

Editorial:

EDI3, A KEY ENZYME OF CHOLINE METABOLISM CONTROLS TUMOUR CELL MIGRATION

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Despite the millions of Euros invested in the fight against cancer, and the progress made in cancer therapy, a major obstacle to winning the war against cancer is the ability of cancer cells to metastasize. The process of metastasis has been extensively studied, and many of the key proteins and pathways that facilitate the escape of rogue cells from the confines of the primary tumour, their use of the vascular system for transportation, and their eventual colonization of secondary sites, are well known. However, the ability to predict the occurrence of these events will occur, with an end goal of better targeted therapies, remains the elusive pot of gold at the end of the rainbow.

Cancer of the endometrium, the inner membrane of the uterus, is usually curable if detected early (Steiner et al., 2003, 2007). Unfortunately, recurrence and/or metastasis are associated with worse prognosis and decreased survival time for the patient. This makes endometrial cancer a perfect example where the ability to predict metastasis will help scientists develop more targeted treatments, and increased survival on the part of the patient. One approach that has some success in predicting metastasis is the detection of biomarkers – proteins, genes, or small molecules that when present at specific levels are indicators of a particular biological state, including disease.

The search for markers of metastasis and worse prognosis in endometrial cancer, has led to the identification and characterization of a promising marker and therapeutic target called EDI3 (Endometrial carci-

noma differential 3), published this month in the prominent journal, The Proceedings of the National Academy of Sciences (Stewart et al., 2012). The initial work to identify EDI3 was performed in Mainz, Germany; where a group of gynaecologists tried to identify genes differentially expressed in primary tumours of patients who went on to develop metastasis. Actually the endometrial cancer - EDI - project was only a small side project in a larger program aimed at identifying prognostic markers in breast and ovarian cancer (Schmidt et al., 2008, 2012; Kammers et al. 2011; Cadenas et al. 2010, 2011; Petry et al., 2010; Tanner et al., 2006). High EDI3 levels were shown to predict metastasis and decreased survival in both endometrial and ovarian cancers. However, the function of EDI3 and how it contributed to metastasis was unknown. The project travelled to Leipzig and then Dortmund, Germany, where most of the characterization was performed, supported by a group of scientists throughout Germany and London, UK. With the generous support of the EU Seventh Framework Programme (FP7) - Health projects Cancercys, EDI3 was identified as a member of the glycerophosphodiesterase enzyme family, and more importantly the first of its kind to be implicated in cancer. The substrate for EDI3, glycerophosphocholine (GPC), was identified, together with the two cleavage products, choline and glycerol-3-phosphate, both precursors to several lipid metabolism pathways. The major hurdle that arose with this finding was to try and connect the en-

zymatic activity of EDI3, as a glycerophosphodiesterase, to metastasis.

Lipid analysis performed by the group of Prof. Gerd Schmitz at the University of Regensburg and funded by another FP7 package, LipidomicNET showed dramatic changes to the lipid profile of cells when EDI3 was altered. Changes were observed for lipids like lysophosphatidic acid and phosphatidic acid, both well-known lipid mediators already shown to activate signaling pathways, including migration, adhesion, and proliferation – all of which are deregulated in cancer. Did EDI3 influence these phenotypes? Altering EDI3 in various cell models showed that EDI3 is indeed associated with cellular migration, a process critical for metastasis, and the activation of protein kinase C was shown to be the pathway of choice. This finding was significant in many ways. It supported once more the importance of lipid metabolism in cancer, in particular the heavily investigated choline metabolic pathway. Several studies have reported elevated levels of total choline, phosphocholine, and decreased levels of GPC in many types of cancer compared to ‘normal’ tissue. Today, the levels of each metabolite in addition to the ratio of GPC to phosphocholine are investigated as possible biomarkers in several cancers. In addition, choline kinase, the enzyme which converts choline to phosphocholine is targeted in clinical trials, as it too is overexpressed in different types of cancer. Our study presents an alternative and perhaps more relevant target that is not only upstream of choline kinase, but also produces a second product G3P that is also a precursor to several lipids implicated in tumorigenesis. So much more is known about that gene, EDI3, which was scraped from a silver stained gel almost 10 years ago, but with the many answers also came many questions that will surely confirm EDI3’s importance in lipid metabolism and its potential importance as a chemotherapeutic target.

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