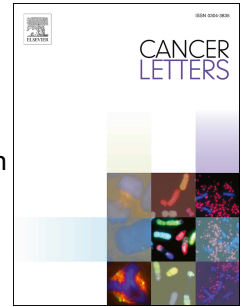


# Accepted Manuscript

Basement membrane destruction by pancreatic stellate cells leads to local invasion in pancreatic ductal adenocarcinoma

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**Abstract**

Stroma invasion is an important step in pancreatic cancer progression. However, how pancreatic ductal adenocarcinoma (PDAC) with ductal structure invades the surrounding stroma has not been clear. Here, we elucidated the mechanism of stromal invasion of PDAC, using organoids. From resected PDAC specimens, we established human PDAC organoids, which developed ductal and basement membrane (BM) structures. When the organoids were co-cultured with pancreatic stellate cells (PSCs) in a collagen matrix, organoids lost their BM and ductal structures, and invaded collagen matrix more frequently than did mono-cultured organoids. Interestingly, direct contact by PSCs to PDAC organoids was observed before BM destruction. Matrix metalloproteinase (MMP) 2 or membrane type-1 MMP (MT1MMP) knockdown in PSCs significantly attenuated BM destruction by PSCs, and retained the ductal structures in organoids. Our results imply that direct contact by PSCs induces BM destruction and stromal invasion of PDAC via MMP2 which binds to MT1MMP on PSCs.

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