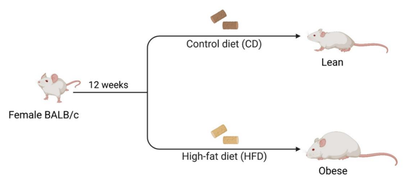


Figure 1. A mouse model of diet-induced obesity. Female BALB/c mice were fed either a control diet (CD) or high-fat diet (HFD) for 12 weeks. The HFD provides 60% calories from fat.

Methods and Materials

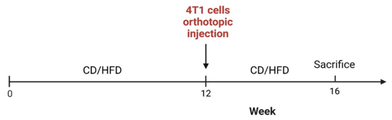


Figure 2. Experimental timeline. Mice were fed their respective diets for 12 weeks. After 12 weeks, mice were transplanted orthotopically with 10^6 4T1-luc2 cells in the fourth mammary fat pad. Mice continued to receive their diets until the sacrifice time (week 16).

Results

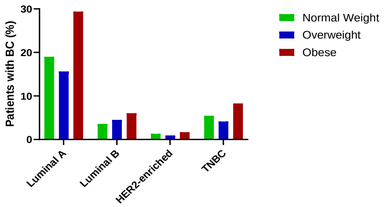


Figure 3. BC subtypes by body mass index (BMI) category. Obese patients (BMI≥30) constitute the largest proportion of individuals across all major BC subtypes, including TNBC.

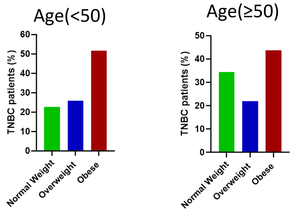


Figure 4. BMI distribution across different age groups in patients with TNBC. Obesity prevalence is higher in younger (<50 years) than older women with TNBC.

Results

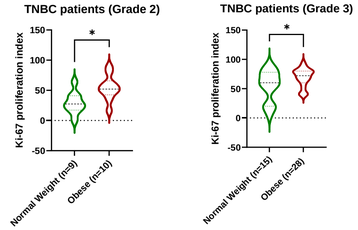


Figure 5. Ki-67 levels in tumors from normal weight and obese TNBC patients with different histological grades. Tumors from obese TNBC patients are characterized by significantly higher Ki-67 levels relative to those from normal weight grade-matched controls (*$p<0.05$).

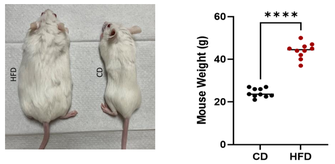


Figure 6. Effect of a HFD on mouse body weight**.** Mice fed the HFD (n=10) for 12 weeks have significantly higher body weights than mice that were kept on a CD (n=10) (****$p<0.0001$).

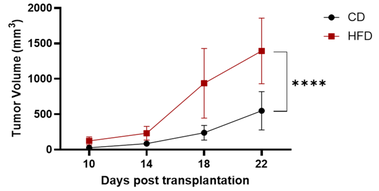


Figure 7. Effect of obesity on tumor size. Tumors of obese mice (n=10) grow at a much faster rate than tumors of lean mice (n=10). Tumor size was measured using digital calipers (****$p<0.0001$).

Results

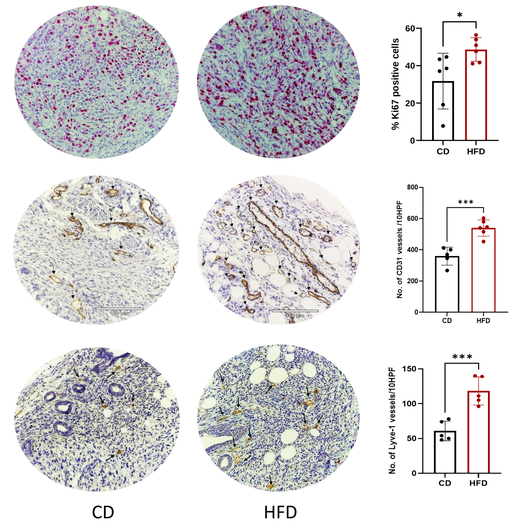


Figure 8. Effect of obesity on tumor proliferation, angiogenesis and lymphangiogenesis. Tumors from obese mice exhibit enhanced proliferative activity, along with increased blood and lymphatic vessel density compared to those from lean mice. Each dot represents an individual mouse (*$p<0.05$,***$p<0.001$). Magnification 200x. HPF= High-power field.

Conclusions

Obesity prevalence is higher among younger (<50 years) than older (≥50 years) women with TNBC. TNBC tumors from obese women exhibit remarkably higher Ki-67 levels than those from grade-matched normal weight women. Obesity enhances tumor proliferation, angiogenesis and lymphangiogenesis in the syngeneic 4T1 orthotopic TNBC model.

Contact

Brusi Kola
University of South Alabama
Email: bk2223@jagmail.southalabama.edu
Phone: 251-381-9538

Funding

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