123-LIPS

Metabolically Activated Macrophages and Their Role in Radiation-Induced Breast Cancer Recurrence

OBJECTIVE

Triple-negative breast cancer (TNBC) is an aggressive subtype of breast cancer characterized by a high likelihood of locoregional recurrence. This study explores how macrophages, specifically those with a metabolically activated (MMe) phenotype, behave after radiation damage and contribute to cancer recurrence. Macrophages are key immune cells that help defend the body against infections and cancer. In adipose tissue, these macrophages help regulate metabolism, but in obesity, they become metabolically activated, leading to increased inflammation and the ability to clear dead fat cells. In triple-negative breast cancer (TNBC), MMe macrophages have been linked to the tumor environment, where they may promote tumor growth, immune evasion, and metastasis. We hypothesized that the microenvironment resulting from radiation therapy, a standard treatment for TNBC, may induce metabolic activation of macrophages, resembling the effects observed in obesity, and contribute to cancer recurrence.

METHODS

This study examines how macrophages contribute to cancer recurrence after radiation damage. We focused on how damage influences the interactions of macrophages with damaged fat cells. We used Western blotting to measure lipid-associated markers ABCA1, Plin2, CD36, and Trem2,

which have been suggested to be upregulated at the gene expression level in MMes, in macrophages that were exposed to palmitate, high levels of glucose, and insulin to induce the MMe phenotype. We additionally exposed macrophages to conditioned media (CM) from irradiated and unirradiated adipocyte spheroids.

RESULTS

At the protein expression level, Plin2 and CD36 were found to be positive MMe markers, showing increased expression in macrophages exposed to media with palmitate, insulin, and glucose, while TREM2 and ABCA1 did not show this response. CM from irradiated adipocyte spheroids additionally increased protein expression of MMe markers. We are currently evaluating how macrophage and adipocyte co-cultures influence MMe marker expression.

CONCLUSION

These results highlight the significant role of macrophages in cancer recurrence following radiation. Given that MMe macrophages are known to promote tumor development, their presence after radiation-induced damage may provide insight into a potential mechanism driving recurrence. This research will help us understand how radiation therapy might inadvertently promote cancer recurrence and guide the development of potential new treatments.