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Extracellular vesicles from carcinoma-associated fibroblasts promote cancer progression

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Carcinoma−associated fibroblasts（CAFs）have been known to promote cancer progression by modifying the primary tumor microenvironment. We aimed to elucidate the intercellular communication between CAFs and other cells via extracellular vesicles（EVs）in cancer progression.
We found that CAF EVs induced lung pre-metastatic niche formation in mice and consequently increased salivary adenoid cystic carcinoma（SACC）lung metastasis. The pre-metastatic niche induced by CAF EVs in lungs was different from that induced by SACC EVs. CAF EVs presented a great ability for matrix remodeling and periostin is a potential biomarker characterizing the CAF EV-induced pre-metastatic niche. We found that lung fibroblast activation promoted by CAF EVs was a critical event at the pre-metastatic niche. Integrin $\alpha 2\beta 1$ mediated CAF EV uptake by lung fibroblasts, and its blockage by TC I-15 prevented lung pre-metastatic niche formation and subsequent metastasis. Plasma EV integrin $\beta 1$ was considerably upregulated in the mice bearing xenografts with high risk of lung metastasis.
In addition, we found that human oral squamous cell carcinoma（OSCC）-derived CAF secreted EVs regulating angiogenesis. The ability of CAF EVs to activate VEGF receptor 2（VEGFR 2）signaling in human umbilical vein endothelial cells（HUVEC）was dependent on the association between EVs and VEGF. In addition, EV-bound VEGF secreted by CAFs further activated VEGFR 2 signaling in HUVEC in a bevacizumab-resistant manner. VEGF was found to interact with heparan sulfate proteoglycans on the CAF EV surface and could be released by heparinase Ⅰ/Ⅲ. The bioactivity of the dissociated VEGF was retained in vitro and in vivo and could be neutralized by bevacizumab. These findings suggest that the combined use of heparinase and bevacizumab might inhibit angiogenesis in patients with high levels of EV-bound VEGF.

Curriculum Vitae

Education

1991－1996 B.A. Dentist, Dalian Medical University, China
2002－2006 Ph.D. Oral Pathology, Tokyo Medical and Dental University, Japan

Research and professional experience

1996－2001 Assistant, Oral Pathology Department, Dalian Medical University, China
2001－2002 Assistant Professor, Oral Pathology Department, Dalian Medical University, China
2007－2010 Postdoc Fellow, Department of Biotechnology, Dalian Institute of Chemical Physics, Chinese Academy of Sciences, China
2006－2012 Associated Professor, Oral Pathology Department, Dalian Medical University, China
2012－2020 Professor, Oral Pathology Department, Dalian Medical University, China
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Selected Publications

1. Li J, Liu X, Zang S, Zhou J, Zhang F, Sun B, Qi D, Li X, Kong J, Jin D, Yang X, Luo Y, Lu Y, Lin B, Niu W*, **Liu T***. Small extracellular vesicle-bound vascular endothelial growth factor secreted by carcinoma-associated fibroblasts promotes angiogenesis in a bevacizumab-resistant manner. ***Cancer Letters***. 2020；492：71－83.
2. Kong J, Tian H, Zhang F, Zhang Z, Li J, Liu X, Li X, Liu J, Li X, Jin D, Yang X, Sun B, Guo T, Luo Y, Lu Y, Lin B, **Liu T***. Extracellular vesicles of carcinoma-associated fibroblasts create a pre-metastatic niche in the lung through activating fibroblasts. ***Molecular Cancer***. 2019；18：175.
3. Ji Y, Qi D, Li L, Su H, Li X, Luo Y, Sun B, Zhang F, Lin B, **Liu T***, Lu Y*. Multiplexed profiling of single-cell extracellular vesicles secretion. ***Proc Natl Acad Sci U S A***. 2019；116(13)：5979－5984.
4. Tian H, Pang J, Qin K, Yuan W, Kong J, Ma H, He J, Yang X, Luo Y, Lu Y, Lin B, **Liu T***. A novel tissue-based liver-kidney-on-a-chip can mimic liver tropism of extracellular vesicles derived from breast cancer cells. ***Biotechnol J***. 2020；15(2)：e1900107.
5. He J, Ye W, Kou N, Chen K, Cui B, Zhang X, Hu S, **Liu T***, Kang L*, Li X*. MicroRNA-29b-3p suppresses oral squamous cell carcinoma cell migration and invasion via IL32/AKT signalling pathway. ***J Cell Mol Med***. 2020；24(1)：841－849.
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