

Treatment induced upregulation of DNA sensing pathways as a mechanism for inducing anti-tumor immune response

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Radiation therapy is a mainstay of cancer treatment with approximately one-half of all cancer patients receiving it as a part of their standard of care. In addition, new treatment modalities are entering clinical practice, among which, gene therapy, more specifically gene electrotransfer (GET) of therapeutic plasmid DNA to tissues, shows potential. The effects of these therapies are not only specific on their targeted mechanism, but, it is becoming more and more evident that they can also modulate the immune response in tumors, which in conjunction with immune checkpoint inhibitors could mediate the tumor's response to therapy or even incite systemic rejection of cancer. The mechanisms of these effects remain unclear; however, DNA sensing pathways were demonstrated to be involved. The DNA, which accumulates in the cytosol of cells following irradiation due to the damage induced by X-ray radiation is sensed by specific pattern recognition receptors, i.e. DNA sensors, which through several signaling pathways induce the production of various cytokines - type I interferons, tumor necrosis factor alpha, interleukin 1 beta and others, depending on the cell type. A similar effect can be seen when plasmid DNA enters the cell after GET, which is also sensed by DNA sensors in the cytoplasm. The released cytokines, which are expressed following the sensing of DNA in the cytoplasm can then mediate the anti-tumor immune response in tumors. Understanding the timing of the activation of the DNA sensing pathways and subsequent cytokine expression induced by different treatment modalities could improve the schedules for combining immune checkpoint inhibitors with standard of care treatment modalities in order to improve the immunotherapy of cancer.