***Peter Vaupel Lecture***

**Hypoxia compromises anti-cancer immune responses**

**G. Multhoff**

*Center for Translational Cancer Research (TranslaTUM), Radiation Immuno-Oncology Group, Campus Klinikum rechts der Isar, TU München, Germany*

*Gabriele.multhoff@tum.de*

**Abstract:** Hypoxia, one of the key hallmarks of cancer, is caused by an insufficient oxygen supply, mostly due to a chaotic tumor microcirculation. It is well established that critically low oxygen levels are counterbalanced by the activation of a number of pro-tumorigenic transcription factors that support tumor progression, angiogenesis, invasiveness, cancer stem cell renewal and metastasis. Hypoxia mediates radiation resistance due to a reduced generation of free radicals and fixation of DNA damage, cell cycle arrest, decreased cell proliferation, modulated gene and protein expression and genetic instability. More recently, it became obvious that hypoxia also plays a pivotal role in anti-cancer immune responses. The tumor microenvironment (TME) consisting of tumor cells, stromal cells and immune cells including of CD4+ T helper cells, CD8+ cytotoxic T cells, FoxP3/CD25+ regulatory T cells (Tregs), natural killer (NK) cells, NK-like T (NKT) cells, myeloid derived suppressor cells (MDSC), M1 and M2 macrophages are highly sensitive to hypoxia- and HIF-driven downstream factors including adenosine (ADO) a metabolite of ATP, vascular endothelial growth factor (VEGF), acidosis, phosphatidylserine (PS) on the outer membrane leaflet and anti-apoptotic heat shock proteins (HSP). Hypoxia negatively affects anti-tumor immune responses by reducing survival, cytolytic and migratory activity of effector cells such as CD4+, CD8+ T cells, NKT and NK cells, by (a) reducing the production and release of effector cytokines, (b) supporting immunosuppressive cells such as Tregs, MDSCs and M2 macrophages, (c) increasing the production and release of immune-suppressive cytokines and (d) inducing the expression of immune checkpoint inhibitors.

Innovative therapeutic strategies including (a) blocking of immune checkpoint inhibitors by antibodies, (b) small molecule inhibitors that interact with EGFR, PI3K, Akt, mTOR, HIF-1α, VEGF pathway, (c) HSP90 inhibitors, (d) cell based therapies, and (e) chimeric antigen receptor (CAR) modulated immune cells either alone or in combination with radiochemotherapy, and might provide promising strategies to overcome hypoxia-induced immunosuppression in cancers.

*Reference:* P. Vaupel & G. Multhoff. Adenosine can thwart antitumor immune responses elicited by radiotherapy. Strahlenther Oncol 192:279-287,2016

I prefer:  