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EDITORIAL

Radiation Therapy and the Immune System: A Scientific Revolution in the Making

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Cancer therapy has long sat atop 3 distinct legs: surgery, systemic therapy, and radiation therapy. Although all of these modalities have been meaningfully enhanced by a steady flow of incremental improvements over the last half-century, there has been a feeling that something new was needed to "break the mold" and make a substantial difference in toxicity and cure. Modulation of the immune system has long been revered as the most likely game-changer in holy grail of cancer therapy, but widespread practical realization has been slow in coming. Nonetheless, the complex field of immunology has been quietly amassing an ever-greater specificity of evidence; the more that tumors were found to be related to viral infection, the likelier it became that tumor-specific antigens might exist and that the full might of the immune system could be harnessed.

In the 1970s, there was great enthusiasm for nonspecific immune stimulation using agents such as the Bacille Calmette-Guérin vaccine.[1,2] It was noted in murine models that Bacille Calmette-Guérin could induce regression of mouse mammary carcinomas—responses that, with the exception of superficial bladder cancers, were not replicated in humans. From 1975 to 1979 enthusiasm peaked with more than 60 papers published annually on this phenomenon. It was later discovered that these murine tumors were uniquely immunogenic in a way that likely related either to their means of induction or their transplant status, and enthusiasm waned.

In the 1980s, there was again great excitement when it was demonstrated that systemic infusions of lymphocytes stimulated by the cytokines interleukin 2 and interferon produced regressions in patients with metastatic renal cancers and melanomas.[3,4] After these high-profile reports, hope surged anew, but disappointment again soon followed. Regressions were seen, but they were infrequent, occurred in only a small percentage of cases, and came at the price of very high toxicity, with many patients having to be admitted to intensive care units for cardiovascular support.

Thirty years later, we are again riding a massive wave of hope, but is anything different this time around? In this special edition of the Red Journal, we answer with a resounding "yes." Today's therapies are now built on a solid foundation of basic science and deep understanding of the molecular biology of the immune response and its antagonism. The 2018 Nobel Prize for Physiology was awarded to James Allison and Tasuku Honjo for their discovery that there was a negative immune regulatory system that could itself be inhibited through PD-1 and PD-L1 modulation.[5,6] From this discovery came new checkpoint inhibitor drugs, which resulted in frequent, durable responses in kidney cancers, lymphomas, and melanoma. But more than that, responses were seen in tumors previously thought to be non- or just weakly immunogenic, such as lung and bladder cancers; after these observations, investigations of checkpoint inhibition have become an unavoidable first consideration for nearly every type of cancer. Regression, or dormancy, has been translated into considerable prolongation of survival time for patients with many types of metastatic cancer and opened new roles and avenues of exploration for radiation oncology. Can radiation be used to eliminate residual masses with synergistic or curative effect? Can it be used to enhance the immune response and extend the duration of therapeutic efficacy or to trigger a near-miraculous abscopal response clearing the body of all cancer? What is the most intelligent sequence of radiation and immunotherapy? What doses, how long, and what types of radiation should be given?

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Our field, excited by these rapidly expanding possibilities, has seized the moment and is exploring all these possibilities in animal models and humans. A large number of trials are registered exploring the integration of radiation and immunotherapy. In this special edition, we showcase the state of the science in 2020. Review and original scientific articles cover the mechanisms of immunotherapy. These now extend well beyond the checkpoint inhibition of T cells to other components of the immune response such as toll-like receptors and B cells. Comparing other species' immune systems to that of humans is a controversial scientific issue, and thus we provide articles describing the available models of immune response in which new strategies can be developed. There are studies looking at clinical outcomes, predictive factors, and the elusive abscopal response. Every bit as important, we include articles documenting unique immunologically mediated toxicities. These latter phenomena will determine what strategies are, in fact, clinically feasible. Although checkpoint inhibitors have proven to be remarkably well tolerated by many patients, a deep understanding of their complex and occasionally severe effects, particularly as combined with radiation therapy, needs further careful study.

We believe that understanding the multiplicity of ways in which cancer cells shield themselves from immune detection (and how to overcome these mechanisms) represents the most important development in oncology in 4 decades, and now, in 2020, we are on the cusp of a scientific revolution. This timely special edition of the Red Journal showcases the science and innovation that these discoveries have spawned in radiation oncology, and we strongly encourage our colleagues to dip in and become enlightened in this field. It is necessary. It is our future.

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