Abstract

Metastasis from primary tumours is the leading cause of death in cancer patients and remains a major therapeutic challenge. Previously, EDI3 (Endometrial carcinoma differential 3) had been shown to be highly expressed in both primary endometrial and ovarian carcinomas that went on to develop metastasis. In addition, high EDI3 expression significantly reduced tumour-free survival time in patients and thus was predictive of worse prognosis in both cancer types. In this study, EDI3 could be characterised as a glycerophosphodiesterase that cleaves glycerophosphocholine to generate glycerol-3-phosphate and choline. In an attempt to achieve an overview of EDI3's possible role in the cell and especially its prometastatic functions, EDI3 expression levels were altered in different human cancer cell lines. Silencing of EDI3 in MCF7, AN3CA, and OVCAR3 cells corrected the low GPC/PC ratio typical for these tumour cells mainly by increasing intracellular GPC levels. Investigations using classic scratch assays showed that EDI3 has a major impact on cellular migration in both MCF7 and AN3CA cells, most likely via its direct influence on PKCα signalling. The modulation of EDI3 in these cell lines caused alterations of PKCα expression on the RNA and protein level, implying a possible role of EDI3 in transcriptional regulation. Further investigations using MCF7 and OVCAR3 cells revealed an influence of EDI3 on both attachment and integrin-mediated cell spreading, two processes that are intimately tied to cellular migration. Loss of the key integrin subunit β1 upon EDI3 knockdown led to decreased cell attachment and spreading on a fibronectin matrix, which was accompanied by delayed formation of membrane protrusions. Accordingly, stable overexpression of EDI3 in MCF7 cells led to an increase in integrin β1 RNA and protein expression and was associated with both enhanced cell attachment and spreading. The underlying mechanisms remain to be elucidated; however, initial results suggest that EDI3 influences the reorganisation of the actin cytoskeleton and the formation of focal adhesions in a FAK/Src-independent manner without affecting the Rho GTPases Rac1 or RhoA. Overall, the present study provides some insight into the biological function of the poorly characterised enzyme EDI3. It is the first study to implicate a member of the GDE family in tumourigenesis, and the first one to investigate EDI3 in a human system. The observations that EDI3 is associated with cell attachment, spreading, and migration are initial steps to understanding how EDI3 can contribute to the metastatic process.