

The hypoxia-adenosinergic protection of tumors from anti-tumor T lymphocytes

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Abstract

Cancer immunotherapy by endogenous or adoptively transferred anti-tumor T cells is complementary to conventional treatments by surgery, radiotherapy, or chemotherapy. However, malignant cells can create a self-protective, immunosuppressive tumor microenvironment (TME) that prevents tumor destruction by anti-tumor T cells.

During last three decades we considered the possibility that cancerous tissues are protected by the same ancient, physiological tissue-protecting mechanism that has evolved to protect inflamed areas of normal tissues from continuing collateral damage during anti-pathogen immune response. Subsequent studies of T cell-mediated tumor rejection and of *in vivo* anti-pathogen immune response supported this view (1, 2).

Hypoxia-adenosinergic inhibition of anti-tumor T lymphocytes by A2 adenosine receptors and hypoxia-inducible factors

This tissue-protecting, negative feedback immunosuppressive mechanism is triggered by excessive tissue damage-associated interruption of local blood and oxygen supply, which results in local tissue hypoxia, stabilization of the Hypoxia Inducible Factors and hypoxia-driven accumulation of extracellular adenosine (3).

The extracellular adenosine then signals via high affinity A2A and low affinity A2B adenosine receptors on the surface of CD8+ and CD4+ T cells and thereby elevates intracellular levels of highly immunosuppressive cAMP. The "Adenosinergic" signaling inhibits the TCR-triggered activation of T cells and of their many effector functions (4, 5).

The Hypoxia-Inducible Factor 1alpha and its isoforms may function to inhibit the T cells "from inside" as suggested by experiments using *RAG-2*^{-/-} blastocyst complementation chimeras and by *in vitro* and *in vivo* studies using tissue-specific deletion of HIF-1alpha gene in T cells (6, 7).

Indeed, some areas of cancerous tissues and of inflamed normal tissues are, indeed, hypoxic and extracellular adenosine-rich (2), although for different reasons. While inflamed tissues areas are hypoxic due to the excessive collateral immune damage to vasculature, some areas of tumors are hypoxic either because of abnormal cancerous tissue infrastructure and/or geometry or because the tumor growth outpaces the growth of supporting vascular bed.

Anti-hypoxia-adenosinergic cancer immunotherapy strategy

The A2A adenosine receptors on the surface of anti-tumor CD8+ T cells strongly inhibit T cell-mediated tumor rejection since genetic deletion or pharmacological antagonism improved T cell-mediated tumor rejection (2). Thus, while the Hypoxia-Adenosinergic inhibition of overactive T cells during acute inflammation protects tissues of vital organs and is life-saving,

the Hypoxia-Adenosinergic inhibition of anti-tumor T cells in TME protects tumors and is to be prevented.

We provided the genetic *in vivo* evidence that one of the approaches to prevent the inhibition of cancer vaccine-induced and endogenously developed or adoptively transferred anti-tumor T cells is to weaken or eliminate the Hypoxia-Adenosinergic signaling. This "Anti-Hypoxia-Adenosinergic" approach may add to the already demonstrated promise of targeting other negative regulators of anti-tumor immune response, such as e.g. CTLA4 and Tregs (8).

We plan to improve tumor rejection by preventing the Hypoxia-Adenosinergic inhibition of anti-tumor T cells by (a) using the A2AR antagonist drug (synthetic or natural compounds) that out-competes the tumor-produced and T cell-inhibiting extracellular adenosine in TME and by (b) treatments that decrease the levels of tumor-produced adenosine and thereby enable the competitive A2AR antagonist to be more effective. The one of unusual features of this approach is in the opportunity to immediately test effects of the non-selective A2A adenosine receptor antagonist 1,3,7-trimethylxanthine (a.k.a. caffeine). The caffeine is the most widely used psychoactive drug in the world with quite acceptable toxicity in humans. *In vivo* preclinical studies suggest that even better immunotherapeutic effects could be expected with longer-lived *in vivo* synthetic A2A receptor antagonists which have been developed for Parkinson disease and shown to be safe in human clinical trials.

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