Immunotherapy against melanoma by pIRE-IL12 Gene electrotransfer (GET): a pre-clinical investigation

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Purpose: Melanoma is the deadliest of skin cancers as frequently diagnosed at a metastatic stage. Until recently, only few treatment options with significant increases in overall survival were available for patients with advanced or metastatic melanoma. Immunotherapies held tremendous promises for improving melanoma treatment. One strategy is to boost the activation of cytotoxic cells and increase the visibility of tumor antigens by immune cells, as melanoma is a low immunogenic tumor type. The aim of our study was to develop a new therapeutic approach, increasing the accessibility of melanoma antigens to effector T cells and improving their level of activation to enhance their efficacy.

Experimental Design: We evaluated the efficacy of a two-step protocol based on the use of electric field pulses on the B16F10 syngenic mouse model of melanoma. First, a high voltage electric field pulse was applied on the tumor inducing a partial Irreversible Electroporation (pIRE) of the tumor cells, leading to the release of hidden tumor antigens. We showed that pIRE induced apoptosis and necrosis of tumor cells. The second step consisted of the Gene-Electro-Transfer (GET), in the healthy skin directly surrounding the tumor, of a plasmid encoding a well-known activator of immune cells: IL-12. IL12-GET was shown to be safe as the plasmid was detected only at the site of injection (skin) during a limited period of time (50 days) [1].

Results: pIRE treatment alone induced a transient decrease in the tumor volume, resulting in a 20 days increase of mouse survival compared to untreated mice. A single pIRE treatment combined with pIL-12-GET led to a significant and stable regression of melanoma growth in a curative protocol (50% survival over 100 days). This was associated with secretion of Interferon-gamma. This treatment reduced the growth of untreated distant tumor mass suggesting a systemic activation of the immune system. Moreover, when challenged on the opposite side, 50% of the complete responders were resistant to the development of a new tumor [2]. We observed that the GET induced a migration of dermal and epidermal dendritic cells from treated skin to the draining lymph nodes.

Conclusion: Our work demonstrated that the combination pIRE/pIL-12-GET induced an efficient activation of the anti-tumor immune response leading not only to tumor eradication but also establishment of an immune memory and long term protection. This approach would provide a new low cost therapeutic strategy for a safe and efficient melanoma treatment.

References:

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