

Letter to the editor:

HIGHLIGHTS IN TUMOR METABOLOME RESEARCH: CHOLINE METABOLISM INFLUENCES INTEGRIN EXPRESSION AND SUPPORTS CELL ATTACHMENT

Ahmed Ghallab

Department of Forensic Medicine and Toxicology, Faculty of Veterinary Medicine,
South Valley University, Qena, Egypt, E-mail: Ghallab@vet.svu.edu.eg

Dear Editor,

Cell attachment or adhesion, either to another cell or a matrix, is a critical feature of many cell types. For example, immune cells attach to endothelial cells that make up the blood vessels before they enter inflamed tissue. Attachment to the endothelium by circulating tumor cells is also a critical step in metastasis. Therefore, it is of high interest to identify key factors that modify a cell's ability to attach.

In a recent issue of *Cell Adhesion and Migration*, Lesjak and colleagues demonstrated that choline metabolism strongly influences adhesion of breast and ovarian cancer cells to a fibronectin matrix (Lesjak et al., 2014). In this study, the authors focused on EDI3 (synonym: GDE5 or GPCD1) a key enzyme in choline metabolism that was recently shown to cleave glycerophosphocholine (GPC) in tumor cells (Stewart et al., 2012). One of the cleavage products is choline, the substrate of choline kinase (Marchan et al., 2012). Currently, many studies focus on choline kinase as a potential target for cancer therapy; indeed, expression of this enzyme has been shown to be increased in many carcinomas (Iorio et al., 2005, 2010; Gallego-Ortega et al., 2011; Ramírez de Molina et al., 2002a, b). The second cleavage product of EDI3 is glycerol-3-phosphate, which can further be metabolized to lysophosphatidic acid, phosphatidic acid and diacylglycerol (Stewart et al., 2012).

A key experiment in the present study of Lesjak et al. (2014) was that silencing EDI3 in breast and ovarian cancer cell lines reduced expression of integrin beta 1. This key integrin receptor can bind to any one of a number of integrin alpha receptors, thus influencing binding to different extracellular matrices, such as fibronectin, laminin and collagen. The binding or heterodimerization of alpha-beta integrins also regulates integrin-mediated signaling, which controls processes such as migration, proliferation, differentiation, attachment and even death (Spangenberg et al., 2006). In addition to reduced integrin beta 1 expression, silencing of EDI3 in these two cancer cell lines resulted in decreased attachment and spreading on a fibronectin matrix. Conversely, overexpressing EDI3 led to enhanced integrin beta 1 expression, increased attachment and spreading. However, a question that still remains open is the mechanism by which EDI3 influences integrin expression.

There is currently a great deal of research focused on understanding which mechanisms influence tumor metastasis and prognosis of carcinomas (Schmidt et al., 2008; Cadenas, 2012; Lesjak et al., 2014; Thanopoulou and Judson, 2012; Mamas et al., 2011; Hammad, 2013). Typical factors of influence include adhesion molecules (Micke et al., 2014; Schmidt et al., 2008; 2011; Botling et al., 2013), components of the immune system (Schmidt et al., 2012; Godoy et al., 2014), and redox factors (Cadenas et al., 2010). Although much effort is invested towards elucidating the influence of tumor metabolism on cancer development, the present

study of Lesjak et al. (2014) is the first to link choline metabolism to tumor cell attachment. These initial observations set the stage for future studies which will focus on whether choline metabolism can be pharmaceutically modified to reduce the capacity of tumor cells to attach and form metastasis.

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