

## **Caloric restriction reduces inflammation to decrease prostate cancer growth and metastases in several prostate cancer models**

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### **Purpose/Objective(s):**

It is well established that inflammation is a key driver in prostate cancer progression, metastases and castrate resistance. Evaluation of the biological mediators of metastatic prostate cancer suggest that chemokines related to inflammation including CXCR7, CXCR4 and CXCR6 may play a role in the aggressive behavior of advanced prostate cancer. Animal models have shown that caloric restriction (CR) can prevent carcinogenesis and decrease systemic inflammation. We propose that CR may be used as a novel therapeutic intervention to decrease inflammation, thereby altering the molecular profile of prostate tumors.

### **Materials/Methods:**

To assess the effect of CR with radiation *in vivo*, eighty 6 week old male nude mice were injected with LNCaP (hormone sensitive) or PC3 (insensitive) tumor cells. Once tumors were palpable, mice were randomized to be treated with one of 4 conditions: ad libitum (AL) diet, 8Gy of radiation (RT), 30% reduction in caloric intake (CR), or CR+RT. Mice were imaged to monitor primary tumor size and metastatic disease. Tumors from each group were dissected and evaluated on a molecular level for apoptosis, proliferation and chemokine expression as a surrogate for inflammation.

### **Results:**

CR was associated with significant reduction in tumor formation. After PC3 tumor injection, compared with AL, the mice had a 22% reduction in tumor size with radiation, 77% with CR ( $p<0.01$ ) and an 80% reduction with CR+RT ( $p<0.01$ ). After LNCaP tumor injection, compared with AL, CR mice had a 49% reduction in tumor size and a 55% reduction with CR+RT ( $p<0.01$ ). Tissue evaluation of mice treated with CR or CR+RT from both the LNCaP and PC3 models revealed decreased Ki-67 and increased apoptosis. Treatment with CR and CR+RT also prolonged time to metastases from 86 days in the AL group to 112 days and 108 days in the CR and CR+RT groups, respectively. In addition, significant downregulation of multiple members of the chemokine family was seen including most significantly an additive decrease in CXCR7 to 0.4 relative mRNA expression in the CR+RT combination group normalized with the AL group ( $p<0.01$ ).

### **Conclusion:**

For the first time, we have shown that inflammation, a major driver of prostate cancer progression and metastases, can be modulated by CR, to improve outcomes in both hormone-sensitive and insensitive prostate cancer models. Future clinical trials in prostate cancer should consider the use of CR to augment standard cancer therapy as it has the potential to change the biology of tumors and enhance clinical benefit of RT in the LAPC and metastatic setting.

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Conflicts of interest: None