Article

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Tenascin-C orchestrates radiotherapy-induced head and neck tumor regression

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Abstract

Given that head and neck squamous cell carcinoma (HNSCC) patients have poor survival outcomes, a better understanding of the therapeutic benefits of ionizing irradiation (IR), the major treatment modality besides surgery, is needed. A confounding factor is the immunosuppressive tumor microenvironment determined by tenascin-C (TNC), a highly abundant extracellular matrix molecule upregulated by IR. We investigated the roles of TNC on radio-induced tumor regression in a murine oral HNSCC model expressing or lacking TNC. While tumors in a TNC-expressing host were radiosensitive, they were radioresistant in TNC genetically depleted mice. We identified fibroblast reticular cells (FRCs) as critical regulators. TNC plays a compartmentalized and dual role in regulating tumor radiosensitivity with a detrimental role in the tumor stroma opposed to an essential role in the tumor-draining lymph nodes. This is relevant as a high FRC signature and high TNC levels together correlate with shorter HNSCC patient survival. TNC-expressing FRCs may be an excellent novel target to improve radiotherapy-induced tumor eradication, as our TNC targeting MAREMO peptide reduced tumor cell numbers and plasticity upon IR.

Keywords Tenascin-C; Radiotherapy; Fibroblast Reticular Cells; Tumor Draining Lymph Nodes; MAREMO Peptide
Subject Category Cancer
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Introduction

Head and neck squamous cell carcinoma (HNSCC) is an aggressive malignancy with poor patient survival despite advances in therapy (reviewed in Chinn and Myers, 2015). Ionizing radiation (IR) remains a key treatment strategy, effectively inducing tumor and stromal cell death and activating anti-tumor immunity through the tumor-draining lymph nodes (TdLNs), which serve as critical sites for T-cell priming and expansion (Buchwald et al, 2020; Koukourakis and Giatromanolaki, 2022). However, IR paradoxically fosters an immunosuppressive tumor microenvironment (IS-TME), which limits its therapeutic efficacy (Menon et al, 2019; Guo et al, 2023). A central component of the IS-TME is tenascin-C (TNC), an extracellular matrix (ECM) glycoprotein implicated in immune modulation and tumor progression across various cancers (Yilmaz et al, 2022). In HNSCC, fibroblast reticular cells (FRCs) are a major source of TNC (Spenlé et al, 2020). TNC promotes immune evasion by inducing tolerogenic molecules, skewing macrophages toward an M2 phenotype, enhancing regulatory T cell (Treg) infiltration, and dampening CD8 + T cell responses (Deligne et al, 2020; Spenlé et al, 2020; Jachetti et al, 2015). Moreover, TNC induces the expression of ECM molecules that form immunosuppressive niches, so-called tumor matrix tracks (TMT) (Spenlé et al,

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The paper explained

Problem

Ionizing radiation is the standard treatment for head and neck tumors and effectively reduces tumor burden. However, it simultaneously induces an immunosuppressive tumor microenvironment, particularly marked by increased expression of the tumor-promoting extracellular matrix glycoprotein tenascin-C (TNC). In this study, we sought to determine the specific contribution of TNC to tumor response following irradiation, using models with genetic or functional loss of TNC.

Results

Our work reveals that tenascin-C plays multiple regulatory roles in tumor radiosensitivity. In addition to directly influencing tumor cells, irradiation profoundly alters the phenotype of fibroblastic reticular cells (FRCs), a major source of TNC both within the tumor and in tumor-draining lymph nodes (TdLNs). Irradiation-surviving FRCs expand and acquire enhanced immunosuppressive properties, thereby promoting tumor progression. We demonstrate that physical interactions between tumor cells and FRCs drive FRC expansion and activation, increased tumor-cell survival and radioresistance, all in a TNC-dependent manner. Irradiation also remodels the TdLNs, where FRCs maintain the structural and functional networks required for adaptive immunity. In TNC-deficient tumor-bearing mice, TdLN immunity is deregulated, which likely contributes to the observed radioresistance.

Impact

TNC supports tumor regrowth after irradiation, in contrast to its protective role within the TdLNs, where TNC maintains immune-supportive functions. Our findings indicate that the balance between these opposing roles critically shapes radiotherapy outcomes. This identifies both FRCs and TNC as promising targets to enhance radiotherapeutic efficacy. Importantly, a high intratumoral abundance of highly TNC-expressing FRCs correlates with reduced survival in irradiated head and neck cancer patients. Finally, we demonstrate that therapeutic targeting of TNC using the MAREMO peptide increases tumor radiosensitivity, underscoring its clinical potential.

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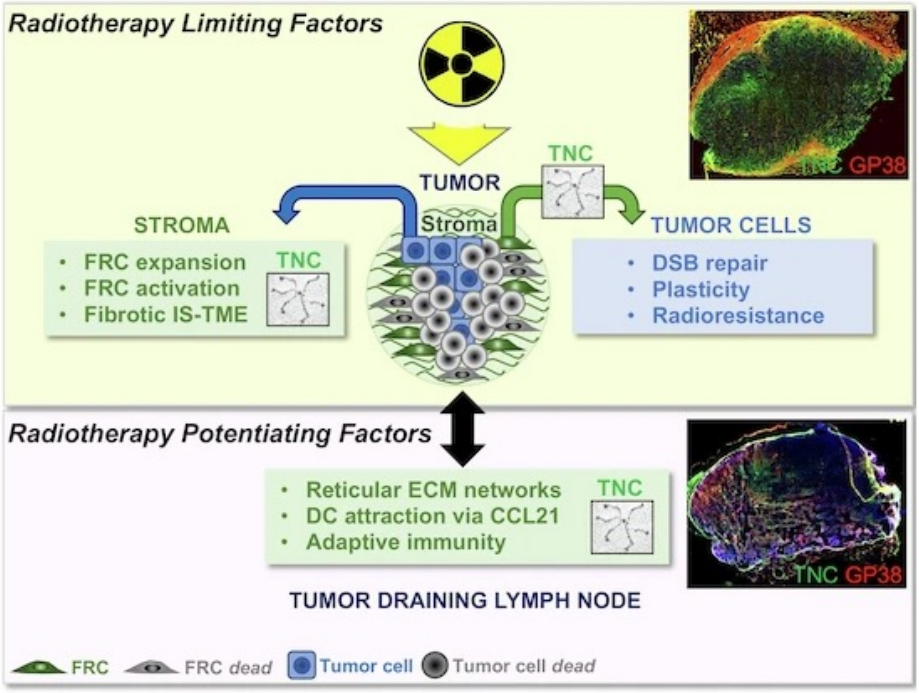
Synopsis



Radiotherapy lowers tumor burden but also induces tenascin-C (TNC), promoting immunosuppression and radioresistance; unlike in radiosensitive tumor draining lymph nodes, TNC-positive reticular fibroblasts promote tumor radioresistance, enabling radiosensitization by a TNC targeting MAREMO peptide.

- In HNSCC, fibroblast reticular cell (FRC) abundance is increased after radiotherapy through tenascin-C (TNC) dependent mechanisms.
- TNC is shown to determine distinct FRC phenotypes in the tumor microenvironment and tumor draining lymph nodes.
- TNC-dependent FRCs are demonstrated to promote tumor cell DNA double-strand break repair, plasticity and radioresistance.
- Radio-induced plasticity and tumor cell survival are shown to be reduced by TNC targeting with the MAREMO peptide.
- High intratumoral abundance of TNC-expressing FRCs is associated with inferior overall survival in HNSCC patients.