Protein Kinase A Type I: A Target For Cancer Therapy

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The mechanism of action of the two isoforms of the PKA,¹ defined PKAI and PKAII, respectively, has been the object of study for almost 25 years. However, only during the past decade, experimental evidences have started to confer distinct functions to PKAI and PKAII and have demonstrated that their intracellular balanced expression may play a critical role in the control of cell growth and differentiation. A new established notion is that PKAI overexpression is transiently induced by physiological stimulation of cell proliferation, preferentially expressed in cancer cells versus normal cells, and associated with a worse prognosis in different types of human cancer, whereas PKAII is expressed prevalently in normal differentiated tissues (1, 2).

In the past years, in the attempt to unravel the connection of PKAI with other proteins involved in the network of intracellular mitogenic signaling, selective pharmacological tools, able to modulate PKAI expression, have been developed. Such agents have provided a major contribution in the understanding of important PKAI functions but have also revealed themselves as potential anticancer agents. Among the most powerful tools developed to accomplish this task, a special place is occupied by the antisense oligonucleotides targeting the PKAI subunit R1α (AS-PKAI), from the early unmodified oligos to the more sophisticated DNA/RNA hybrid MBOs, which are active also after p.o. administration (3, 4). Modulation of PKAI versus PKAII and selective inhibition of PKAI expression by different tools, including the AS-PKAI, have demonstrated that: (a) PKAI has a direct interaction with the activated EGFR and is downstream of various hormones and growth factors, favoring the propagation of their mitogenic signals; (b) PKAI is associated with the multidrug resistant phenotype; (c) down-regulation of PKAI is balanced by a rapid compensatory increase of PKAII, especially the PKAIβ isofrom; and (d) PKAI inhibition is associated to early inhibition of expression of growth factors and their receptors, such as vascular endothelial growth factor and basic fibroblast growth factor, to induction of apoptosis; and finally, to growth arrest, as demonstrated both in vitro and in vivo in mice models (1, 2, 4). A recent seminal paper from Cho-Chung’s group, using the gene chip array technology, has provided for the first time the demonstration that the novel hybrid MBO AS-PKAI is able to modulate a wide set of genes related to cell proliferation and transformation, including those indicated above, versus others mostly involved in growth arrest and differentiation (5). This novel approach has, therefore, confirmed and extended the findings generated by studies spanning about a decade and based on experiments conducted with “conventional” biochemical, molecular biology, and translational approaches.

Recently, different studies have established a more direct link between PKA and apoptosis, reporting a specific PKA phosphorylation site on bcl-2 protein, a structural link between PKAI and the cytochrome c oxidase, and the ability of AS-PKAI to induce bcl-2 phosphorylation, cleavage of poly(ADP-ribose) polymerase, caspase 3 activation, and, finally, apoptosis (6–8). Cho et al. (9), in this issue of Clinical Cancer Research, clearly demonstrate that the MBO AS-PKAI can induce phosphorylation of bcl-2 and hypophosphorylation of BAD, thus causing bcl-2 inactivation and induction of apoptosis in androgen-independent human prostate cancer cells. This effect may be relevant in light of the reported association of bcl-2 with prostate cancer switch and progression from androgen-dependent to androgen-independent growth (10). Equally fascinating, another major contribution of this report is the elegant demonstration that the effect of the novel hybrid MBO AS-PKAI is attributable to site- and sequence-specific inhibition of R1α expression and PKAI formation, unambiguously established by analyzing the biochemical and molecular hallmarks of PKA isoforms functions. This demonstration is a strong support for the therapeutic antisense oligonucleotides approach, which, despite the increasing evidences of activity in a clinical setting, still raises doubts about the specificity of the action observed.

To date, the interpretation of the mechanistic role of PKAI in cell proliferation and transformation is still debated, because it is not clear yet whether PKAI plays a “passive” role by titrating the catalytic subunit and, thus, preventing the formation of the growth arrested-associated PKAIβ isoform, or it has an “active” role by phosphorylating selected targets in specific subcellular regions where it may be located. An interesting and therapeutically relevant implication is that, whatever the case, down-regulation of R1α expression prevents PKAI formation, favors PKAII expression, and eventually leads to cell growth arrest.

PKAI As Therapeutic Target. The demonstration of the central role of PKAI as a protein integrating multiple signaling pathways in the cancer cell clearly supports the use of the selective inhibitors of PKAI, originally devised as investigational tools, as potentially relevant therapeutic agents. PKAI inhibitors, such as 8-Cl-cyclic AMP and the hybrid MBO AS-PKAI, have demonstrated the ability to exert a cooperative antitumor effect when used in combination with certain cyto-

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²The abbreviations used are: PKA, protein kinase A; MBO, mixed backbone oligo; EGFR, epidermal growth factor receptor.
toxic drugs, especially taxanes and platinum derivatives, with ionizing radiations and with specific EGFR inhibitors, such as the monoclonal antibody C225 and the tyrosine kinase inhibitor ZD1839 (Iressa). The cooperative and long-lasting antitumor effect, observed both in vitro and in vivo in a wide variety of human tumor models, is attributable to block of cell proliferation and growth factors expression, inhibition of angiogenic factors expression and vessels formation, and induction of apoptosis. Among the PKAI inhibitors, 8-Cl-cyclic AMP has completed Phase I trials but has never been studied further, whereas the hybrid AS-PKAI is now completing Phase II trials in combination with cytotoxic drugs.

The therapeutic application of a PKAI inhibitor, such as the AS-PKAI, could be both in combination with other agents to enhance their antitumor activity and trigger apoptosis and for prolonged periods of time after conventional therapy to turn off mitogenic signals and induce a status of tumor dormancy. This therapeutic strategy would allow the use of low doses of cytotoxic drugs and a more selective and long-term control of cancer with moderate toxicity. In this regard, the good p.o. bioavailability of the MBO AS-PKAI, as well as of other signaling inhibitors showing cooperation with AS-PKAI, like ZD1839 (Iressa; Ref. 11), certainly improves the compliance to such kind of therapeutic approach. Moreover, because PKAI seems to participate in the signals triggered by proteins implicated in the process of neoplastic transformation, PKAI inhibitors may have a role in the field of chemoprevention.

We believe that the large amount of experimental evidences built up to date provide enough warranty to regard PKAI as a valuable target for cancer treatment and recognize that time has come to transfer this information in a clinical setting.

References


