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Artemin regulates CXCR4 expression to induce migration and invasion in pancreatic cancer cells through activation of NF-κB signaling

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Abstract

Pancreatic ductal adenocarcinoma (PDAC) is the most lethal human malignant tumor because of the early onset of local invasion and distant metastasis. Perineural invasion is a prominent characteristic of pancreatic adenocarcinoma, which is a multifactorial process that involves various signaling molecules from different signaling pathways. The glial cell line-derived neurotrophic factor family of ligands was reported to be involved in perineural invasion in pancreatic cancer. Artemin is one member of the glial cell line-derived neurotrophic factor family of ligands. Although Artemin has previously been demonstrated to promote invasiveness of pancreatic cancer, the mechanisms remain poorly understood. In this study, we performed an analysis to determine the effects of Artemin on modulating tumor cell metastatic potential and invasion activity and explored its mechanisms in pancreatic cancer. We indicated that Artemin and CXCR4 were overexpressed in cancer tissues and widely expressed in pancreatic cancer cell lines. We observed that activation of ERK1/2 and Akt in Artemin-treated cells led to enhanced nuclear accumulation of NF-κB, which then induced CXCR4 expression. Through regulation of the expression of CXCR4, Artemin functionally promoted the migration and invasion in pancreatic cancer cells. The present study indicated that Artemin induced CXCR4 expression by activating Akt and ERK 1/2/NF-κB signaling, thereby modulating tumor cell metastatic potential and invasion activity in pancreatic cancer by regulating SDF-1α/CXCR4 axis. Artemin might be an effective and potent therapeutic target for pancreatic cancer metastasis, especially in perineural invasion.

Keywords

Artemin; CXC chemokine receptor 4; perineural invasion; metastasis; pancreatic cancer

Introduction

Pancreatic cancer is one of the most malicious human malignancies with the lowest 5-year survival rate[1]. The poor prognosis of pancreatic cancer is related to its local recurrence, lymph nodes and early metastasis[2, 3]. Perineural invasion (PNI) is a prominent characteristic of pancreatic adenocarcinoma and is thought to be an indicator of aggressive tumor behavior. PNI is defined as the presence of cancer cells within the epineural, perineural, and endoneurial spaces of the neuronal sheet and around nerves[4, 5]. PNI is a multifactorial process that involves various signaling molecules from different signaling pathways. Pancreatic ductal adenocarcinoma cells have strong neurotrophic effects, but the mechanisms contributing to the invasion of intrapancreatic nerves and spread of cancer cells along extrapancreatic nerves during pancreatic tumorigenesis remain poorly understood.

Certain factors, including neurotrophins, chemokines and their receptors, have been shown to be involved in the process of PNI[6, 7]. Artemin is one member of the glial cell line-derived neurotrophic factor (GDNF) family of ligands[8]. The GDNF family has been reported to be involved in PNI in pancreatic cancer. The GDNF family selectively binds to GDNF family receptors, which results in the formation of multicomponent receptor complexes that include a glycosyl-phosphatidylinos-itol