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Perspective

Novel Therapeutic Avenue of Heat Shock Protein 90 C-Terminal Inhibitor in Enhancing Anticancer Immune Response

Manfred Clarke*

Department of Molecular Medicine, University of Maryland, Baltimore, United States of America

DESCRIPTION

Cancer remains one of the leading causes of mortality worldwide, necessitating the exploration of innovative strategies for effective treatment. Immunotherapy, which harnesses the immune system to target and eliminate cancer cells, has emerged as a potential approach. Among the various immune cell subsets, Cluster of Differentiation 8 (CD8+T) cells play a central role in orchestrating the immune response against cancer. Heat Shock Protein 90 (Hsp90) is a molecular chaperone that regulates the folding, stability, and function of numerous client proteins, including those critical for cancer cell survival and growth. Hsp90 is a highly conserved molecular chaperone that plays a pivotal role in protein homeostasis and cell survival. It assists in the proper folding, maturation, and stabilization of a wide range of client proteins, including signaling molecules, transcription factors, and kinases. These client proteins are frequently implicated in essential cellular processes such as cell cycle control, apoptosis, and immunological responses. In cancer, Hsp90 is particularly relevant due to its involvement in maintaining the stability of oncoproteins and promoting the survival and growth of malignant cells. CD8+ T cells, also known as cytotoxic T lymphocytes, are key players in the immune response against cancer. These immune cells are capable of recognizing and eliminating cancer cells expressing tumor-specific antigens presented on major histocompatibility complex class I molecules.

CD8+ T cells can induce apoptosis in target cells through the release of cytotoxic granules containing perforin and granzymes, thereby exerting a potent antitumor effect. However, the effectiveness of CD8+ T cells can be dampened by various immunosuppressive mechanisms employed by cancer cells. Hsp90 inhibition has emerged as an attractive therapeutic strategy for cancer treatment due to its ability to simultaneously target multiple oncogenic pathways. Hsp90 inhibitors disrupt the chaperone function of Hsp90, leading to the degradation of client proteins, including those involved in promoting cell survival and proliferation. Importantly, Hsp90 inhibition can also modulate the immune response by affecting the function of immune cells, including CD8+ T cells. The immunomodulatory effects of Hsp90 inhibitors stem from their impact on antigen presentation, T cell activation, and cytokine production. One specific class of Hsp90 inhibitors, the C-terminal inhibitors, has garnered attention for its potential to enhance the anticancer immunology of CD8+ T cells. Not only does Penisuloxazin A (PNSA) target Hsp90-mediated client protein stabilization, but it also interferes with the interaction between Hsp90 and Programmed Cell Death Ligand 1 (PD-L1), a key immune checkpoint molecule.

This dual inhibition can potentially overcome immune evasion mechanisms employed by cancer cells and enhance the activation of CD8+ T cells. Hsp90 C-terminal inhibition by PNSA can promote enhanced antigen presentation by cancer cells. Hsp90 chaperones play a crucial role in facilitating the proper folding and presentation of antigens on Major Histocompatibility Complex (MHC) class I molecules. By inhibiting Hsp90, PNSA may enhance the presentation of tumor antigens, leading to increased recognition and activation of CD8+ T cells. This phenomenon could augment the immune response against cancer cells and contribute to tumor regression. Immune checkpoints, such as PD-L1, play a critical role in regulating immune responses and preventing excessive immune activation. Cancer cells often exploit immune checkpoints to evade immune surveillance. PNSA's ability to disrupt the interaction between Hsp90 and PD-L1 has the potential to block immune checkpoint signaling and restore CD8+ T cell activity. This dual mechanism of action has the potential for overcoming immune suppression within the tumor microenvironment.

The immunomodulatory effects of PNSA extend beyond antigen presentation and immune checkpoint regulation. Hsp90 inhibition can influence cytokine production by immune cells, impacting the inflammatory milieu within the tumor microenvironment. Moreover, the activation of CD8+ T cells by

Correspondence to: Manfred Clarke, Department of Molecular Medicine, University of Maryland, Baltimore, United States of America, E-mail: mnfrdck@yahoo.com

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PNSA may lead to the formation of memory T cells, which can provide long-lasting protection against tumor recurrence. While Hsp90 C-terminal inhibitors like PNSA have the potential to improve the anticancer immunology of $CD8^+$ T cells, several challenges and concerns must be addressed. These include potential off-target effects, optimization of dosing regimens, and the development of resistance mechanisms. Additionally, the translation of preclinical findings into clinical applications requires careful evaluation through well-designed clinical trials.

CONCLUSION

The intersection of Hsp90 inhibition and CD8+ T cell immunology offers a compelling avenue for advancing cancer immunotherapy. The immunomodulatory properties of Hsp90 C-terminal inhibitors, exemplified by PNSA, hold the potential to enhance the antitumor activity of CD8+ T cells by promoting antigen presentation, disrupting immune checkpoints, and modulating the cytokine environment. While limitations remain, the possibility of improving anticancer immunology of CD8+ T cells by Hsp90 C-terminal suppression provide better cancer treatment and patient care.