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Tumor-derived extracellular vesicles in angiogenesis

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ABSTRACT

Angiogenesis is crucial for tumor growth and metastasis. Recent studies revealed that tumor cells promote angiogenesis by secreting extracellular vesicles, which can be captured by endothelial cells. These tumor-derived extracellular vesicles carry microRNAs, long non-coding RNAs, and proteins, which activate pro-angiogenic signaling in endothelial cells. In this review, we will summarize the roles of tumor-derived extracellular vesicles in angiogenesis and the underlying molecular mechanisms.

1. Introduction

Angiogenesis refers to the growth of new blood vessels from pre-existing capillaries [1]. During tumor progression, an extensive vascular network arises to deliver oxygen and nutrients to support cancer cell growth, and remove metabolic wastes. Tumor cells cannot grow beyond 1–2 mm without an adequate vascular supply [2,3]. Moreover, angiogenesis is required for invasive tumor growth and metastasis. Cancer cells exfoliating and entering blood circulation is a pivotal step for hematogenous metastasis [4,5]. Targeted modulation to angiogenic process has become an effective anti-cancer therapeutic strategy [2].

Recent studies demonstrated that multiple types of tumor cells secrete extracellular vesicles (EVs) involved in the regulation of both physiological and pathological processes [6,7]. EVs are membrane vesicles enclosed in a lipid bilayer, and contain cytosol and functional biomolecules from the parental cells, including microRNAs (miRs), long non-coding RNAs (lncRNAs), transcription factors, cytokines, growth factors and mRNAs [8,9]. There are three types of EVs: exosomes, microvesicles and apoptotic bodies [10]. As a biomarker in circulating serum, EVs are potentially useful for diagnosis [11]. Indicators for detection of EVs include the level of EVs and non-coding RNAs, mRNAs, DNA and proteins in EVs [12]. In addition, EVs may function as a drug carrier [12]. Tumor-derived EVs transfer genetic information or proteins to vascular endothelial cells (ECs) to promote tumor angiogenesis [13–15]. Here, we summarize the recent findings of the mechanisms underlying tumor-derived EVs in regulating angiogenesis. These findings will help explore novel treatments targeting tumor angiogenesis.

2. Formation of EVs

2.1. Exosomes

Exosomes, the smallest EVs with sizes between 30 nm and 100 nm, are released through multivesicular bodies (MVBs) [6]. Exosomes are formed in the endosomal system that guides intraluminal vesicle formation and transportation [16]. During endocytosis, early endosomes are firstly formed, followed by functional molecules in the cytoplasm entering into early endosomes [16]. Then, the early endosomes develop into late endosomes which are rich in intraluminal vesicles (ILVs) [16]. It remains unclear how these functional molecules enter early

Abbreviations: AMPK, AMP-activated protein kinase; ARF6, ADP-ribosylation factor 6; AKT, protein kinase B; BBB, blood brain barrier; bFGF, b-fibroblast growth factors; b-FGFR, b-fibroblast growth factors receptor; ccRCC, clear cell renal cell carcinoma; ECs, endothelial cells; ERK, extracellular signal-regulated kinase; EFNA3, ephrin-A3; eNOS, endothelial nitric oxide synthase; FOXM1, forkhead box M1; HR-MM, hypoxia-resistant MM; HIF-1α, hypoxia-inducible factor-1α; FIH-1, factor inhibiting hypoxia inducible factor 1; HCC, hepatocellular carcinoma; ILVs, intraluminal vesicles; IL-6, interleukin-6; LncRNAs, long non-coding RNAs; miRs, microRNAs; MVBs, multivesicular bodies; MLCK, myosin light-chain kinase; MLC, myosin light-chain; MM, multiple myeloma; MVs, microvesicles; MALAT1, metastasis-associated lung adenocarcinoma transcript 1; MMP-9, matrix metalloproteinase-9; NSCLC, non-small cell lung cancer; NF-κB, nuclear Factor -κB; PLD, Phospholipase D; pAKT, phosphorylated protein kinase B; PHDs, Prolyl hydroxylases; PHD1, prolyl hydroxylase 1; PHD2, prolyl hydroxylase; PTP1B, phospho-tyrosine phosphatase-1B; PML, promyelocytic leukemia; PDGF-β, platelet-derived growth factor-β; PTEN, phosphatase and tensin homologue; SOCS5, suppressor of cytokine signaling 5; JAK-STAT, the Janus kinase-signal transducer and activator of transcription; pVHL, von Hippel-Lindau protein; VASH2, vasohibin 2; VEGF, vascular endothelial growth factor

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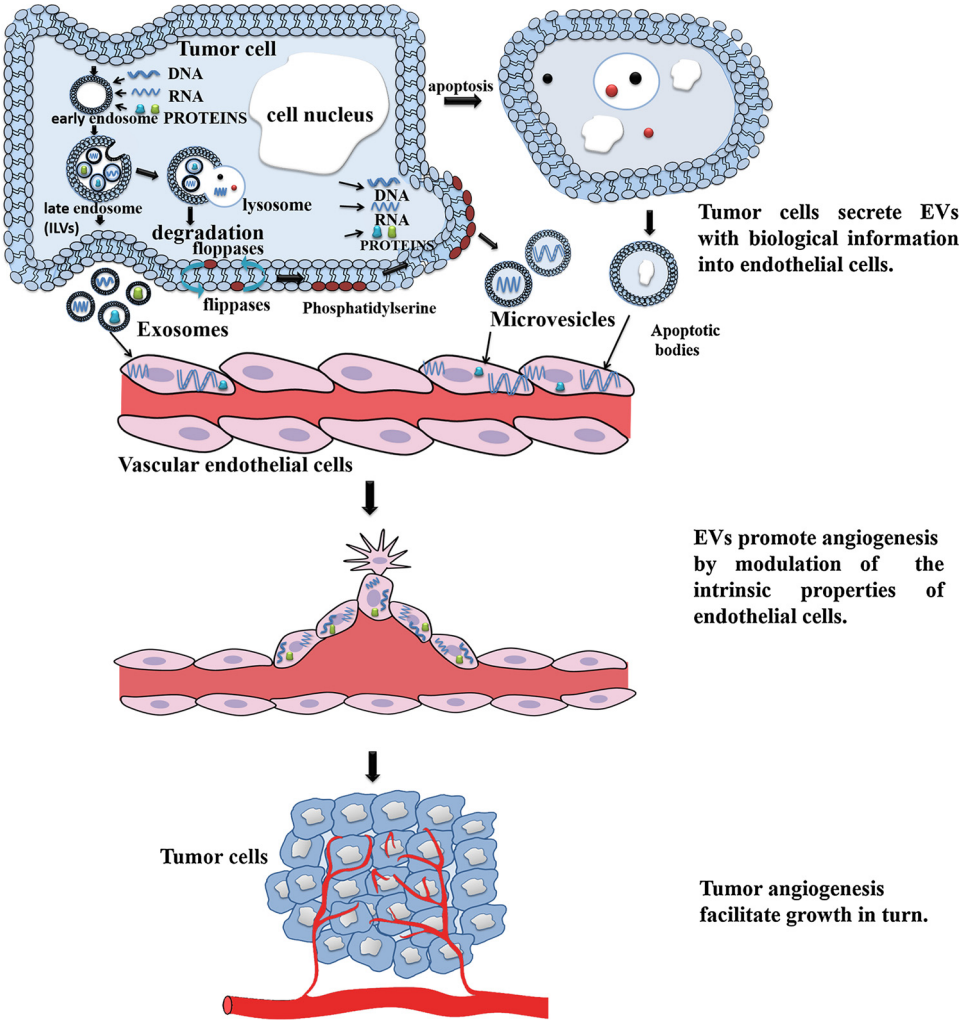

Fig. 1. Formation of extracellular vesicles (EVs).
During endocytosis, early endosomes are formed following syntheses of functional molecules in the cytoplasm, and then mature into late endosomes enriched ILVs. The secreted ILVs are called exosomes. MVs are secreted via budding and shedding from the plasma membrane. Apoptotic bodies are formed during programmed cell death mediated by actin-myosin interaction.

endosomes and their roles in the transition of the early endosomes to the late endosomes. Due to their morphological features, late endosomes are referred as MVBs [16]. Generally, MVBs have two fates, degradation in lysosomes or fusing with plasma membrane, which results in ILVs secretion. The secreted ILVs are also called exosomes (Fig. 1) [16].

2.2. Microvesicles

Microvesicles (MVs), with sizes of 100–1000 nm, are secreted via budding from the plasma membrane [6,16]. In the plasma membrane, the asymmetric distribution of proteins and phospholipid is regulated by aminophospholipid translocases [17]. Flippases transfer phospholipids from the outer leaflet to the inner leaflet while floppases have the opposite effect [16]. Phosphatidylserine is transferred to the outer-membrane leaflet, which induces plasma membrane budding and MVs formation (Fig. 1) [18]. Studies have shown that GTP-binding protein ADP-ribosylation factor 6 (ARF6) is tightly related to increased microvesicles formation and secretion [19]. Activated ARF6 promotes the activation of phospholipase D (PLD), which recruits the extracellular signal-regulated kinase (ERK) to the plasma membrane [19]. Phosphorylation of ERK activates myosin light-chain kinase (MLCK). MLCK-mediated myosin light-chain (MLC) phosphorylation is required for microvesicles release [19].

2.3. Apoptotic bodies

Apoptotic bodies released by apoptotic cells are the biggest EVs with sizes up to 4 μm [20]. Membrane blebbing of apoptotic bodies is mediated by actin-myosin interacting (Fig. 1) [16,21]. They are formed only during programmed cell death, and their release mechanism remains unclear.

3. Physiological role of extracellular vesicles

Tumor-derived EVs function significantly in tumor growth and metastasis [7]. Murine melanoma B16BL6-derived exosomes increase the proliferation of B16BL6 cells via up-regulating proliferation-related proteins, including Cyclin D1 and phosphorylated protein kinase B (pAKT) [22]. In addition, miR-25-3p and miR-92a-3p are packaged in exosomes secreted from liposarcoma cells [23]. Both of them stimulate tumor-associated macrophages to secrete proinflammatory cytokine interleukin-6 (IL-6) through the Nuclear Factor-κB (NF-κB) pathway [23]. Studies have shown that cancer cells secrete more exosomes than normal cells [24]. These tumor-derived exosomes enhance migration, invasion, and proliferation of tumor cells by depositing their cargo in target cells [24]. In addition, they may confer drug resistance and promote immune evasion [24]. EVs are able to cross the blood brain barrier (BBB), spread to body fluids and reach tissues distant from the