ARTICLE

Anoikis resistant gastric cancer cells promote angiogenesis and peritoneal metastasis through C/EBPβ-mediated PDGFB autocrine and paracrine signaling

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Anoikis is a type of programmed cell death induced by loss of anchorage to the extracellular matrix (ECM). Anoikis resistance (AR) is crucial for the survival of metastatic cancer cells in blood, lymphatic circulation and distant organs. Compared to ordinary cancer cells, anoikis resistant cancer cells undergo various cellular and molecular alterations, probably characterizing the cells with unique features not limited to anoikis resistance. However, the molecular mechanisms connecting anoikis resistance to other metastatic properties are still poorly understood. Here, the biological interaction between anoikis resistance and angiogenesis as well as their involvement into peritoneal metastasis of gastric cancer (GC) were investigated in vitro and in vivo. The prognostic value of key components involved in this interaction was evaluated in the GC cohort. Compared to ordinary GC cells, GC^{AR} cells exhibited stronger metastatic and pro-angiogenic traits corresponding to elevated PDGFB secretion. Mechanistically, transcription factor C/EBPβ facilitated PDGFB transcription by directly binding to and interacting with PDGFB promoter elements, subsequently increasing PDGFB secretion. Secreted PDGFB promoted the survival of detached GC cells through a C/EBPβ-dependent self-feedback loop. Moreover, secreted PDGFB promoted angiogenesis in metastases via activation of the MAPK/ERK signaling pathway in vascular endothelial cells. Both C/EBPβ activation level and PDGFB expression were significantly elevated in GC and correlated with metastatic progression and poor prognosis of patients with GC. Overall, interaction between GC^{AR} cells and vascular endothelial cells promotes angiogenesis and peritoneal metastasis of GC based on C/EBPβ-mediated PDGFB autocrine and paracrine signaling. C/EBPβ-PDGFB-PDGFRβ-MAPK axis promises to be potential prognostic biomarkers and therapeutic targets for peritoneal metastasis of GC.

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INTRODUCTION

Gastric cancer (GC) is one of the most prevalent and lethal malignancies worldwide [1], with particularly high incidence in East Asia [2]. Majority has poor prognosis due to its tropism for rapid peritoneal metastasis (PM), which is resistant to currently approved therapy [3, 4]. The median survival of the GC patients with PM under systemic chemotherapy is 12.5 months with a 5-year survival rate <2% [5, 6]. Therefore, uncovering the underlying mechanisms of PM as well as identifying potential therapeutic targets for GC with PM are urgent needs.

As programmed apoptosis triggered by detachment from the extracellular matrix (ECM), anoikis becomes an essential barrier to detached cell survival and re-attachment to new matrix in ectopic locations [7]. Anoikis resistance (AR) has been demonstrated as prerequisite for hematogenous [7], lymphatic metastasis [8] and peritoneal dissemination [9]. In comparison to ordinary cancer cells, anoikis resistant cancer cells undergo variety of distinct cellular and molecular alterations [10], suggesting that the cells might acquire some unique features not limited to anoikis resistance. Consistently, our previous study revealed that GC^{AR} cells branched out multiple invadopodia [11], which is associated with advanced invasion of cancer cells [12]. However, the biological association between AR and some metastatic properties and their involvement in the metastatic cascade remain elusive.

Formation of neo-vessels induced by pro-angiogenic molecules in the tumor milieu is a crucial event during carcinogenesis and metastasis [13, 14]. Tumor neo-vessels grow highly tortuous, leaky and irregular, resulting in abnormal and poorly functioning vasculature [15]. The loose junctions between the endothelium in the neovasculature favor intravasation of tumor cell, thereby promoting metastatic spreading [16] and formation of malignant ascites [17]. Moreover, induction of angiogenesis provide the primary foci and metastases with oxygen and nutrients for further progression [14]. Tumor cells regulate angiogenic events by activating normal, quiescent cells in the metastatic niche through secretion of cytokines, chemokines and growth factors [18].

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