

## Original Article

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### Regulation of glioblastoma cell invasion by PKC $\iota$ and RhoB

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## Abstract

**Glioblastoma multiforme is the most aggressive form of primary brain tumor and remains largely incurable, in large part, due to its highly invasive nature. The phosphoinositide (PI) 3-kinase pathway is often constitutively active in these tumors due to activating mutations in the epidermal growth factor receptor, or deletion/loss of function of the tumor suppressor PTEN. Protein kinase C type  $\iota$  (PKC $\iota$ ), a member of the atypical protein kinase C family, is activated by the PI 3-kinase pathway and is an important downstream mediator. Here, we have assessed the role of PKC $\iota$  in glioblastoma cell invasion. Depletion of PKC $\iota$  with RNA interference caused an increase in actin stress fibers and a decrease in cell motility and invasion. Gene expression microarray analysis of U87MG cells showed that PKC $\iota$  repressed expression of mRNA for RhoB, which has previously been shown to have a role in actin stress fiber formation. Western blot analysis showed that both PKC $\iota$  depletion and pharmacological inhibition of PKC $\iota$  caused an increase in the protein levels of RhoB, as did inhibition of PI 3-kinase. Expression of RhoB from a constitutive promoter caused changes in actin stress fibers and cell invasion that were similar to those seen with PKC $\iota$  depletion. These data show that PKC $\iota$ , activated as a consequence of aberrant upstream PI 3-kinase signaling, mediates glioblastoma cell motility and invasion, and that repression of RhoB is key downstream event in PKC $\iota$  signaling leading to enhanced cell motility. In addition, constitutive expression of RhoB repressed PKC $\iota$  activity, as assessed by its phosphorylation status on Thr555. PKC $\iota$  and RhoB are, therefore, mutually antagonistic, potentially creating a sensitive switch between invasive and non-invasive phenotypes.**

**Keywords:** atypical PKC, RhoB, PI 3-kinase, PTEN, glioblastoma