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Mini-review

Dichotomous role of protein kinase A type I (PKAI) in the tumor microenvironment: A potential target for 'two-in-one' cancer chemoimmunotherapeutics

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ABSTRACT

An emerging trend in cancer chemoimmunotherapeutics is to develop 'two-in-one' therapies, which directly inhibit tumor growth and progression, as well as enhance anti-tumor immune surveillance. Protein kinase A (PKA) is a cAMP-dependent protein kinase that mediates signal transduction of G-protein coupled receptors (GPCRs). The regulatory subunit of PKA exists in two isoforms, RI and RII, which distinguish the PKA isozymes, PKA type I (PKAI) and PKA type II (PKAII). The differential expression of both PKA isozymes has long been linked to growth regulation and differentiation. RI/PKAI is particularly implicated in cellular proliferation and neoplastic transformation. Emerging experimental and pre-clinical data also indicate that RI/PKAI plays a key role in tumor-induced immune suppression. More briefly, RI/PKAI possesses a dichotomous role in the tumor microenvironment: not only contributes to tumor growth and progression, but also takes part in tumor-induced suppression of the innate and adaptive arms of anti-tumor immunosurveillance. This review specifically discusses this dichotomous role of RI/PKAI with respect to 'two-in-one' chemoimmunotherapeutic manipulation. The reviewed experimental and pre-clinical data provide the proof of concept validation that RI/PKAI may be regarded as an attractive target for a new, single-targeted, 'two hit' chemoimmunotherapeutic approach against cancer.

Introduction

Cancer chemoimmunotherapeutics strategically integrate chemotherapy and immunotherapy in order to optimize the chance for cure. The holy grail of chemoimmunotherapeutic treatment regimens is to execute a 'double-edge sword' impact, able on the one hand to mount a robust anti-tumor immune response, and on the other hand, selectively eradicate tumor growth and progression. Tremendous progress is being, and has been, made in this sense by evaluating a variety of drug combinations, including pharmacological and biological agents, with complimentary mechanisms of action [1–4]. A novel concept in cancer chemoimmunotherapeutics is focused on developing single-targeted 'two hit' therapies by manipulating the molecular events having dichotomous role – promote tumor growth and aid tumor immunoescape – in the tumor microenvironment [5]. In this regard, the multilevel pharmacological manipulation of tumor-derived, adenosine- and prostaglandin E2 (PGE2)-induced, cyclic adenosine monophosphate (cAMP)/protein kinase A (PKA) signaling in the tumor microenvironment seems to be an attractive approach [6].

PKA is a multi-unit serine-threonine protein kinase comprising regulatory (R) subunits; including RIα, RIβ, RIIα, and RIIβ isoforms, and the catalytic (C) subunits; including Cα, Cβ, and Cγ isoforms [7]. Structurally, PKA exists as two distinct isozymes; PKA type I (PKAI) and PKA type II (PKAII). Both PKA isozymes differ in R subunits, termed RI in PKAI and RII in PKAII, while the C subunit remains the same. RI and RII have two cooperative cAMP-binding sites, called A and B (Fig. 1). Functionally, both PKA isozymes are inactive heterotetrameric holoenzymes of two R and two C subunits [7]. The dissociation of PKA holoenzyme complex, via G-protein coupled receptors (GPCRs)-induced cAMP signaling, releases the free and activated forms of two C and two R subunits, which ultimately perform certain kind of functional activities (Fig. 1). More briefly,

Abbreviations: 3LL, Lewis lung carcinoma; AC, adenylyl cyclase; AS-PKAI, antisense oligonucleotide targeted against RI/PKAI; ATP, adenosine-5'-triphosphate; bFGF, basic fibroblast growth factor; C, catalytic subunit; cAMP, cyclic adenosine monophosphate; COX, cyclooxygenase; EGFR, epidermal growth factor receptor; GM-CSF, granulocyte macrophage colony stimulating factor; GPCRs, G-protein coupled receptors; IFN, interferon; IL, interleukin; LAK, lymphokine-activated killer; LPA, lysophosphatidic acid; MBOs, mixed backbone oligonucleotides; MDR, multidrug resistance; NK, natural killer; PG, prostaglandin; PKA, protein kinase A; RI, regulatory subunit I; RII, regulatory subunit II; S1P, sphingosine-1-phosphate; TGF, transforming growth factor; TNF, tumor necrosis factor; Tr1, adaptive Treg; Treg, T regulatory cells; VEGF, vascular endothelial growth factor.

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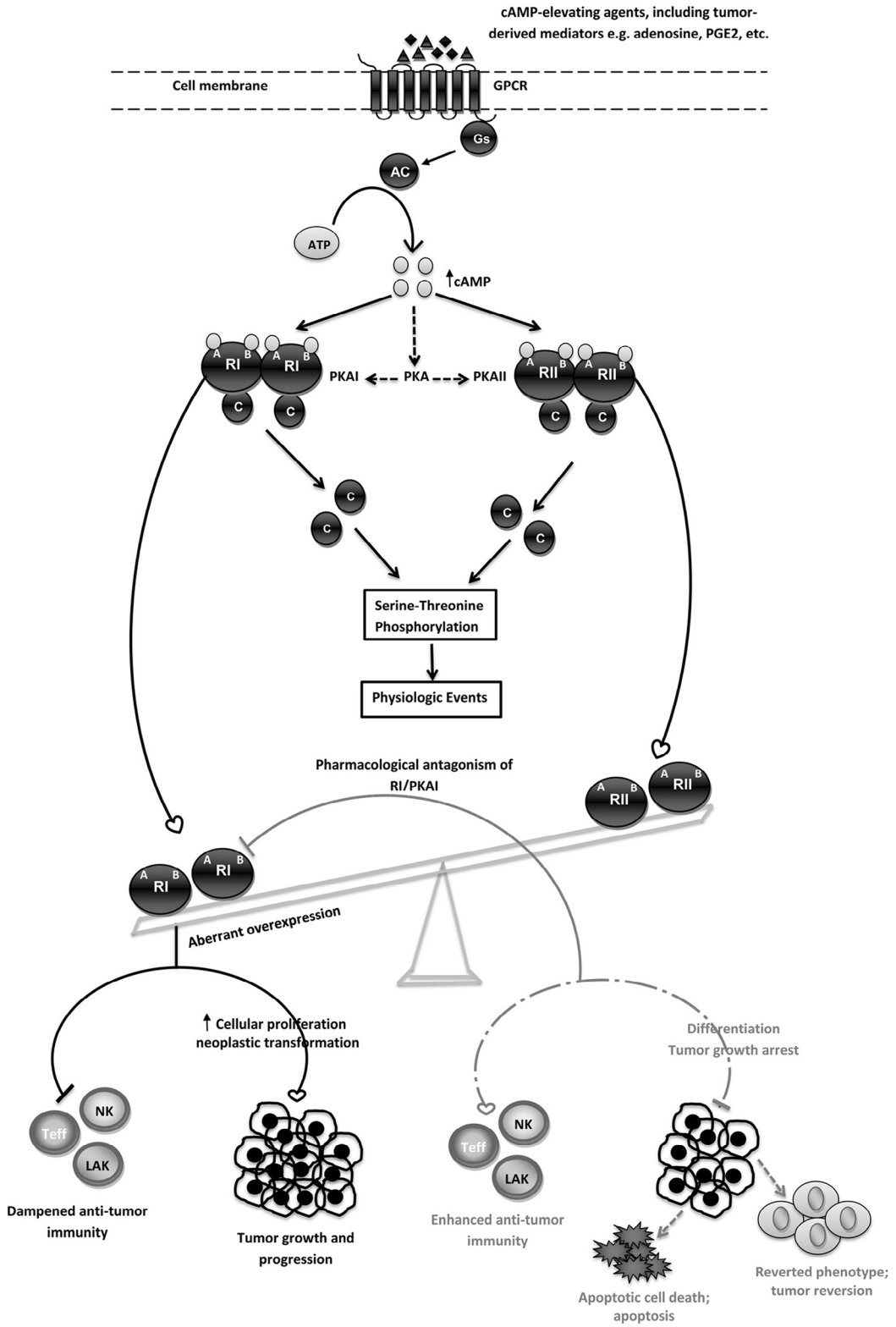

Fig. 1. A brief description of the dichotomous role of RI subunit of PKAI in the tumor microenvironment, and its 'two hit' chemoimmunotherapeutic manipulation. The cAMP-elevating agents via GPCRs initiate a signaling pathway that culminates with the increased intracytoplasmic cAMP levels leading to activation of PKA. The binding of two cAMP molecules to each of the R subunits results in the dissociation of holoenzyme complex, leading to release of two C subunits. These C subunits then phosphorylate serine and threonine residues on specific substrate proteins, including various transcription factors, thereby inducing genetic regulation of different proteins involved in several physiological processes. At the same time, the dissociation of PKA holoenzyme complex also releases allosterically modified free R subunits, posing them certain kind of functional activity related to cellular proliferation and differentiation. The tumor-derived mediators may induce the aberrant expression of RI subunits, tilting the intracellular balance between RI/PKAI–RII/PKAII toward RI/PKAI, which ultimately suppresses antitumor immunity and enhances tumor initiation and progression. Finally, the selective pharmacological antagonism of RI/PKAI may provide a 'two-in-one' chemoimmunotherapeutic opportunity: tumor growth arrest leading to tumor reversion or apoptosis, as well as enhancement of the endogenous anti-tumor immune responses. ATP, Adenosine-5'-triphosphate; PGE_2, prostaglandin E_2; AC, Adenylate cyclase; cAMP, Cyclic adenosine-5'-monophosphate; PKA, protein kinase A; GPCR, G-protein coupled receptor; PKA, Protein kinase A; PKAI, PKA type I; PKAII, PKA type II; RI, Regulatory subunit I of PKA; RII, Regulatory subunit II of PKA; C, Catalytic subunit; NK, Natural killer cells; Teff, T effector cells; Treg, T regulatory cells.

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