## conferenceseries.com International Conference on Tumor & Cancer Immunology and Immunotherapy

July 28-30, 2016 Melbourne, Australia

## Hypoxia induced autophagy: A new regulator of the anti tumor immune response

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Hypoxia, a common feature of the tumor microenvironment has been widely described as a major contributor to tumor resistance to anti cancer therapies. It has been reported that hypoxic stress in the tumor plays a key role in shielding tumor cells from the immune attack. Indeed, tumor cells acquire the capacity to circumvent immune cell attack and hijack the tumor microenvironment to support their own growth and metastasis. Natural Killer (NK) cells are effectors of the innate immune system, capable of killing cancer cells through the release of the cytotoxic granules containing perforin and Granzyme B. We have recently reported that hypoxia dependent activation of autophagy operates in the tumor as an intrinsic resistance mechanism leading to tumor escape from fully functional cytotoxic T-lymphocytes and NK cells mediated lysis. We provided evidence that targeting autophagy was sufficient to restore NK mediated tumor cell killing under hypoxia *in vitro* and *in vivo* by inducing a massive infiltration of NK cells into the tumor bed. The molecular mechanism underlying the infiltration of NK cells in autophagy defective tumors is currently under investigation. Our data argue that targeting autophagy in hypoxic tumors revert the immunosuppressive to immuosupportive tumor microenvironment at least in part for NK cells through the regulation of micro environmental factors involved in the NK cell recruitment. Taken together, this study provides a cutting edge advance in our understanding of the critical role of hypoxia induced autophagy in the impairment of NK mediated tumor cell killing and paves the way for formulating more effective NK based antitumor therapy by combining autophagy inhibitors.

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## Harnessing the natural way to fight cancers: Immunotherapy

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The immune system is a complex body system that plays a key role in keeping the host safe from infections and cancers. Cancer cells are actually the progeny of transformed host cells that have lost their ability to control the cell cycle process. These cells are capable of rapid growth and metastasis. Lymphocytes, in particular the T-lymphocytes have very crucial roles to play in the fight against cancers. However, as tumors are actually "self" that have transformed, it is extremely difficult to activate host immune system against cancers. The immune system generally does not mount responses against "self" due to immunological tolerance. So, the T-lymphocytes have to be appropriately activated so that the host can generate effective anti-cancer effects. The T-helper cells, when activated, direct the overall immune response by producing different cytokines. The T-helper cells were originally classified as Th1 and Th2 cells and the reciprocal effects of these cells have been well documented. The Th1 cells mediate cell-mediated immune responses, which play a crucial role in the fight against cancers. More recently, many more T-helper subsets have been reported. The T-helper cells undergo dynamic epigenetic changes as they develop and respond to various challenges to the immune system. Several approaches have been used to activate host immune system against cancers such as dendritic cell (DC) immunotherapy, adoptive T-cell immunotherapy, nutrition and other types of adjuvants as well as selective suppression of the T-regulatory cells. This paper will discuss the effectiveness of some of these immunotherapeutic approaches in the fight against cancers.

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