Protein kinase C links to cancer

The protein kinase C (PKC) enzymes are a group of serine/threonine kinases that are intimately involved in signal transduction pathways. This family of enzymes has been implicated in a variety of diseases including cancer, asthma and cardiovascular disorders, such as hypertension and atherosclerosis [Bradshaw, D. *et al. Agents Actions* (1993) 38, 135–147]. There are twelve known PKC isozymes, which may offer potential as therapeutic targets for a wide range of disease states [Gordge, P.C. *et al. Cell. Signal.* (1994) 6, 871–882].

Tumor activation

The involvement of PKC in signal transduction and thus its association with cell differentiation and growth has linked inappropriate PKC activation to tumor growth. The two-stage model of carcinogenesis, in which bound PKC is directly activated by 12-O-tetradecanoylphorbol-13-acetate (TPA) and similar phorbol esters known to be potent tumor promoters, clearly established a link between PKC activity and tumorogenicity [Niedel, J.E. *et al. Proc. Natl. Acad. Sci. U. S. A.* (1983) 80, 36–40]. In fact, it is now known that many clinically proven anticancer agents are either inhibitors or activators of PKC. For example, the PKC inhibitor staurosporine and various staurosporine analogs have proven efficacious in a variety of *in vitro* and *in vivo* tumor models [Harris, W. *et al. Drugs of the Future* (1993) 18, 727–735]. In contrast, the anticancer agent bryostatin is a potent activator of PKC *in vitro*, which uses the same binding site on PKC as the phorbol esters [Hennings, H. *et al. Carcinogenesis* (1987) 8, 1342–1346]. It acts by initiating tight membrane binding by PKC, which eventually leads to degradation of the enzyme itself. These examples correlate with the seemingly anomalous behavior of phorbol esters, which have been shown to either induce or inhibit cellular differentiation depending on the cell type.

The role of PKC in modulating MDR

More recently, PKC has been linked to the multiple drug resistance (MDR) exhibited by some cancers through its interaction with the plasma membrane protein P-glycoprotein (PGP). PGP is a product of the *mdr*1 gene, and has been linked to MDR through its ability to act as an ATP-dependent drug efflux pump. The mechanism of action of well-understood MDR-reversal drugs, such as verapamil and cyclosporin A, is simply to compete with the anticancer drug for PGP binding, and therefore retard efflux of the anticancer agent. The drawback of these reversal agents is acute toxicity, therefore novel MDR treatments without this side effect are highly desirable.

Although the action of PKC appears to be ambiguous, with reports of both increased and decreased drug sensitivities, this enzyme certainly offers a unique opportunity for the treatment of MDR. As phosphorylation of PGP by PKC activates PGP and leads to increased resistance in drug-resistant cell lines, attempts have been made to modulate PKC activity using phorbol esters. For example, Posada, J. A. and coworkers [*Cancer Commun.* (1989) 1, 285–292] showed that prolonged TPA treatment of wild-type cells and adriamycin-resistant S-180 cells led to increased resistance to adriamycin in both cell types. Paradoxically, TPA treatment of A253 carcinoma cells has been shown to sensitize them to cisplatin treatment. [Basu, A. *et al. J. Biol. Chem.* (1990) 265, 8451–8457].

A recent study details a unique approach to overcoming MDR in human-breast-cancer MCF7 and MCF7-MDR cell lines. Phorbol ester treatment of MCF7 cells causes PKC to phosphorylate PGP more efficiently, thus causing MDR by increasing the rate of the PGP efflux pump. Gupta, K.P. and coworkers [*J. Biol. Chem.* (1996) 271, 2102–2111] identified a novel pseudosubstrate of PKC-α (an *N*-myristoylated peptide), which blocks the PGP-phosphorylation site in MCF7 and MCF7-MDR cells, thereby inhibiting phosphorylation of PGP and increasing drug accumulation within the cells.

The variety of MDR responses elicited by different PKC-related stimuli are apparently due to a number of factors. Specific and relative levels of PKC isozymes present in the different cell lines, modes of drug action and differences in experimental protocols, such as short-term versus long-term phorbol ester exposure, all affect the PKC/MDR paradigm. These complexities are further exacerbated by the fact that many MDR cell lines display elevated levels of PKC when compared with the wild type. It is therefore apparent that individual tumor cell lines must be studied in some depth to establish the effect of PKC modulation on MDR in each case.

The future

While connections between PKC and cancer are indisputable, many questions remain unanswered. The intricate workings of signal transduction pathways coupled with variable tissue and cell distributions, not only of PKC as a family but of individual PKC isozymes, only serve to complicate an already challenging field. To date, the most well understood target of MDR and its links, in particular, to PKC-α have given new insight into areas of research that will continue to improve the understanding of cancer chemotherapies at the subcellular level.

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Inhibition of angiogenesis as a potential therapeutic strategy

Angiogenesis is defined as the growth of new capillary blood vessels, and plays a fundamental role in growth and development. In mature adults the ability to initiate an angiogenic response is present in all tissues, but is held under strict control. Normally, angiogenesis is only mobilized for wound repair, or in highly specific situations such as endometrial regulation. In these circumstances angiogenesis is very tightly regulated in both time and space. This overall situation of suppressed angiogenic potential relies on a very fine balance between numerous stimulatory and inhibitory factors including enzymes, growth factors and cytokines.

The role of angiogenesis in disease states

Inappropriate angiogenesis is now recognized as playing a crucial role in a number of disease states. These conditions include rheumatoid arthritis (blood vessels invade the normally avascular pannus),

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