Macrophage migration to sites of tissue injury has been described in many models of infection, sepsis, inflammation, cancer, ischemia-reperfusion, and trauma. Using a thermal injury mouse model, we have recently demonstrated that both the endogenous peritoneal macrophages and the exogenous murine cells that were transplanted into the peritoneal cavity of mice migrated to the site of inflammation induced by thermal injury to the hindlimb. Using a similar experimental approach, we explored the possibility that endogenous macrophages (with or without an accompanying payload) might migrate to a tumor, subjected to focused radiation therapy as the primary inflammatory trigger. We evaluated this possibility in a subcutaneous colorectal cancer xenograft model in nude mice using localized $\gamma$-radiation (8 Gy, a dose used clinically for palliation of pain due to due tumor encroachment of surrounding normal structures). A commercially available Multimodal in vivo imaging system was used to obtain X-ray and fluorescence (NIRF) images at different time intervals. We demonstrate that peritoneal macrophages migrate to the irradiated region of the animal (figure below). Trafficking of peritoneal macrophages to the irradiated tumor has immense potential in the development of platforms for targeted delivery of drugs, vectors, nanoparticles, and other payloads directly and in high concentrations to the tumor using a radiation beam physically collimated to conform to the edges of the tumor, minimizing unnecessary exposure of other parts of the body to these agents. The role of clinically relevant radiation doses, in the infiltration of compartmentalized macrophages into the tumor environment, and the prospects of developing novel therapeutic strategies utilizing cell trafficking will be discussed.
Radiation induced tumor infiltration of NIR fluorescence signal (Macrophages).
Increased Migration of Tumor-Targeting Monocytes/Macrophages by Radiation

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Radiotherapy for cancer treatment has been used for primary or adjuvant treatment in many types of cancer and approximately half of all cancer patients are undergoing radiation. Hypoxia in solid tumors has been known as the main cause of resistance to ionizing radiation therapy of cancer by inducing genomic and proteomic changes of cancer cells. Monocytes/macrophages are continually recruited in hypoxic areas of tumor due to the hypoxic release such macrophage chemoattractant as VEGF and MCP-1. Using this characteristic of monocytes/macrophages, we have attempted to develop biocarriers loading radiosensitizing anticancer agents that can lead to enhance the therapeutic effect of radiation in cancer treatment. Macrophages taken iron oxides has been observed in a tumor site effectively with a MRI imaging. Furthermore, functionalized liposomes carrying radiosensitizing anticancer agents, such as doxorubicin and cisplatin, has been successfully loaded in mouse peritoneal macrophages that migrated into tumors from subcutaneous and metastasis mouse model. Taken together, these results provide monocytes/macrophages as a biocarrier which may be able to use as a selective tool for amplification of the therapeutic effects of radiation in cancer treatment and improvement in the efficacy of radiotherapy will benefit a large number of patients.

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A New Twist on Radiation Oncology: Low-Dose Irradiation Elicits Immunostimulatory Macrophages that Unlock Barriers to Tumor Immunotherapy

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Refers To

- Felix Klug, Hridayesh Prakash, Peter E. Huber, Tobias Seibel, Noemi Bender, Niels Halama, Christina Pfirschke, Ralf Holger Voss, Carmen Timke, Ludmila Umansky, Kay Klapproth, Knut Schäkel, Natalio Garbi, Dirk Jäger, Jürgen Weitz, Hubertus Schmitz-Winnenthal, Günter J. Hämerling, Philipp Beckhove
- Low-Dose Irradiation Programs Macrophage Differentiation to an iNOS⁺/M1 Phenotype that Orchestrates Effective T Cell Immunotherapy
- Cancer Cell, Volume 24, Issue 5, 11 November 2013, Pages 589-602

Tumor-infiltrating macrophages typically promote angiogenesis while suppressing antitumoral T cell responses. In this issue of Cancer Cell, Klug and colleagues report that clinically-feasible, low-dose irradiation redirects macrophage differentiation from a tumor-promoting/immunosuppressive state to one that enables cytotoxic T cells to infiltrate tumors and kill cancer cells, rendering immunotherapy successful in mice.
Low-Dose Irradiation Programs Macrophage Differentiation to an iNOS$^+$/M1 Phenotype that Orchestrates Effective T Cell Immunotherapy

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Highlights

- Local LDI efficiently recruits effector T cells into tumors
- LDI enables efficient T-cell-mediated tumor rejection and improved survival
- LDI acts through iNOS induction in tumor-associated macrophages
- INOS raises TH1 chemokines and inhibits angiogenic and immune suppressive cytokines

Summary

Inefficient T cell migration is a major limitation of cancer immunotherapy. Targeted activation of the tumor microenvironment may overcome this barrier. We demonstrate that neoadjuvant local low-dose gamma irradiation (LDI) causes normalization of aberrant vasculature and efficient recruitment of tumor-specific T cells in human pancreatic carcinomas and T-cell-mediated tumor rejection and prolonged survival in otherwise immune refractory spontaneous and xenotransplant mouse tumor models. LDI
(local or pre-adoptive-transfer) programs the differentiation of iNOS+ M1 macrophages that orchestrate CTL recruitment into and killing within solid tumors through iNOS by inducing endothelial activation and the expression of TH1 chemokines and by suppressing the production of angiogenic, immunosuppressive, and tumor growth factors.

Figures and tables from this article:

Figure 1.

Increased T Cell Infiltration after Local LDI

(A) Invasive growth of RT5 tumors in 24-week-old mice. Left: hematoxylin and eosin (H&E) staining; right: IHC costaining of tumor cells (Tag: green) and endothelial cells (CD31: red). Scale bar, 50 μm.

(B) Tumor infiltration by host T cells. Tumors of RT5 mice (n = 8) were treated with indicated irradiation doses and analyzed after 7 days with immunohistochemistry (IHC) for indicated T cell populations.

(C) Schematic experimental procedure for combined LDI and adoptive transfer of Tag-specific TCRtg T cells.

(D) Increased infiltration of myeloid CD11b+ and transferred CD3+ or CD8+ T cells, or both, in intratumoral areas of LD-irradiated RT5 tumors (IHC). Tumor areas are indicated (T) and delineated (dashed lines). Magnification: 200×.

(E) Tumor infiltration by TCRCD8+ (n = 22, upper graph) or TCRCD4+ (n = 13, lower graph) T cells analyzed by IHC for indicated T cell populations.

(F) Tumor T cell infiltration 7 days after vaccination with MHC-I restricted SV40-Tag peptide and LD irradiation at indicated doses. Mean ± SEM are shown. *p < 0.05 (two-tailed Student’s t test).

See also Figure S1.