Tumor microenvironment: the promising target for tumor therapy

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Cancer associated fibroblast cells (CAFs) are activated fibroblast cells in tumor microenvironment, which are involved in the development of tumors. Recently, more and more researches about tumor treatment are focused on targeting CAFs in tumor microenvironment to alleviate the supportive effect of CAFs to tumor cells. In this brief report, we discussed our work about indirect effect of retinoic acid (RA) to tumor migration, which was through the inhibition of IL-6 secretion of CAFs by RA and the downregulation of IL-6 of CAFs related with inhibition of epithelial-mesenchymal transition (EMT) of tumor cell. Furthermore, our ongoing and future work is about the relationship of cell factors secreted by tumor microenvironment and the growth of tumor cells to evaluate more about the effect of tumor microenvironment to parenchymal cells.

Keywords: tumor microenvironment; cancer associated fibroblast cells; tumor migration; EMT; retinoic acid

Abbreviations: cancer associated fibroblast cells, CAFs; extracellular matrix, ECM; epithelial-mesenchymal transition, EMT; endothelial-mesenchymal transition, EndoMT; Pancreatic ductal adenocarcinoma, PDAC; retinoic acid, RA.


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Tumor microenvironment is gradually attracting researchers’ attention, which plays important roles in initiation, proliferation, differentiation, migration and metastasis of tumor cells. Our lab are focusing on the researches of development of pancreatic cancer for decades, one of our work is about the tumor microenvironment of pancreatic cancer. Pancreatic ductal adenocarcinoma (PDAC) is characterized by a dense desmoplastic reaction [1]. The stroma part of PDAC supports parenchyma by secreting various factors, producing extracellular matrix (ECM), mediating immune escape, regulating of angiogenesis and hypoxia, affecting chemoresistance and radioresistance. Among stroma of PDAC, cancer associated fibroblast cells (CAFs) is activated fibroblast cells which are major components in tumor microenvironment. The sources of CAFs are reported as activation of quiescent fibroblast cells in pancreatic stromal [2], endothelial-mesenchymal transition (EndoMT) [3], epithelial-mesenchymal transi- tion (EMT) [4] or differentiation of mesenchymal stem cells [5]. After activation, CAFs acquire properties of myofibroblasts, such as α-SMA expression, secreting growth factors, elevating migration potential and producing more ECM [6-10], by which cause desmoplasia and support growth of tumor cells. PSCs are star-shaped cells located in the periacinar and periductal regions of the exocrine pancreas storing Vitamin A and when they are activated, the Vitamin A stored in cytoplasm are gradually lost [11]. Some researchers...
found that the loss of Vitamin A was related with desmoplasia of pancreatic lesion, including chronic inflammation, precancerous lesion and cancer [12,13]. Furthermore, restoration of Vitamin A were reported associated with low expression of α-SMA and less production of ECM in activated fibroblast cells [14,15].

Recently, we treated CAFs in PDAC with retinoic acid (RA), a small lipophilic molecule derived from Vitamin A and found that CAFs showed a relatively static status as lower expression of activation markers, less ECM production and changed secretion of cell factors. And when cultured with conditioned media from the treated CAFs, tumor cells showed reduced migration potential. Furthermore, we found that the low secretion of IL-6 of CAFs induced by RA treatment was responsible for the inhibition of EMT of tumor cells, which is the early event of migration of tumor cells. While, treated with RA directly, tumor cells didn't show low migration potential. So, RA inhibited tumor cells migration in an indirect way.

Retinoids are derivatives of natural or synthetic Vitamin A, combined with retinoic acid receptors to play its biological role [16]. Under physiological conditions, retinoic acid has an important role in embryonic development and cell differentiation, while its role in treatment of cancer and fibrotic diseases are gaining in importance [17,18]. Retinoic acid for the treatment of tumors is not through toxic effects on cells, but through the induction of differentiation and apoptosis of tumor cells [19-21]. As a differentiation-inducing agent, combination therapy of retinoic acid and cytotoxic drugs may play a synergistic therapeutic effect. On the other hand, there is inhibitory effect of retinoic acid on fibers production by stromal cells and the treatment of emphysema, renal fibrosis and hepatic fibrosis by RA have been reported [17, 18]. We found that RA could indirectly inhibited migration of tumor cells by impacting cell factor secreting of CAFs, which add new evidence that supports

**Figure 1.** RA (ATRA/9-cis-RA) attenuated migration of tumor cells by inhibiting IL-6 secretion of CAFs, which decreased the supportive role of CAFs to EMT of tumor cells. While, treated with RA directly, tumor cells didn't show low migration potential. So, RA inhibited tumor cells migration in an indirect way.
the uses of RA as a treatment for pancreatic adenocarcinoma. We found the direct effect of RA to tumor cells are various on different tumor cell lines. In the next step, we would like to investigate the indirect effect of RA on proliferation of tumor cells, which is expected to take effect through the inhibition of supportive role of CAFs to tumor cells.

Accumulating evidence suggests that the characteristic extensive desmoplasic reaction in pancreatic cancer play an important role in supporting tumor cells. Attenuating this stromal barrier is a promising strategy to improve treatment effect of malignant tumors with abundant desmoplasia. We anticipate that future therapies will have to target components of the microenvironment to achieve long lasting therapeutic response.

Acknowledgements

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References