SAT-336: Time Restricted Feeding Delays Breast Cancer Initiation and Growth in a Mouse Model of Postmenopausal Obesity

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Background: The prevalence of obesity and the metabolic syndrome (MetS) has increased dramatically in developed countries over the last three decades (Flegal et al., 2012). Numerous studies indicate that adiposity and the MetS are independent risk factors for multiple diseases including cancer, particularly postmenopausal breast cancer (Kim et al., 2018). Therefore improving the metabolic health of obese postmenopausal women may mitigate their risk for breast cancer. Accumulating evidence suggests that time-restricted feeding (TRF), a form of intermittent fasting in which food intake is limited to a defined period during the normal active phase, can have a positive influence on metabolic health. Importantly, interventional studies in obese mice and small clinical studies in humans have demonstrated that TRF can improve metabolic health even though obesity is maintained (Sutton et al., 2018). Time restriction rather than calorie restriction is thus a promising method to control the negative sequelae of obesity, due to the hunger and irritability that reduces compliance with long-term calorie restriction. The objective of this study was to investigate whether TRF attenuates breast cancer in a mouse model of postmenopausal obesity and whether this effect is mediated by reducing the hyperinsulinemia associated with obesity.

Methods: Ovariectomized mice were used as postmenopausal mice model. The ovariectomized mice were initially made obese by feeding 60% high fat diet (HFD) for 10 weeks and then grouped into a continued ad libitum group (24 h access to food) or a TRF group (8 h access to food during active phase). For an orthotopic tumor model, mice were injected with E0771 breast cancer cells into four mammary fat pads per mouse three weeks following the start of TRF. As a tumor initiation model, transgenic PyMT mice were used to assess tumor onset and growth following the same TRF or AL access to the HFD. The insulin dependency of tumor growth was studied by increasing insulinemia using an implanted insulin pump, or by reducing insulin secretion using diazoxide. Insulin effects on tumor cell proliferation and migration was further validated in vitro.

Results and Conclusion: TRF had a dramatic effect, reducing tumor growth in obese mice fed a high fat diet (HFD) to levels seen in lean mice. Tumor growth and initiation was also delayed in the transgenic PyMT model of mammary tumorigenesis. Our results further suggest that the antitumor effect of TRF is at least partially mediated by reducing hyperinsulinemia, suggesting that this intervention may be effective in breast cancer prevention and therapy.

References: Flegal, K. M. et al., (2012), *JAMA* 307, 491-497. Kim, N. H. et al. (2018). *Dig Dis Sci* 63, 3126-3133. Sutton, E. F. et al. (2018). *Cell Metab* 27, 1212-1221 e1213.

Presentation Date: Saturday, March 23
Presentation Time: 1 p.m. – 3 p.m.
Location: Expo Hall