A modified standard American diet increases oncogenic programming and alters DNA damage and repair in breast tumors

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Obesity and diabetes are critical risk factors for the development of breast cancer, its progression, and treatment. Despite the known associations between obesity and diabetes and breast cancer, there is limited information about how dietary factors that contribute to these disease states alter DNA repair pathways. In particular, American diets, which may be energy dense but nutrient poor, have unknown effects on DNA damage and repair.

We previously published that high glucose environments induced base excision repair pathways in breast cancer cell lines, increasing resistance to genotoxic chemotherapy. Base excision repair pathways are critical genomic surveillance systems that, when dysregulated, can confer resistance to cisplatin, radiotherapy, and other genotoxic chemotherapies. To better understand the effects of an American-style diet on breast cancer cells and their DNA repair pathways, we examined how a modified standard American diet (SAD2) affects mammary tumor development in the MMTV-PyMT mouse model, a commonly used model of breast cancer (*Breast Cancer Res* 2025, PMID: 40713647).

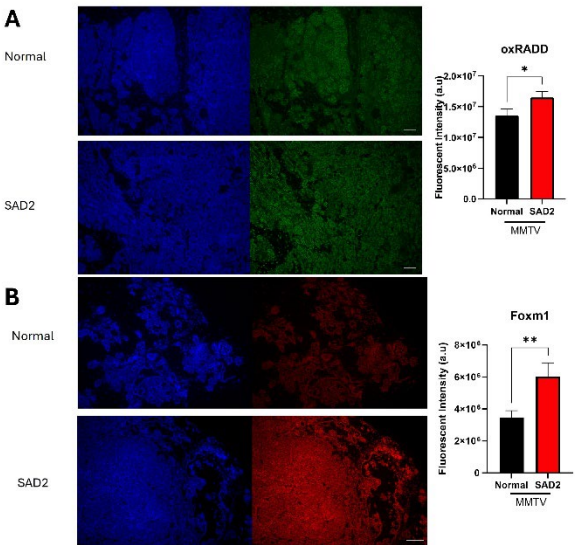

Figure 1. A. DNA lesions measured by the Repair-Assisted Damage Detection (RADD) assay specific for oxidative lesions. B. Immunofluorescent staining of Foxm1. *n* = 7 normal chow and *n* = 8 SAD2.

In this experiment, MMTV-PyMT mice and FVB/N controls were fed either normal chow or the SAD2 diet for up to 12 weeks. The SAD2-fed MMTV-PyMT mice gained more weight and accumulated more visceral and gonadal fat than control-fed animals. We also observed earlier tumor onset, faster progression, and reduced survival. Tumors showed increased oxidative DNA damage and advanced glycation end products (AGEs), suggesting that the diet induced cellular injury and reactive metabolites, which are often observed in obese and diabetic patients. We also observed increased expression of the oncogene Foxm1, which is known to regulate the transcription of DNA repair proteins, and Glut1, a glucose transporter, in SAD2 tumors. Both genes are linked to breast cancer biology and are associated with aggressive disease in patient samples, raising the possibility that dietary exposure may help drive oncogenic signaling programs relevant to human cancer progression. Our results demonstrate that even a short interval of exposure to an American-style diet can reshape tumor biology in ways that may favor more aggressive disease.

Critically, this study found that diet-related changes were not limited to weight gain or adiposity; they were also associated with oxidative DNA damage, AGE accumulation, and the induction of growth-related tumor pathways, such as Foxm1. In the context of our other studies, this work suggests that DNA repair pathways respond to dietary changes to protect cells from increased stress; however, these protective mechanisms can also preserve cancer cells, promoting their growth, enhancing genomic instability, and allowing survival even when genotoxic chemotherapy is used. More work is needed to understand how to mitigate or target these effects to improve therapeutic outcomes for obese and diabetic patients or patients whose diets feature energy dense, nutrient poor structure.

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