Secreted kinase FAM20C promotes stromal remodeling via inflammatory cancer-associated fibroblast activation in pancreatic cancer microenvironment

Mi Rim Lee1,2, Yu-Sun Lee1, Sumin Kang1,2, Hye Won Shon1,2, Sang Mung Woo1,2 and Yun-Hee Kim1,2

1National Cancer Center Graduate School of Cancer Science and Policy, Goyang, 10448, South Korea. 2Research Institute and Hospital, National Cancer Center, Goyang, 10448, South Korea.

ABSTRACT

Background: Cancer-associated fibroblasts (CAFs) play a key role in the tumor microenvironment by promoting ideal circumstances for cancer cell proliferation, angiogenesis, metastasis, and chemoresistance. Pancreatic ductal adenocarcinoma (PDAC) growth is fueled by autocrine and paracrine interaction between tumors and cancer-associated fibroblasts and macrophages in the tumor microenvironment. We recently discovered that a family of proteins with sequence similarity to 20-member C (FAM20C), a novel secreted kinase that phosphorylates extracellular proteins or an ectodomain of membrane proteins containing an S-E motif, promotes cancer progression and metastasis through tumor-associated macrophages (TAMs) implying a novel role for stromal remodeling in cancer.

Purpose: In this study, we demonstrated FAM20C’s potential for metastasis in the tumor microenvironment by validating CAF development using pancreatic cancer cells (FAP) and mesenchymal stem cells (MSCs), which are primary sources of CAFs.

Methods: The conditioned medium of FAM20C-overexpressing cells, which reflected the pancreatic cancer milieu, was used to confirm the effect on differentiation of MSCs or PSCs into CAFs, as well as the microenvironment remodeling effect in pancreatic cancer orthotopic mouse models. Results: Under the conditioned medium of FAM20C-overexpressing CFPAC-1 cells, the mRNA expression of a-smooth muscle actin (α-SMA), a hallmark of myofibroblastic CAFs (myCAFs) was reduced in both MSCs and PSCs. In contrast, CAF marker expression was dramatically elevated, including fibroblast activation protein (FAP), IL-6, and IL-11. Moreover, FAM20C secretion promoted collagen accumulation and migration. Furthermore, tumor growth was accelerated in an orthotopic model using FAM20C-overexpressing pancreatic cancer cells derived from patients. Collagen was also consistently deposited in the tumors as compared to the control cell-injected orthotopic model. Conclusion: FAM20C might be a critical regulator of PDAC progression by remodeling microenvironment including TAMs, CAF, and extracellular matrix in pancreatic cancer.

RESULTS

1. FAM20C promotes tumor growth in tumor microenvironment

2. FAM20C induces differentiation from PSC to iCAF in tumor microenvironment

3. Secreted FAM20C accelerates tumor microenvironment remodeling by iCAF activation

CONCLUSION

1. The secreted kinase FAM20C increases differentiation from progenitor cell to iCAF.

2. FAM20C secreted from tumors or TAMs to induces differentiation of iCAF and accumulation of collagen in pancreatic cancer.

3. FAM20C might have a crucial role in tumor microenvironment remodeling through regulation of CAF composition.

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Reference

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