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Review

Extracellular vesicle docking at the cellular port: Extracellular vesicle binding and uptake

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ABSTRACT

Extracellular vesicles (EVs), lipid bilayer-enclosed structures that contain a variety of biological molecules shed by cells, are increasingly becoming appreciated as a major form of cell-to-cell communication. Indeed, EVs have been shown to play important roles in several physiological processes, as well as diseases such as cancer. EVs dock on to the surfaces of recipient cells where they transmit signals from the cell surface and/or transfer their contents into cells to elicit functional responses. EV docking and uptake by cells represent critical, but poorly understood processes. Here, we focus on the mechanisms by which EVs dock and transfer their contents to cells. Moreover, we highlight how these findings may provide new avenues for therapeutic intervention.

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Contents

1. Introduction

Cells release extracellular vesicles (EVs), which are lipid-enclosed vesicles ranging from ~30–1000 nm in diameter. EVs contain a variety of cargo, including mRNA [1–3], microRNA [1,4,5], long non-coding RNA [6,7], DNA [7], and proteins [2,4,8–13] (Fig. 1A). In order to elicit functional effects, EVs dock onto recipient (target) cells, at which point the EVs can initiate signaling events at the cell surface or are internalized by cells. In either case, EVs are capable of promoting phenotypic changes in recipient cells, which are dependent on their cargo [1,3–5,10,14,15].

At least two different types of EVs have been identified: microvesicles (MVs) and exosomes. Size is one distinguishing feature between these two classes of EVs. MVs typically range in size

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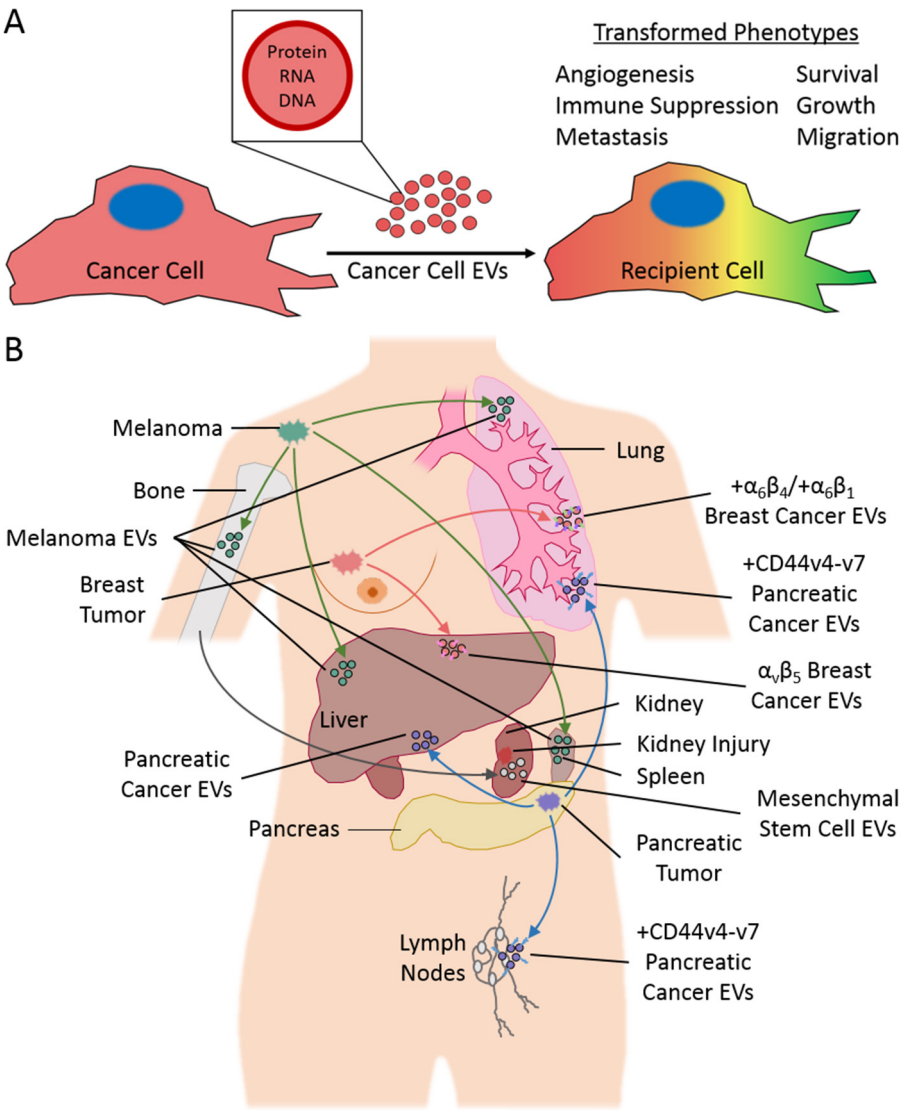

Fig. 1. (A) EVs generated by cancer cells contain a variety of cargo (i.e., protein, RNA, and DNA) that can be transferred to other cells. This causes the phenotypes of recipient cells to change (denoted by the color change) in ways that promote cancer progression. (B) EVs derived from bone marrow or different types of cancer cells accumulate in specific organs in animal models. For example, EVs generated by bone marrow cells accumulate in the kidney where they promote injury recovery (grey arrow and EVs). However, cancer-derived EVs appear to promote metastasis in a variety of organs. Specifically, EVs from melanoma cells preferentially accumulate in the bone, liver, spleen, and lung (green arrows and EVs), EVs from breast cancer cells accumulate in the liver and lungs (pink arrows and EVs), and EVs from pancreatic cancer cells accumulate in the liver, lung, and lymph nodes (blue arrows and EVs).

from 200 to 1000 nm in diameter, while exosomes are smaller, averaging between 30 and 120 nm. MVs and exosomes also differ in how they are formed. Exosome biogenesis involves the redirection of multivesicular bodies (MVBs) within the traditional endosomal sorting pathway, from the lysosome where they would typically be degraded, to the cell surface. These redirected MVBs fuse with the plasma membrane and release their contents (i.e., exosomes) into the extracellular environment [16,17]. Consistent with the idea that exosomes originate from MVBs, it has been shown that interfering with the machinery in the endosomal sorting pathway, such as endosomal sorting complexes required for transport (ESCRT) proteins, blocks exosome formation and release [16]. In contrast, MVs are thought to bud from the plasma membrane through Arf6- [18] and RhoA-dependent [19] rearrangements of the actin cytoskeleton. Although exosomes and MVs appear to be shed via different mechanisms, it is not known whether these two major types of EVs are capable of mediating distinct biological outcomes. However, one study found that MVs deliver functional plasmid DNA and proteins to recipient cells more efficiently than exosomes [20], suggesting that different classes of EVs may be functionally distinct.

It is also worth emphasizing that the field is still debating what properties define exosomes versus MVs and how to best isolate each class of EVs. Moreover, it is becoming increasingly clear that several sub-types of exosomes and MVs likely exist, adding an additional layer of complexity to this issue. As a result, many studies claiming to specifically study either exosomes or MVs are, instead, isolating a mixture of EVs. This has prompted the EV community to adopt new guidelines that include using the term EVs, rather than MVs or exosomes, in cases where it is not absolutely clear that a particular class of EVs is being isolated and studied. However, for the purposes of this review, we decided to use the terminologies (i.e., EVs, MVs, or exosomes) chosen by the authors when describing their work.

EVs participate in a variety of physiological processes, including pregnancy [21], stem cell differentiation [22], inflammation [23,24], and blood coagulation [23,24]. For instance, MVs play a role in implantation, one of the earliest and most important stages of

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