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Exosomal PGAM1 promotes prostate cancer angiogenesis and metastasis by interacting with ACTG1

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Tumor-derived exosomes and their contents promote cancer metastasis. Phosphoglycerate mutase 1 (PGAM1) is involved in various cancer-related processes. Nevertheless, the underlying mechanism of exosomal PGAM1 in prostate cancer (PCa) metastasis remains unclear. In this study, we performed in vitro and in vivo to determine the functions of exosomal PGAM1 in the angiogenesis of patients with metastatic PCa. We performed Glutathione-S-transferase pulldown, co-immunoprecipitation, western blotting and gelatin degradation assays to determine the pathway mediating the effect of exosomal PGAM1 in PCa. Our results revealed a significant increase in exosomal PGAM1 levels in the plasma of patients with metastatic PCa compared to patients with non-metastatic PCa. Furthermore, PGAM1 was a key factor initiating PCa cell metastasis by promoting invadopodia formation and could be conveyed by exosomes from PCa cells to human umbilical vein endothelial cells (HUVECs). In addition, exosomal PGAM1 could bind to γ-actin (ACTG1), which promotes podosome formation and neovascular sprouting in HUVECs. In vivo results revealed exosomal PGAM1 enhanced lung metastasis in nude mice injected with PCa cells via the tail vein. In summary, exosomal PGAM1 promotes angiogenesis and could be used as a liquid biopsy marker for PCa metastasis.

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INTRODUCTION

The tumor microenvironment (TME) plays a crucial role in cancer metastasis [1]. Tumor metastasis is a highly coordinated, dynamic multi-step process involving invasion, extravasation, migration, and angiogenesis [2]. In the TME, angiogenesis plays a significant role in cancer metastasis [1] and podosome formation, a key component of neovascularization [1, 3, 4]. However, studies have identified only a few TME-related biomarkers for the diagnosis and prognosis of patients with cancer [5, 6]. Globally, prostate cancer (PCa) is the most prevalent cancer in men endangering their health [7]. Furthermore, angiogenesis and metastasis are the leading cause of PCa-related deaths [8, 9]. Therefore, there is an urgent need to identify PCa progression-related biomarkers [10].

Cell-cell communication aids cells in adjusting to changes in intra- and extracellular environments [11]. Exosomes are extracellular vesicles with a 40–150 nm diameter and contain proteins, lipids, and nucleic acids [12]. Exosomes and their contents mediate signaling and exchange between cells [13, 14]. Mounting evidence suggests cells or plasma-derived exosomes promote angiogenesis in several cancers [6]. Furthermore, exosomes derived from the plasma of patients with cancer can serve as reliable markers for cancer diagnosis [15]. However, the mechanism underlying angiogenesis and cancer metastasis mediated by tumor-derived exosomes is unclear and should be investigated further.

Phosphoglycerate mutase 1 (PGAM1) is a key enzyme involved in aerobic glycolysis that catalyzes the conversion of 3-phosphoglycerate (PG) to 2-PG [16]. Previous studies have shown the involvement of the glycolytic enzymatic activity of PGAM1 in cell proliferation, whereas the non-metabolic activity of PGAM1 plays a role in the migration and invasion of cancer cells [17, 18]. In addition, studies have shown the involvement of PGAM1 in cancer progression. Moreover, in PCa, PGAM1 secreted by exosomes induces cancer progression [19–22]. However, the correlation between exosomal PGAM1 and PCa metastasis is still unclear.

ACTG1 encodes for the cytoskeletal protein γ-actin, which plays a role in non-muscle cells. γ-actin is an essential component of the cell migration machinery involved in rearranging dynamic cytoskeletal networks. Studies have shown the involvement of γ-actin in the onset and progression of several diseases like cancer, brain malformations, and hearing loss [23]. However, there is a lack of research on ACTG1 and PCa metastasis.

Our results revealed an increase in exosomal PGAM1 levels in the plasma of patients with metastatic PCa compared to patients with non-metastatic PCa and healthy controls. Further, an increase in the angiogenic and proliferative capacities of human umbilical vein endothelial cells (HUVECs) treated with exosomal PGAM1 was observed. Next, we evaluated the correlation between PGAM1 and

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