Intermittent calorie restriction reverses the adverse effects of obesity and advanced age on tumor growth in a mouse model of breast cancer

Advanced age and obesity are two major risk factors for breast cancer (BC) mortality. This presents a significant public health concern as the number of older individuals and incidence of obesity are increasing worldwide. In our mouse models of BC, we have demonstrated that, similar to obesity, advanced age accelerates mammary tumor growth. Mechanistically, obesity and advanced age suppress tumor gene expression relating to antitumor immunity and reduce tumoral abundance of cytotoxic CD8+ T cells. Thus, advanced age- and obesity-related enhancement of mammary tumor growth is explained, in part, through the development of an immunosuppressive tumor microenvironment. Given the aging of our populations and the increasing prevalence of obesity, interventions capable of reversing the tumor-promoting effects of advanced age and obesity are needed.

We have previously demonstrated that weight loss by intermittent calorie restriction (ICR), in which mice are placed on a 5:2 calorie restriction (CR) regimen (5 days 14% CR, 2 nonconsecutive days 70% CR per week), attenuates tumor growth and immunosuppression in formerly obese mice. This project tests if ICR will provide similar benefit to aged and aged obese mice. Cohorts of young control (5 mos), young diet-induced obese (DIO; 5 mos), aged control (15 mos), and aged DIO (15 mos) mice were generated and subsequently randomized to either remain on their baseline diet or switch to the ICR intervention. Following 9 weeks on ICR or baseline diet, serum samples were collected and then tumor development induced by orthotopic transplantation of E0771 cancer cells into the 4th mammary fat pad of mice. At tumor endpoint mammary tumors were collected and weighed. To determine if ICR alters systemic inflammation in each experimental group, cytokine levels were measured in serum samples collected prior to tumor inoculation. Multiple inflammatory cytokines were downregulated following ICR intervention in young DIO, aged control, and aged DIO mice, including CCL7, CCL10, and CCL24. Downregulation of inflammatory cytokines was correlated with decreased tumor burden in young DIO, aged control, and aged DIO mice placed on ICR, compared with their respective non-intervention controls. Ongoing analyses are investigating if ICR increases the abundance of cytotoxic CD8+ T cells within the tumor microenvironment of young DIO, aged control, and aged DIO mice. These findings demonstrate that ICR may be effective in reversing obesity- and advanced age-related enhancement of mammary tumor growth in mouse models of breast cancer. More research is needed to test if these preclinical findings translate to obese and aged humans with BC. Identifying dietary interventions that may attenuate obesity- and age-related tumor growth has the potential to improve both patient outcomes and quality of life.