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Guest editorial:

HIGHLIGHT REPORT: IMPORT OF FATTY ACIDS BY METASTASIZING TUMOR CELLS

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Recently Pascual and colleagues have contributed a study about the identity of cells that initiate metastasis (Pascual et al., 2017). They identified a cell type in human oral carcinomas with the following properties: (1) slow-cycling, (2) CD44-bright, (3) low expression of mesenchymal genes, (4) ability to initiate metastasis in mouse models and (5) high expression of the fatty acid receptor CD36. CD36 is a membrane protein on the surface of many mammalian cells that imports fatty acids (Yang et al., 2018; Umbarawan et al., 2018; Son et al., 2018). CD36 has been shown to be critical for supply with fatty acids and for maintenance of energy metabolism under numerous conditions (Wen et al, 2017; Chen et al, 2016; Nakatani et al., 2015; le Foll et al., 2015, 2013). In their recent study Pascual et al. report that neutralizing antibodies against CD36 reduce the formation of metastasis in orthotopic mouse models of oral cancer (Pascual et al., 2017). A further finding of this study is that NOD scid gamma mice developed larger lymph node metastases in a CD36 dependent manner, when the mice received a high-fat diet. Moreover, the authors report that CD36 positive cells are metastasis initiating and are characterized by a lipid metabolism signature (Pascual et al., 2017). Based on publicly available data, high expression of CD36 was associated with poor disease-free survival in breast, lung and urinary bladder cancer (Pascual et al., 2017).

In the past decade much progress has been made in understanding the principles that control formation of metastases (McGranahan et al, 2017; Lambert et al., 2017; Adawy, 2017; Marchan, 2012; Cadenas, 2012; Mantovani et al., 2017; Zhan et al, 2017). It is generally accepted that the cellular and humoral immune system play an important role in preventing metastasis (Schmidt et al., 2018, 2012, 2008; Godoy et al., 2014; Heimes et a., 2017a, b; Sicking et al., 2014).

In many tumor types high expression of proliferation associated genes has been shown to lead to an increased risk of metastasis (Schmidt et al., 2008; Siggelkow et al., 2012; Jabs et al., 2017; Wei et al,, 2017; Knaack, et al, 2018). Moreover, high expression of antioxidative factors (Cadenas et al, 2010), disturbed expression of genes involved in the control of circadian rhythm (Cadenas et al., 2014) and actin binding proteins (Stock et al., 2015) are associated with shorter metastasis-free interval.Different principles have been shown to control breast cancer metastasis that occurs within the first three years after the primary tumor or later (Hellwig et al., 2016; Hammad et al., 2016). Finally, factors involved in glycerophospholipid metabolism have been shown to influence the capacity of tumor cells to migrate, attach to surfaces and to metastasize (Stewart et al., 2012; Lesjak et al., 2014; Marchan et al., 2017).

In conclusion, Pascual and colleagues bring forward an interesting concept that metastasis-initiating tumor cells rely on dietary lipids in a CD36 dependent manner. It remains to be shown, whether CD36 is a promising target for anti-cancer therapy.

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