Oncogenic intelligence

Oncogenes and inositol lipids

from Bob Michell

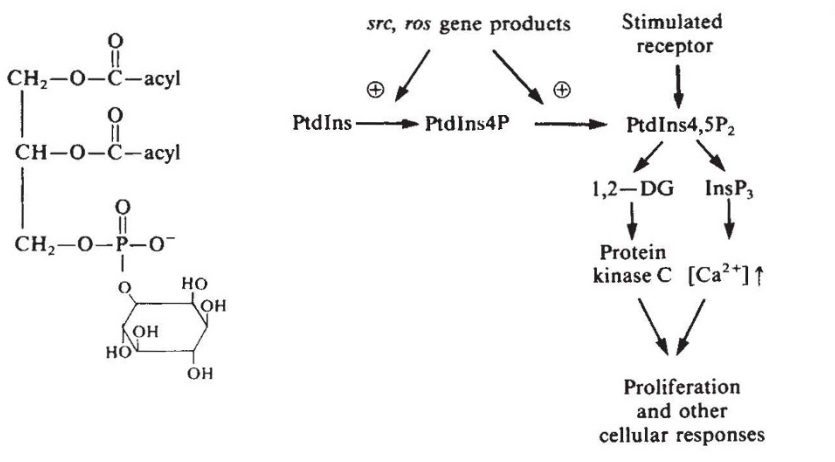
THE discovery of oncogenes opened a new era in studies of the control of the proliferation of both normal and malignant cells. The suspicion that the proteins coded by cellular oncogenes are participants in normal biochemical pathways essential to cellular growth control, and that these may go subtly awry in malignancy, is strengthened by the knowledge that the proteins encoded by oncogenes include a secreted growth factor[1-3], a homologue of a growth factor receptor[4] and several 'tyrosine-directed protein kinases'[5] which catalyse the same reaction as some activated growth factor receptors (see ref.6). What has been lacking is any clear knowledge of the nature of the cellular control pathway(s) affected by these proteins. But now studies by two communicating research groups indicate that some oncogene products act on the receptor-activated pathway in which the breakdown of an inositol lipid is stimulated, leading via an increase in cytoplasmic Ca^{2+} concentration and activation of protein kinase C to cell proliferation[7,8].

The primary evidence of both groups is that certain oncogene products can act as inositol lipid kinases. Thus, Sugimoto *et al.* show that purified $pp60^{v\text{-}src}$, the tyrosine kinase coded by the *src* oncogene of Rous sarcoma virus (RSV), can phosphorylate phosphatidylinositol (PtdIns), phosphatidylinositol 4-phosphate (PtdIns4P) and 1,2-diacylglycerol (1,2-DG)[7]. And Macara *et al.* demonstrate that $p68^{v\text{-}ros}$, the tyrosine kinase coded by the *ros* oncogene of the avian sarcoma virus UR2, can phosphorylate PtdIns[8]. The final product of the pathways of inositol lipid biosynthesis is phosphatidylinositol 4,5-bisphosphate ($PtdIns4,5P_2$), which is hydrolysed when appropriate receptors are activated[9-11]. Sugimoto *et al.* found that the transformation of fibroblasts by a temperature-sensitive mutant of RSV led to a large increase in the cellular content of $PtdIns4,5P_2$, PtdIns4P and phosphatidate only at the permissive temperature[7]. Cells transformed by UR2 showed both an increase in ^{32}P-labelling of PtdIns4P and $PtdIns4,5P_2$ relative to other phospholipids and an accumulation of inositol trisphosphate ($InsP_3$) and bisphosphate.

A clear and unbroken association between rapid inositol lipid turnover and rapid cell proliferation was first clearly established by Diringer[12] and has been maintained in all subsequent studies (reviewed in refs 13 and 14), suggesting that the turnover of these lipids is either an essential element in control of cell proliferation or an invariable consequence of that proliferation. The former view is supported by the fact that several, though not all, receptor-directed agents that stimulate cell proliferation cause a very rapid increase in the turnover of inositol lipids, long before any overt proliferative response. The initiating reaction is probably the breakdown of $PtdIns4,5P_2$ to 1,2-DG and $InsP_3$ (refs 9–11), with these two cellular messenger molecules activating, respectively, protein kinase C (which is also the cellular target of tumour promoters[15]) and the mobilization of Ca^{2+} ions from an intracellular store[16]. The new data suggest that one way in which some oncogenes (and possibly also growth-promoting hormones that activate tyrosine kinases) act is by enhancing the kinase activities responsible for supplying $PtdIns4,5P_2$, either by acting as inositol lipid kinases or by modifying the activities of the intrinsic cellular kinases.

Why should the breakdown of $PtdIns4,5P_2$ be a normal control reaction in nonproliferating cells and also a stimulus to proliferation? Possibly there is some sort of threshold of signal intensity that has to be exceeded before proliferation is triggered in competent cells. This might provide a rationale for the frequent observation that a combination of tyrosine-kinase-directed stimulus (insulin, epidermal growth factor) and $PtdIns4,5P_2$ breakdown directed stimulus (bombesin, vasopressin, prostaglandin $F_{2\alpha}$) is a much more potent activator of proliferation than is either stimulus alone[17,18]. In this interpretation it would be envisaged that one stimulus enhances the supply of substrate to the signalling reaction activated by the other stimulus, so leading to a greater intensity of signal input to the cell than can be achieved by either stimulus alone. An exception would be platelet-derived growth factor, which seems to be a potent stimulus both to a tyrosine kinase[19] and to inositol lipid breakdown[20].

If activation of proliferation does indeed require a combination of a high rate of $PtdIns4,5P_2$ synthesis and a signal that activates $PtdIns4,5P_2$ breakdown, then any oncogene product that could enhance the activity of either of these pathways might act as a proliferative signal, provided that normal environmental signals ensure some activity of the other arm of the system. If so, it may be anticipated that oncogene products that control, have or may have kinase activity (*sis, erb-B, src, ros, fps, fes, abl, yes*) will serve to control $PtdIns4,5P_2$ supply, whereas other oncogenes might encode proteins (for example, receptors, $PtdIns4,5P_2$ phosphodiesterase or protein kinase C) involved in the pathways in which $PtdIns4,5P_2$ breakdown acts as a signal. There is some evidence that the latter pathways involve a guanine nucleotide-binding regulatory protein[21]: could this be p21, the GTP-binding protein coded by *ras* oncogenes? □



Structure of phosphatidylinositol (left) and diagram of interactions between oncogene products, cell-surface receptors and inositol lipid metabolism (right).

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