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Targeting Platelets and NK Cells to Improve Radiation Therapy Outcomes

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For decades, radiotherapy has been considered primarily as a cytotoxic tool to eradicate cancer by inducing DNA damage and subsequent death of cancer cells. However, the current understanding of tumor immunology has challenged this traditional perception of radiation therapy. In addition to killing malignant cells, radiotherapy reshapes the tumor microenvironment (TME) and the dynamic balance between immune activation and immune suppression, potentially via regulating the function of natural killer (NK) cells and platelets, two crucial components of the tumor immune repertoire. Among the most intriguing yet underappreciated interactions lies a three-way relationship between tumor cells, platelets, and NK cells, a triad that may determine whether radiotherapy enhances or hinders anti-tumor immunity.

The NK cells, as frontline defenders of the innate immune system, play a decisive role in identifying and eliminating malignant cells in circulation. However, tumor cells have evolved highly sophisticated mechanisms for escape. One such mechanism is using platelets as a biological shield, thus preventing NK cells from interacting with malignant cells. By cloaking themselves in platelet membranes, tumor cells not only evade NK cell surveillance but also acquire a "pseudo-self" phenotype through the transfer of platelet-derived MHC class I molecules (1). These platelet-mediated alterations suppress NK cell cytotoxicity, thereby facilitating the metastasis process. Moreover, platelet-derived transforming growth factor-β (TGF-β) further dampens NK cell function by downregulating NKG2D receptors, undermining the "induced-self" recognition critical for NK activation (2).

Radiotherapy, while a cornerstone of modern oncology, can inadvertently intensify these dynamics. Ionizing radiation triggers a cascade of cellular stress responses, including cytokine secretion, reactive oxygen species generation, and latent TGF-β activation, all of which contribute to immunosuppressive, pro-inflammatory, and fibrotic signaling within the TME (3, 4). Beyond its well-known genotoxic effects, radiation-induced DNA damage may also engage HIF-1- and TGF-β/Smad-dependent pathways that promote epithelial-mesenchymal transition (EMT), stromal remodeling, and enhanced metastatic potential (5, 6). In this sense, radiotherapy functions as a double-edged sword: Capable of sensitizing tumors to immune attack or, conversely, of reinforcing tumor survival and dissemination through platelet-mediated and cytokine-driven protection.

Nevertheless, radiotherapy also offers an immunological opportunity. Controlled low-dose irradiation, typically within the range of 0.1 to 2 Gy per fraction, has been shown to upregulate NK-activating ligands such as MICA/B and ULBPs on tumor cells and to induce stress molecules like Hsp70, thereby enhancing NK recognition and cytotoxicity (7, 8). Moreover, the radiation-induced release of damage-associated molecular patterns (DAMPs) can recruit and activate immune effector cells, while radiogenic chemokines, such as CXCL16, facilitate NK cells migration toward irradiated tumor sites (9). Thus, depending on the radiation dose and timing, exposure may either

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potentiate or suppress NK cell immunity, a delicate balance critically influenced by platelet-tumor interactions.

Given this complexity, the concept of combinatorial therapy emerges as both logical and necessary. Studies combining low-dose chemoradiotherapy with NK cell infusion have shown promising synergistic effects, where radiation primes tumor cells for NK-mediated killing (10). Simultaneously, deactivating platelets by targeting platelet activation pathways, through P2Y12 inhibitors, thrombin blockers, or CXCR4 antagonists, may dismantle the protective "platelet cloak", exposing circulating tumor cells to NK attack (11). The intersection of these approaches could redefine immunoradiotherapy as a precisely tuned strategy rather than a purely destructive one.

In addition, platelets, being a rich source of TGFβ, play a pivotal role in post-radiation fibrosis and chronic inflammation, further underscoring the need for an integrated view. By driving TGFβ-mediated fibrotic remodeling, platelets contribute not only to local tissue toxicity but also to systemic immune suppression (12). Blocking the platelet-TGFβ axis, for instance, using bifunctional molecules such as M7824 (anti-PD-L1/TGFβ), has demonstrated superior tumor control and prevention of metastasis in preclinical models (13). Ultimately, the next generation of radiotherapy should be defined not by how much DNA it destroys, but by how effectively it orchestrates anti-tumor immunity.

Future Directions

Understanding the radiotherapy-platelet-NK cell axis invites a paradigm shift in oncology. Instead of viewing platelets solely as bystanders in hemostasis, they must be recognized as dynamic regulators of tumor–immune crosstalk. Future translational efforts should focus on:

- Combining radiotherapy with NK cell-based immunotherapy to enhance tumor clearance and prevent recurrence.

- Developing selective anti-platelet or anti-TGFβ strategies to restore NK cell function without increasing bleeding risk.

- Exploring the SDF-1/CXCR4 axis as a therapeutic target for mitigating radiation-induced injury and fibrosis while amplifying NK-driven immunity.

Ultimately, the true success of radiotherapy will depend not only on its physical precision but also on its biological harmony — its capacity to destroy tumor cells while simultaneously preserving and empowering the body's natural defenses, specifically via upregulating the NK cell function. Integrating immune, vascular, and cellular insights into the design of radiotherapy protocols represents the next frontier in achieving durable, metastasis-resistant cancer control.

Footnotes

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