How do benign myoepithelial cells from in situ areas of carcinoma ex-pleomorphic adenoma favor tumor progression?

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Abstract In this brief commentary, we have shown how the benign myoepithelial cells from in situ areas of carcinoma ex-pleomorphic adenoma from salivary gland can favor tumor progression, not only dying by autophagy/senescence phenomena, disrupting the physical barrier, but also providing fuel for tumor progression.

Keywords Myoepithelial cells · In situ condition · Carcinoma ex-pleomorphic adenoma

In carcinoma ex-pleomorphic adenoma (CXPA), a rare salivary gland tumor, it is usually the epithelial cells of the ductal structures that suffer transformation. Initially, there is a carcinoma in situ situation where malignant luminal cells are surrounded by an intact layer of myoepithelial cells, which originate from a pre-existing pleomorphic adenoma (PA) (Altemani et al. 2005). However, this situation is short-lived, with the disappearance of the benign myoepithelial cells. In ex vivo studies of CXPA using immunohistochemistry, myoepithelial cells in direct contact with malignant epithelial cells were observed to be more differentiated than benign myoepithelial cells from PA, the site from which they had originated (Araújo et al. 2006). The presence of markers of differentiation, such as p21 and p16, were also observed in these cells (Silva et al. 2015).

These signs of benign myoepithelial cell differentiation intrigued us. Therefore, in order to better understand the cross-

talk between the malignant epithelial and adjacent benign myoepithelial cells, we created an in vitro model that would mimic an in situ CXPA situation (Martinez et al. 2012b), in which the benign myoepithelial cells spontaneously surrounded the carcinoma cell clusters. Although a tumor suppressor role has been described for myoepithelial cells in breast carcinoma, we demonstrated that this cell could, in fact, favor tumor progression, at least in the proposed model.

Firstly, we demonstrated that the malignant epithelial cell conditioned medium induces FGF2 secretion by the myoepithelial cells, favoring malignant tumor growth (Martinez et al. 2010, 2012a). Interestingly, the myoepithelial cells do not express the FGF-2 receptor, being present only in the malignant cells. This fact indicates a paracrine role for benign myoepithelial cell-derived FGF-2. Abnormal paracrine myoepithelial/epithelial cell interactions, as well as myoepithelial/stromal cell interactions could favor tumor growth, invasion and metastasis.

Secondly, we evaluated the role of cytokines in the regulation of the neoplastic process. In this in situ condition, myoepithelial cells are known to produce IL6, in particular, reaching higher levels after 9 days of cell culture (Martinez et al. 2013). IL6 is well recognized as acting as a growth factor in several human tumors (Aoki et al. 1999; Kinoshita et al. 1999; Jee et al. 2001).

Recently, we also demonstrated that the myoepithelial cells from in situ areas of CXPA suffer senescence/autophagy phenomena, leading to their disappearance (Silva et al. 2015). According to Capparelli et al. (2012), an autophagic tumor stroma contributes to cancer metabolism via paracrine production of high-energy mitochondrial fuels transferred to the cancer cells.

In line with our previous reports, Zacarias-Fluck et al. (2015), in an elegant study, showed senescent tumor cells within the bulk of HER2-positive breast carcinomas

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producing high levels of IL-6. This fact enabled the authors to demonstrate that “senescence, a potent antitumor mechanism, can be perverted in order to generate factors that foster the growth of non-senescent cells”. They concluded that these senescent cells displayed a senescence secretome that included IL-6, which is important in the progression of breast carcinomas. Hence, the malignant cells take advantage of both their own tumor cells, as well as the cells in the stroma, as presented in our myoepithelial cell studies.

In conclusion, the results of these studies revealed that myoepithelial cells are encouraged by malignant cells to provide fuel for tumor progression and, they eventually disappear via autophagy/senescence phenomena, disrupting the first barrier to tumor invasion.

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