We read with interest the review article by Mackay and Twelves (2003) on the efficacy of protein kinase C (PKC) inhibition in cancer treatment and we wish to comment on it.

As highlighted by the authors, although PKC involvement in tumorigenesis is an old notion, contradictory findings are reported in the literature concerning the effects of PKC on cell invasivity, growth and apoptosis. That cancer cells exhibit high levels of PKC and/or express certain PKC isoforms preferentially is a fact. On the other hand, it has been suggested for a long time that Ras protooncogenes too are targets of carcinogenesis and likely participate in the initiation of neoplastic transformation (Barbacid 1987). PKC and Ras are sequential effectors of the same cascade that leads to mitogen-activated kinase (MEK)/extracellular-activated kinase (ERK) 1/2 phosphorylation and then to transcription of genes involved in cell proliferation. PKC and Ras are linked at the level of Raf-1, which is, at the same time, a Ras downstream effector and a target/substrate for PKC. It is generally accepted that Raf-1 can be phosphorylated and hence activated by PKC. However, since Raf-1 phosphorylation by protein kinase A (PKA) blocks Raf-1 binding to Ras/GTP, resulting in the inhibition of ERK 1/2 activation and growth arrest (Wu et al. 1993), it remains unclear how PKA and PKC enzymatic activity on Raf-1 could either block or activate the same substrate respectively. In fact, both PKA and PKC are serine/threonine kinases and Raf-1 is phosphorylated at Ser 259 (at least) by both protein kinases (Kolch et al. 1993, Dumaz & Marais 2003). This phosphorylated site is one of the targets for 14.3.3 protein, whose binding prevents Raf-1 recruitment to the plasma membrane (Dumaz & Marais 2003).

In this regard, the recent paper by Corbit et al. (2003) is particularly instructive. This group reports, for the first time, a mechanism by which classic and atypical (not novel) PKCs activate Raf-1: PKC phosphorylates a Raf kinase inhibitory protein (RKIP) causing its dissociation from Raf-1, thus enhancing downstream signalling to ERK 1/2. Therefore, Raf-1 is not always a PKC substrate, but rather a target.

We now know that the length and strength of ERK activation is the determinant for the final proliferative response. In fact, a low or a brief activation leads to a proliferative response, while a strong or long-lasting stimulation leads to p21 or p38 induction and thus growth arrest or apoptosis (Shanmugan et al. 2001, Deng et al. 2003).

By integrating old concepts and recent progress, a new scenario is beginning to emerge that might reconcile the plethora of contradictory findings about the role of PKC in cell cycle control. A synthetic conclusion could be that the effects of PKC on cell growth are likely determined by the combination of the PKC isoforms and the degree of stimulation. In fact, those PKC isoforms able to phosphorylate RKIP, thus allowing the activation of the Ras/Raf-1/MEK/ERK cascade, could promote either cell growth or growth arrest and/or apoptosis depending upon a transient or a sustained ERK activation respectively; conversely, those PKC isoforms directly targeting Raf-1 should inhibit ERK at any degree of PKC activation and hence induce cell cycle arrest in the G1 phase. If this is true, both processes likely occur simultaneously in cells expressing more than one PKC isoform, making the system particularly variable and unpredictable, but also very finely tuned.

To conclude, we do believe that the crucial question of the cell cycle control by PKC will soon be solved. It is important and urgent to complete our knowledge, not only from a mechanistic point of view, but also for (and before) the design of anticancer drugs targeting PKC isoforms.

References


