The clinical relevance of immunogenic cell death-associated signaling and molecules in cancer therapy

The capacity of cancer cells to induce anticancer immune responses relies on multiple factors, including the antigenic repertoire of cancer cells and their ability to provide adjuvant signals, as represented by danger-associated molecular patterns (DAMPs), which are exposed and released by malignant cells during immunogenic cell death (ICD). The release and secretion of DAMPs can orchestrate the activation of innate and adaptive tumor-targeting immunity, resulting in tumor regression. Various chemotherapies, radiation therapy, physical modalities, and targeted anticancer agents have been described as potent ICD inducers, which besides being directly cytotoxic, can activate clinically relevant anticancer immune responses. Therefore, patients whose tumor microenvironment (TME) is shows defective DAMP release or downstream DAMP-sensing signaling pathways do not fully benefit from ICD-inducing treatments, which can lead to overall therapeutic failure. My dissertation contributes to this field by exploring the impact of ICD on the development of innate anticancer immune responses, with a particular focus on natural killer (NK) cells, showing that surface-exposed calreticulin (ecto-CALR) positively impacts the frequency and cytotoxicity of NK cells in peripheral blood of acute myeloid leukemia (AML) patients. Additionally, our findings support the previous observation that active danger signaling, and the release of DAMPs, can enhance the clinically relevant responses to standard of care therapy and immunotherapy in cancer patients. Moreover, ICD inducers have been harnessed in the preparation of dendritic cell (DC)-based vaccines, such as DCVAC, antibody–drug conjugates, and other therapies with promising clinical results. Therefore, the identification of reliable predictive biomarkers could further support the clinical development of such personalized treatments. Finally, to this end, we identified a predictive gene signature for future clinical management of DCVAC therapy in prostate, lung, and ovarian cancer patients. In conclusion, the concept of ICD is currently regarded as a prominent pathway for activation of long-lasting anticancer immune responses, which to a significant degree determines the outcome of anticancer therapies.

Key words: Immunogenic cell death, danger associated molecular patterns (DAMPs), anticancer immune response, combined treatment, anticancer cell therapy**.**