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Highlights

Radiotherapy and the tumor microenvironment: The "macro" picture

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ABSTRACT

In this issue of the *Biomedical Journal*, we explore the inner workings of tumor-associated macrophages and seek to understand how these cells can boost or limit the efficacy of radiotherapy, depending on the context. We also highlight a study revealing that staffing patterns in the intensive care unit may affect the outcome of patients with severe sepsis. Finally, we learn how an advanced imaging technique can improve endodontic treatment planning.

Spotlight on reviews

Radiotherapy and the tumor microenvironment: the "macro" picture

Radiotherapy has for many years been a cornerstone of cancer treatment. But to fully understand its effects and maximize them requires zooming out from individual cancer cells and looking at the tumor as a whole. In this issue of the *Biomedical Journal*, Wu et al. [1] describe how ionizing radiation affects macrophages in the tumor and what this means for cancer therapy of the future.

Zapping tumors with high doses of IR normally amounts to a death sentence for highly proliferating cancer cells, but it also has profound effects on the tumor microenvironment, the support system of non-cancerous cells and stroma that play a major role in determining the outcome of malignancy. An important component of the tumor microenvironment is immune cells, in particular tumor associated macrophages (TAMs). These cells are typically thought to drive tumor progression by stimulating cell proliferation, metastasis and angiogenesis, and inhibiting the T cell-mediated anti-tumor immune response [2]. Thus, understanding how TAMs react to IR, for better or worse, has important implications for cancer therapy.

As Wu et al. point out however, the response of these cells is not easy to predict and depends on a range of factors. Whereas low-dose IR induces an anti-inflammatory "M2" like phenotype, doses above 1 Gy induce a pro-inflammatory "M1" like phenotype resulting in the production of nitric oxide and several pro-inflammatory cytokines [3,4]. However, the exact response is also likely to depend on host genetic factors and age, with rodent macrophages exhibiting different responses to the same dose depending on the strain and age of the animal from which they were isolated [5,6]. These findings are reflected in *in vivo* studies to some extent, although small doses of IR have also been reported to induce M1 phenotypes in some settings [7].

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Thus, the multitude of factors that influence how macrophages respond to IR complicates the important question of what happens to irradiated or bystander TAMs *in vivo* and can we manipulate these effects to our advantage from a therapeutic perspective? It is not surprising that IR has been shown to induce either the pro-inflammatory and anti-inflammatory activation of TAMs, depending on the context. For example, in an oral cancer mouse model, IR caused the infiltration of M2-like TAMs that promoted vascularization and hence tumor progression [8]. However, in another cancer murine model, IR increased the abundance of nitric oxide-producing pro-inflammatory macrophages, which in this context, contributed to anti-tumor responses [9].

One result that emerges more clearly however is that IR seems to promote the recruitment of macrophages to tumors [10]. Since TAMs are thought to contribute to cancer progression in established tumors [11], compounds that block the macrophage recruitment pathways are an obvious adjuvant to radiotherapy. The colony stimulating factor 1 (CSF-1) is implicated in the recruitment of macrophages to tumors [12], and the CSF-1 receptor is exclusively expressed in monocytic cells, which makes the CSF-1/CSF-1R pathway an attractive target to interfere with TAMs. In a mouse model of glioblastoma, blockade of CSF-1R using a chemical inhibitor combined with irradiation significantly impaired the accumulation of M2-like cells in the tumor and led to improved tumor control and longer survival [13]. Likewise, similar results have been reported in other cancer models [14].

Although it may appear too soon to connect the dots and build a unified model for the influence of IR on TAMs [Fig. 1], manipulating TAM activity to our advantage, be it in the context of radiotherapy or not, is an exciting therapeutic avenue to explore. Ultimately, "macrophage reprogramming" therapies that polarize TAMs may one day provide an effective string to the bow in tackling tumor progression.

Spotlight on original articles

Intensivist wanted: staffing pattern and risk of sepsis-related death in the intensive care unit

Improving patient care is not just about providing better treatments, it is also about ensuring that our healthcare services are adequately staffed and optimally organized. In this issue of the *Biomedical Journal*, Lin et al. [15] investigate how staffing pattern in the intensive care unit (ICU) affects a patient's chance of succumbing to severe sepsis.

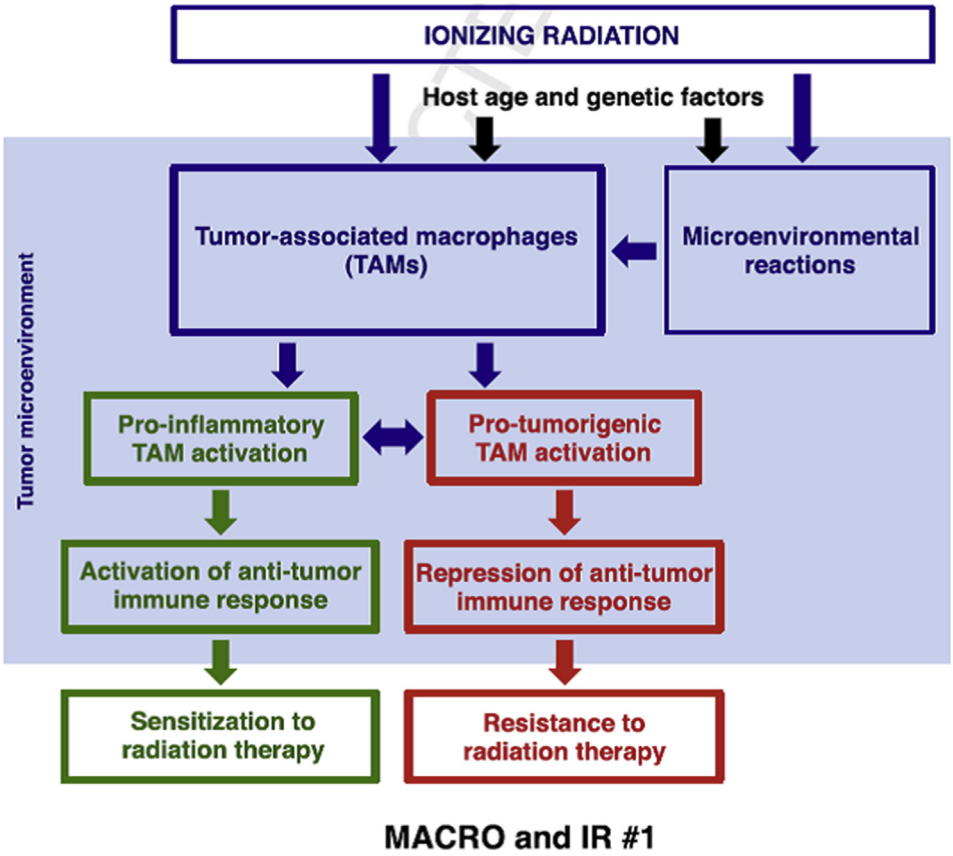

Fig. 1 The effect of ionizing radiation on tumor-associated macrophages (TAMs). Depending on a multitude of factors, including dose, genetics and age, ionizing radiation may either promote a pro-inflammatory M1 like response or an anti-inflammatory M2 like response in tumor-associated macrophages (TAMs). As a result, TAMs may either promote or inhibit anti-tumor responses thus making the tumor sensitive or resistant to radiotherapy, respectively. Figure kindly provided by Wu et al. [1].