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Commentary

miR-146a: Overcoming coldness in ovarian cancer

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Ovarian cancer remains a challenging disease with limited treatment options, especially for the high-grade serous carcinoma (HGSC) subtype.[1] In recent years, immunotherapy has emerged as a promising avenue for various cancer types. Despite the progress, its application in ovarian cancer has encountered obstacles that hinder its effectiveness. One of the key challenges is the immunologically "cold" nature of the tumor microenvironment.[2] Ovarian tumors often exhibit a low number of infiltrating immune cells, making them less susceptible to immune-mediated destruction.[3] Additionally, the dynamic tumor ecosystem is influenced by a variety of immunosuppressive factors and cells such as neutrophils, tumor-associated macrophages, and myeloid-derived suppressive cells, which collectively contribute to immunosuppression within the tumor.[4] Understanding the mechanisms of immune resistance, identifying effective targets, and overcoming the immunogenically cold tumor microenvironment are essential for harnessing the full potential of ovarian cancer immunotherapy.

In a recent study published in *Molecular Therapy - Oncolytics*, Chen and colleagues discovered that miR-146a, a microRNA, has the potential to reshape the tumor microenvironment and enhance anti-tumor immune responses.[5] The researchers discovered the role of miR-146a by sampling tumors collected from patients diagnosed with HGSC to assess a panel of 54 tumoral microRNA (miRNA) expression levels. Extensive analysis revealed a positive correlation between miR-146a expression and the expression level of CD8 mRNA, suggesting a potential role of miR-146a in promoting anti-tumor immune responses. These findings serve as a foundation for exploring the therapeutic potential of miR-146a in modulating the tumor microenvironment.

To further investigate the effects of miR-146a modulation, the researchers utilized two murine HGSC models. They employed tumor-targeting nanoparticles to deliver miR-146a, resulting in a significant reduction of 45% in tumor growth in the *ID8-p53*$^{-/-}$ murine HGSC model. Similar findings were observed in the transduced IG10 model, where miR-146a overexpression is confined to tumor cells, leading to a significant reduction in tumor size by 81% compared to the control. These reductions in tumor size were attributed to the increased infiltration of CD8+ T cells into the tumor microenvironment, as evidenced by the higher density of these immune cells within the omental tumor islet through immunofluorescence staining. Moreover, the analysis of immunosuppressive neutrophils revealed a decrease in their population following miR-146a modulation. By targeting immunosuppressive neutrophils and regulating the infiltration of cytotoxic CD8+ T lymphocytes, miR-146a demonstrated its ability to enhance the body's defense against cancer.

Furthermore, they uncovered the underlying mechanisms through which miR-146a exerts its effects in the tumor microenvironment. In the initial screening, they did not find any signs of major histocompatibility complex (MHC) class I pathway upregulation in intratumoral antigen presentation. It was revealed that miR-146a targeted interleukin-1 (IL-1) receptor-associated kinase 1 (IRAK1) and tumor necrosis factor receptor-associated factor 6 (TRAF6), the key components in the nuclear factor κB signaling pathway. By doing so, miR-146a reduced the production of the downstream chemoattractant C-X-C motif chemokine ligand 1 (CXCL1), which is known to mediate neutrophil recruitment. CXCL1 downregulation impeded the infiltration of neutrophils into tumors while allowing improved infiltration of CD8+ T cells into tumors. The intricate interplay between miR-146a and the tumor microenvironment highlights its potential as a therapeutic target for enhancing immunotherapy efficacy.

While this finding is highly promising, further preclinical and clinical investigations are necessary to validate the efficacy and safety of miR-146a modulation. Optimizing delivery methods to ensure targeted and efficient delivery of miR-146a to tumor sites will be crucial in translating these findings into the clinical practice.[6] Additionally, exploring the potential synergy between miR-146a-based therapies and other immunomodulatory agents, such as immune checkpoint inhibitors, may amplify the clinical benefits even further.[7] This groundbreaking study opens up new avenues for research and clinical development of miR-146a-based therapies to treat cold tumors, offering renewed hope for patients with cancer worldwide.

DECLARATION OF INTERESTS

Y.Y is an employee of ViroMissile, Inc., and N.G.C is an employee and shareholder of ViroMissile, Inc.

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