Defining the Effects of a High Advanced Glycation End Product Diet on Mammary Development During Puberty

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Abstract

The mammary gland is a unique organ because its functional development and differentiation are completed postnatally during puberty, pregnancy, lactation and involution. These cycles of mammary gland development are potential windows of breast cancer susceptibility. Due to links between diet and increased risk of breast cancer, we hypothesized that consuming large amounts of sugar derived metabolites known as advanced glycation end products (AGEs) during puberty may cause mammary gland dysregulation and increase the risk for future pre-neoplastic lesions. AGEs are a heterogeneous group of macromolecules that are generated through non-enzymatic glycation and oxidation of proteins, lipids, and nucleic acids. Accumulation of AGEs leads to pro-inflammatory and pro-oxidant effects which can contribute to the development and complications associated with multiple chronic diseases.

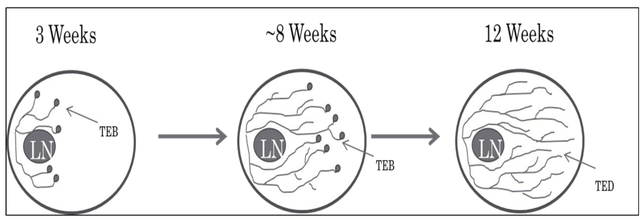
Our previous research showed that consuming a high AGE diet causes the formation of hyperplastic lesions which resembled pre-neoplastic lesions. This study expands on our findings by examining the effects of diet switching on the formation of hyperplastic lesions. Mice (3 weeks old) were initially fed the high AGE diet for 4 weeks followed by a regular diet (regular mouse food) for 5 weeks. At the experimental endpoint of 12 weeks, mice were sacrificed and mammary tissues were collected for whole mounting and hematoxylin and eosin staining. This model mimics the concept of "metabolic memory" which postulates that events that occur early in disease onset are imprinted within cells and promote disease progression later in life.

Our data showed that consuming a high AGE diet during pubertal development altered mammary gland morphology forming abnormal cell structures and promoted the formation of hyperplastic lesions, despite intervention with the regular diet. In summary, the data supports the hypothesis that a diet high in AGE metabolites during puberty may induce metabolic memory and may represent a window of susceptibility for breast cancer.

Introduction

Advanced glycation end products (AGEs) are a heterogeneous group of macromolecules that are formed by the non-enzymatic glycation of proteins, lipids, and nucleic acids. Humans are exposed to two main sources of AGE: endogenous AGEs that are formed in the body and exogenous AGEs that are ingested in foods (Turner 2015). Accumulation of AGEs in the body leads to pro-inflammatory and pro-oxidant responses when signaling through the receptor for advanced glycation end products (RAGE).

Located inside of the breast, the mammary gland is primarily designed to produce milk for offspring. It develops in 3 distinct stages which are shown to below.

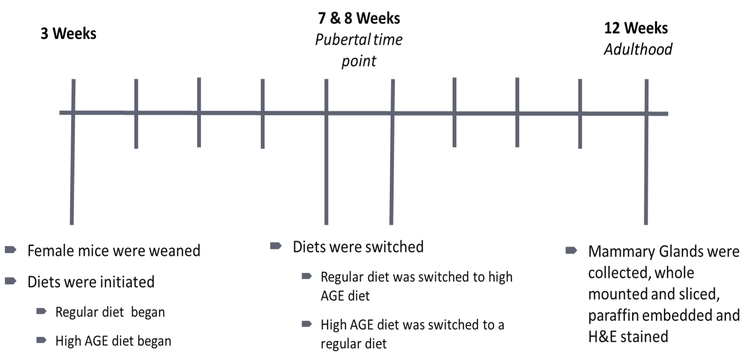


This organ is one of the very few that continues to develop postnatally through stages including puberty, pregnancy, lactation, and involution. These stages which are known as windows of susceptibility increase breast cancer risk.

Our previous data shows that consumption of a high AGE diet in pubertal mice causes the formation of hyperplastic lesions. This study aims to examine if the timing of administration of the high AGE diet is critical to the formation of the hyperplastic lesions. This hypothesis was tested by examining whether hyperplastic lesions persist after switching from a high AGE diet to a regular diet in mice diet during puberty.

Materials and Methods

Diet Reversal Time Line



Results

Figure 1: H&E Staining of Mammary Tissue from 12 Week Old Mice fed a High AGE Diet then Switched to a regular diet

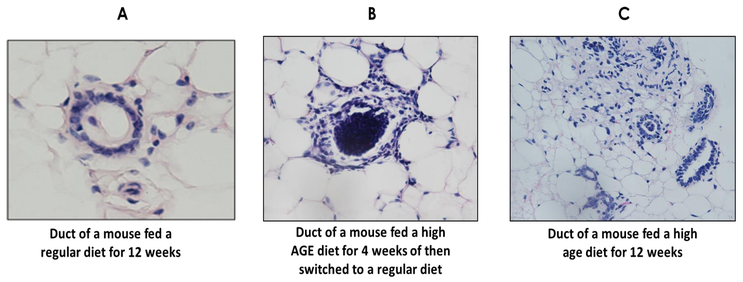


Figure 2: H&E Staining of Mammary Tissue from 12 Week Old Mice fed a Regular Diet then Switched to High AGE Diet

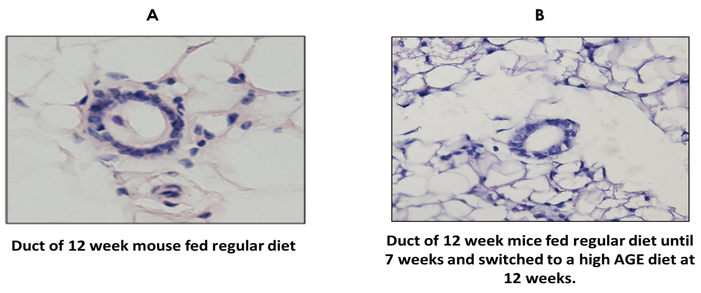


Figure 3: Average Number of Lesions

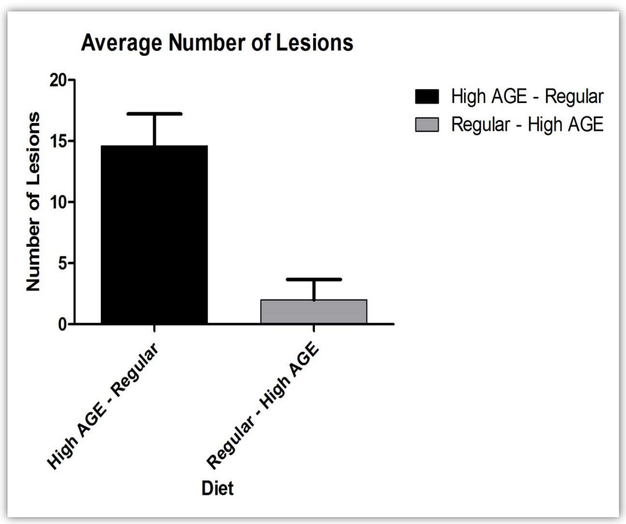
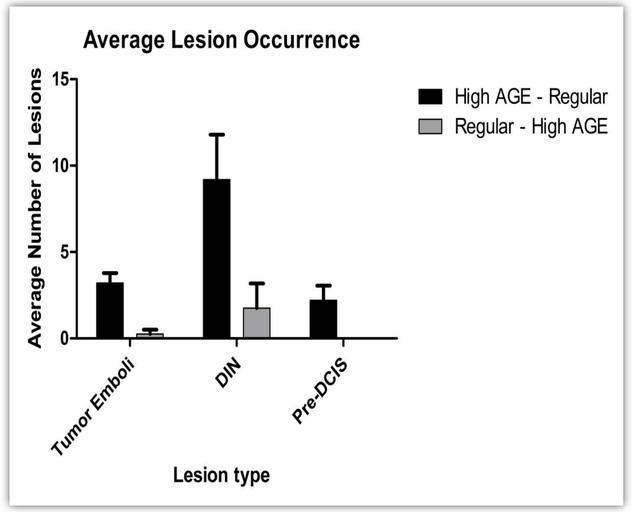


Figure 4: Average Lesions Occurrence



Conclusion

Based on the results obtained:

- Hyperplastic lesions persist even when mice are initially fed a high AGE diet then switched to regular diet
- There is a greater number of lesions present in mice fed a high AGE then regular diet than mice fed a regular than high AGE diet
- This indicates that early events as a result of consuming a high AGE diet may be imprinted on cells and may influence disease progression later in life
- Diet intervention to reduce AGE consumption during puberty may be beneficial in reducing disease risk later in life

Future Plans

Future plans include:

1) Assessing markers of pre-neoplastic lesions in the AGE induced lesions in pubertal (7 and 8 week) and adult (12 week) mice

2) Use RAGE knockout mouse models to assess the role of AGE-RAGE signaling in lesion formation

References

Turner, David P. "Advanced Glycation End-Products: A Biological Consequence of Lifestyle Contributing to Cancer Disparity." *Cancer research* 75.10 (2015): 1925–1929. *PMC*. Web. 8 Oct. 2017.

Acknowledgements

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