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Understanding the pluses of pulses

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For the majority of cancer patients, the benefits of radiotherapy far outweigh the risks of acute toxicities and adverse sequelae. A goal of current research efforts is to maximize the former while minimizing the latter. One attractive strategy is to deliver the total dose of radiation in a pulsatile fashion, an evolving practice known as pulsed low dose rate radiotherapy (PLDR). This approach was originally based on observations that low doses (typically <1 Gy) cause levels of DNA damage that apparently fail to trigger the signals for DNA repair in vitro. The threshold dose at which repair is triggered is reportedly higher in many tumor cells as compared with normal tissue, therefore providing a window of opportunity. Accordingly, spreading the total doses into short, low-dose pulses been shown to effectively limit tissue toxicity and minimize complications.[1,2] Although PLDR has been validated in pre-clinical and clinical studies, the molecular basis of reduced necrosis and preserved normal tissue integrity has remained unclear.

The toxic effects of high-dose radiation are closely related to the post-treatment levels of local inflammatory cytokines, including the prototypic cytokine TGF-β. Among the highly sensitive tissues is the lung, and the risk of radiation-induced pneumonitis is dose-limiting for thoracic radiotherapy. Pharmacologic inhibitors of TGF-β have been proposed as a means of mitigating this inflammatory response and preventing subsequent fibrosis,[3] a concept that has been broadened to include connective tissue growth factor, which mediates the effects of TGF-β.[4] In this volume of *Cell Cycle*, Meyer et al.[5] provide direct evidence that PLDR minimizes TGF-β induction in normal murine tissues that are highly radiosensitive, including the lung, bone marrow, and the small intestine. Most striking was the observed reduction in post-treatment atrophy in both the bone marrow and cecum, 2 organs that typically exhibit dose-limiting toxicities.

The entire field of oncology has undergone a major paradigm shift in the past several years, with a rapidly growing appreciation for the primacy of the innate and adaptive immune responses in tumor suppression. This paradigm shift has inevitably influenced our view of radiotherapy, which has rapidly refocused on the complex interplay between DNA damage, immune activation, and the paracrine factors that contribute to clinical tumor responses.[6,7] While the differential threshold for DNA repair induction in normal cells and tumor cells may account for some of the apparent benefits of PLDR, this new study by El-Deiry and colleagues underscores the overriding importance of the local innate immune response and the remarkable impact of inflammatory cytokines. Fully understanding the innate and adaptive immune responses to ionizing radiation - and learning to effectively harness them – will likely be critical to future progress.

Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.

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