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Cancer Biology PhD Program, Fourth Year

Intervention with probiotics and muscadine grape extract shifts western diet-associated metabolic, microbial, and inflammatory parameters to reduce breast tumor growth

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Objectives: Western diet consumption (WD) is associated with increased risk and poor prognosis for breast cancer (BC) due to altered inflammation, metabolism, and microbial colonization. This study will determine whether intervention with probiotics (prbx) and muscadine grape extract (MGE) reduces these effects.

Methods: Female C57Bl/6 mice were placed on either control diet (CD) or WD (45% fat and 25% sugar). Mice were randomized into six groups per diet: diet alone, antibiotics (abx), prbx, MGE, MGE+abx, and MGE+prbx (n=8). Prbx groups received 1×10^5 CFU of a 10-strain probiotic 3x weekly. MGE (0.1 phenolics/mL) and abx (5 mg/mL streptomycin, 1 mg/mL ampicillin, 1 mg/mL colistin) were administered in drinking water. Body weights were measured, and feces was collected for 16S sequencing. EchoMRI was performed on mice (total body adiposity) and livers at the end of the study (13 weeks). Immunohistochemistry (IHC) was used to compare mammary gland (MG) and visceral adipose (VA) inflammation (CD68 and MCP-1). To determine whether dietary interventions effected breast cancer growth, female BALBc mice consuming either CD or WD, were injected with 1.0×10^6 4T1-luc triple negative breast cancer cells into the R4/5 MG. Tumors progressed to 100 mm³ prior to treatment. Size was monitored with calipers and IVIS for 21 days.

Results: MGE+prbx administration in WD-fed mice resulted in reduced body weight. All intervention groups displayed reduced VA and MG weight compared to WD-fed mice. Significant intervention-mediated gut microbial alterations included changes in proportional abundance of *Bacteroidetes*, *Lactococcus*, *Lactobacillus*, and *Bifidobacterium* taxa. Interventions modulated VA and MG inflammatory markers. Dietary intervention with MGE, prbx, and MGE+prbx reduced 4T1 tumor growth rate in WD-fed mice, but not in CD-fed mice.

Conclusions: Our data suggests that MGE+prbx modulates diet-induced metabolic, inflammatory, and microbial factors. Treatment with MGE+prbx reduced tumor growth rate in WD-fed mice, but not CD. Further analyzing tumor tissue will determine whether MGE+prbx altered the tumor microenvironment to improve WD-associated BC prognosis.

Funding Sources: Chronic Disease Research Fund