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Targeting tumor-associated immune suppression with selective protein kinase A type I (PKAI) inhibitors may enhance cancer immunotherapy

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ABSTRACT

Despite the tremendous progress in last few years, the cancer immunotherapy has not yet improved disease-free because of the tumor-associated immune suppression being a major barrier. Novel trends to enhance cancer immunotherapy aims at harnessing the therapeutic manipulation of signaling pathways mediating the tumor-associated immune suppression, with the general aims of: (a) reversing the tumor immune suppression; (b) enhancing the innate and adaptive components of anti-tumor immunosurveillance, and (c) protecting immune cells from the suppressive effects of T regulatory cells (Tregs) and the tumor-derived immunoinhibitory mediators. A particular striking example in this context is the cyclic adenosine monophosphate (cAMP)-dependent protein kinase A type I (PKAI) pathway. Oncogenic cAMP/PKAI signaling has long been implicated in the initiation and progression of several human cancers. Emerging data indicate that cAMP/PKAI signaling also contributes to tumor- and Tregs-derived suppression of innate and adaptive arms of anti-tumor immunosurveillance. Therapeutically, selective PKAI inhibitors have been developed which have shown promising anti-cancer activity in pre-clinical and clinical settings. Rp-8-Br-cAMPS is a selective PKAI antagonist that is widely used as a biochemical tool in signal transduction research. Collateral data indicate that Rp-8-Br-cAMPS has shown immune-rescuing potential in terms of enhancing the innate and adaptive anti-tumor immunity, as well as protecting adaptive T cells from the suppressive effects of Tregs. Therefore, this proposal specifically implicates that combining selective PKAI antagonists/inhibitors with cancer immunotherapy may have multifaceted benefits, such as rescuing the endogenous anti-tumor immunity, enhancing the efficacy of cancer immunotherapy, and direct anti-cancer effects.

Background

Disruption of protein kinase functioning upon genetic mutations or dysregulated activity as underlying signaling component of transforming oncogenes is extensively implicated in the complex networks of essential signaling pathways leading to tumor initiation and progression [1]. In addition to their role in tumorigenesis, many protein kinases also modulate the signaling networks that coordinate many aspects of tumor-associated immune cells' functioning in anti-tumor immunosurveillance. Examples include phosphoinositide 3 kinase (PI3K) signaling pathway, mitogen-activated protein kinase (MAPK) pathway, and the cyclic adenosine monophosphate (cAMP)-dependent protein kinase A (PKA) pathway, to name but a few [2–4]. From the therapeutic point of view, small-molecule kinase inhibitors targeting oncogenic signaling pathways as well as modulating the immune cell functions may facilitate their potential use, either alone or in combination with conventional immunotherapeutic agents, for the improved treatment of cancer.

PKA Type I (PKAI) in tumor and immune cells: two sides of a coin

PKA is a key regulatory enzyme comprising two isoforms, type I (PKAI) and type II (PKAII), which possess different structural fea-

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tures and perform distinct functions in the same cell on selective activation by the same intracellular messenger, cAMP. PKAI enhances cellular proliferation and active cell growth, while PKAII inhibits proliferation and induces differentiation [5,6]. The cAMP-dependent aberrant activation of PKAI has long been implicated in the formation and progression of several highly prevalent human cancers, and has been proposed not only as a novel biomarker for cancer detection but also as potential molecular target for cancer treatment [7]. Therapeutically, pharmacologically-devised selective PKAI inhibitors, such as site-selective cAMP analogs and antisense oligonucleotides, have been developed which have proved themselves as potential anti-cancer agents in pre-clinical and clinical settings [8,9]. On the other hand, the aberrant expression of PKAI has also been implicated in the negative modulation of normal immune responses. Several studies have demonstrated that hyperactivation of PKAI may impair both the initiation and effector phases of T cell responses through inducing defective activation and proliferation, as well as may suppress the natural killer (NK) cell cytotoxicity. Moreover, it may also inhibit antigen-specific B cell proliferation [10,11]. This outlines a pivotal immunomodulatory role of PKAI and also makes it a potentially attractive drug target for immunomodulation in variety of human immune dysfunctional disorders, including common variable immunodeficiency (CVI) and acquired immune-deficiency syndrome (AIDS); thus, embarking selective PKAI antagonists as potential combinatorial therapeutics with conventional treatment regimens [10,12].

The focus of this research topic, however, is to specifically propose the immunotherapeutic potential of selective PKAI inhibitors with respect to cancer therapy. Due to the documented pleiotropic effects of PKAI on multiple cell types, including tumor cells and the tumor-associated immune cells (Fig. 1), the combination of PKAI inhibitors with cancer immunotherapy seems to be attractive.

Hypothesis

Selective PKAI antagonists/inhibitors may rescue or enhance the functional activity of tumor-associated immune cells in the immunosuppressed tumor microenvironment and, thus, may promote the effective anti-tumor immunosurveillance. They may be used either alone or as adjunctive couple with conventional immunotherapeutics to restore or induce an improved immune status against cancer.

Evaluation and discussion

Harnessing the therapeutically targeted tumor-associated immune suppression for cancer immunotherapy

The interactions between malignant and host immune cells devising tumor elimination are referred as tumor immunosurveillance. Such interactions are driven by a complex and dynamic network of intercellular mediators (e.g. cytokines, chemokines, inflammatory enzymes, etc.) and cellular cross-talks involving both the innate, especially natural killer (NK) cells, and the adaptive, in particular CD4+ and CD8+ T cells, components of the immune system [13]. However, the tumor microenvironment privileges a variety of immune-suppressive regulators, rather than immune effectors, particularly including; tumor-associated macrophages and fibroblasts [14], T regulatory cells (Tregs) and myeloid-derived suppressor cells (MDSCs) [15], and various immunoinhibitory mediators such as enzymes, molecules, soluble factors and cytokines [16], all contributing to suppression of anti-tumor immunity, ultimately leading to tumor immune evasion/escape. Pharmacological/biological targeting of the extrinsic and/or intrinsic pathways induced by cells or mediators favoring tumor-

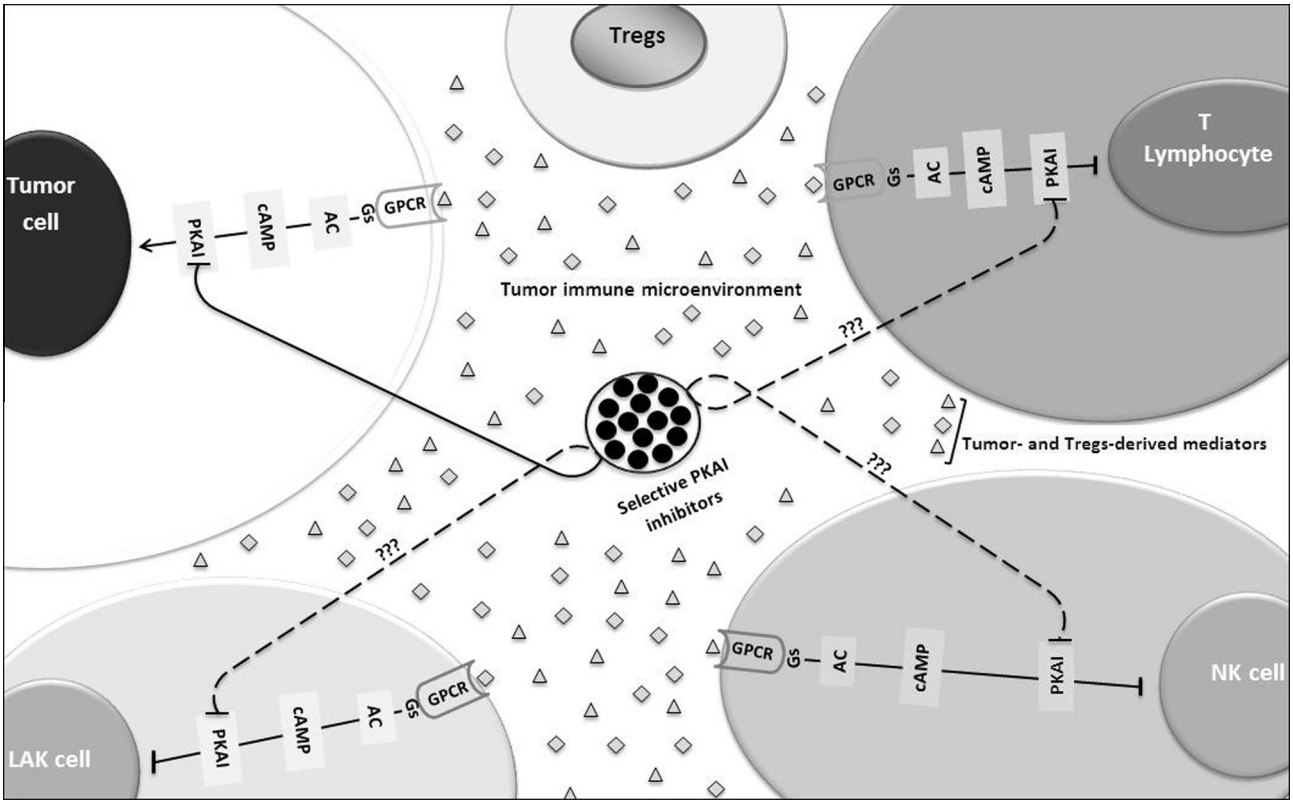

Fig. 1. Brief description of cAMP-PKAI signaling in the tumor and immune cells, and its potential pharmacological blockade by small-molecule PKAI inhibitors to enhance cancer immunotherapy. AC, adenylate cyclase; cAMP, cyclic adenosine-5′-monophosphate; GPCR, G-protein coupled receptor; Gs, G-stimulatory protein; LAK, lymphokine-activated killer; NK, natural killer; PKAI, protein kinase A type I; Tregs, T regulatory cells; ???, still to be elucidated in the tumor settings.