Journal of
Clinical and Experimental Pharmacology

Tsai et al., Clin Exp Pharmacol 2014, 4:2
DOI: 10.4172/2161-1459.1000154

Commentary Open Access

Role of Exosomes in Intercellular Signaling, Maintenance of Normal Physiology, and their Therapeutic Potentials

Cheng-Chang Tsai[1], **Chen-Han Yang**[1] **and Nan-Shan Chang**[1-3*]

[1]*Institute of Molecular Medicine, National Cheng Kung University Medical College, Tainan, Taiwan*

[2]*Department of Neurochemistry, New York State Institute for Basic Research in Developmental Disabilities, New York, NY, USA*

[3]*Department of Neuroscience and Physiology, State University of New York Upstate Medical University, Syracuse, NY, USA*

[*]**Corresponding author:** Nan-Shan Chang, Institute of Molecular Medicine, National Cheng Kung University Medical College, Tainan, 70101, Taiwan, Tel: 06-2353535; E-mail: changns@mail.ncku.edu.tw

Received: February 15, 2014; **Accepted:** March 26, 2014; **Published:** March 31, 2014

Commentary

Exosomes are mainly derived from intracellular multivesicular bodies and can be secreted to the extracellular spaces, which has been known for the past two decades [1-4]. Exosomes have been implicated in intercellular communications, maintaining normal cellular physiology and, importantly, potentials roles in clinical therapeutics. Many studies have documented the compositions of exosomes. Namely, exosomes are rich in specific sets of proteins, DNAs, RNAs, and lipids [5]. Exosomes are vesicles of 40-100 nm in diameter. They are normally released from healthy cells, and are present in diverse body fluids including semen, blood, urine, cerebrospinal fluid, and etc. After binding to specific recipient cells, exosomes may dock on membrane, directly fuse with plasma membrane, and are then endocytosed [1-4].

Unlike the spherical exosomes, live migrating cells may discard a portion of membrane/cytoskeleton materials. These materials are amphorous and adherent, and can be greater than 10 μm in one of the longest diameters. Yet, they are not the ghosts of dead cells. Despite their large sizes, visiting neighbor cells can engulf them completely. Later on, these fed cells secrete or dump another big chuck of amphorous membrane/cytoskeleton materials, and again other migrating cells phagocytose these adherent materials. This type of cell behavior can readily be observed by time-lapse microscopy. Nonetheless, the molecular nature of this type of exosomes is largely unknown and remains to be characterized.

Cancer cells also embark on intercellular communications, in part, via exosomes to enhance their invasiveness. A recent elegant study showed that fibroblast-secreted exosomes promote breast cancer cell protrusive activity and motility via WNT-Planar Cell Polarity (PCP) signaling [6]. The WNT-PCP pathway controls the distribution of cells within a plane. Many proteins are involved in the signaling, including WNTs Frizzled (FZD) receptors, Van-Gogh-like (Vangl), Dishevelled (Dvl), Smurf, and Prickle-like proteins (PKs), which are needed for cancer metastasis. By mass analysis, CD81 was found to be a key component in the exosomes to direct the breast cancer cell invasiveness. The study appears to provide a link from fibroblast-derived exosomes to mobilize autocrine WNT-PCP signaling to drive the invasive behavior of breast MDA-MB-231 cancer cells. That is, breast MDA-MB-231cancer cells endocytose CD81-positive exosomes, and then secrete new exosomes possessing Wnt11 and CD81 markers. Once uptake of these Wnt11- and CD81-expressing exosomes by other breast cancer cells, these cells become activated or polarized due to the autocrine WNT-PCP signaling to exhibit their protrusions, mobility and metastasis. Whether these cells migrate collectively or individually in a directional or non-directional manner is unknown. These experiments were carried out directly using purified exosomes from conditional culture supernatants to feed breast MDA-MB-231 cancer cells and to show the effect *in vitro*. Indeed, the CD81/Wnt11-exosomes are like floating rafts, and their guidance for MDA-MB-231 cells to move along is not directional. Unfortunately, there was no study using time-lapse microscopy to show one cell secretes exosomes and these exosomes are endocytosed by another cell in real time. MDA-MB-231 cells, which were used in the experiments, are very keen to their surrounding environment. They can migrate to a specific, friendly spot in a specific organ(s), where they dock and build a new niche or, they can migrate in a retrograde manner to keep away from an unfriendly or a dangerous environment, as shown in time-lapse microscopy.

The beauty of this study is that CD81/Wnt11-exosomes can be utilized as vehicles to carry therapeutic drugs for targeting cancer (Figure 1). Conceivably, a specific drug is designed to bindCD81/Wnt11-exosomes *in vivo*. Once the drug-tagged CD81/Wnt11-exosomes bind cancer cells, the drug will block stromal cells to release new exosomes, and meanwhile kills cancer cells. Without the signal released from stromal cell, the tumor cell's migration will decrease.

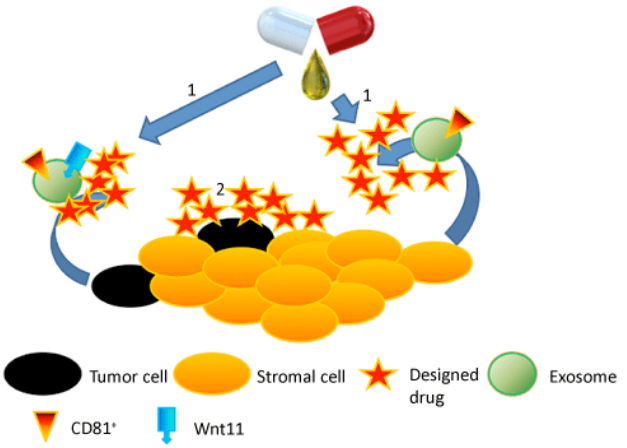

Figure 1: Exosomes as carriers for therapeutic cancer-targeting drugs. An anticancer drug, for example, is designed to interact with CD81/Wnt11-exosomes *in vivo* **(Route 1)**. The drug will kill cancer cells and cut off the signal transduction between stromal cells and cancer cells, so that no new exosomes are released by stromal cells **(Route 2)**. Cancer cell migration and metastasis can thus be blocked.

Exsosomes are also known to play a role in the communications between neurons and glials *in vivo* [7]. Another recent elegant study reported that myelinating oligodendrocytes secrete exosomes to support the normal physiological functions of neurons [8]. The authors demonstrated that glutamate derived from neurons acts as a neurotransmitter to induce oligodendrocytes to release exosomes (Figure 2). Experiments were designed to show the involvement of activation of ionotropic glutamate receptors in oligodendrocytes to cause horizontal transfer of exosomes from the oligodendrocytes to neurons. Supporting evidence revealed that glutamate secreted by neurons drives the influx of extracellular Ca^{2+} to oligodendrocytes via NMDA and AMPA receptors. These cells then secrete exosomes, which are endocytosed by neurons. The exosomes appear to be intended for sustaining the normal neuronal metabolism even under stress conditions (oxidative stress and starvation) [8]. It would be of interest to see whether oligodendrocyte-derived exosomes express CD81/Wnt11. Nonetheless, formation of exosomes in oligodendrocytes does not necessarily require neuronal signals.

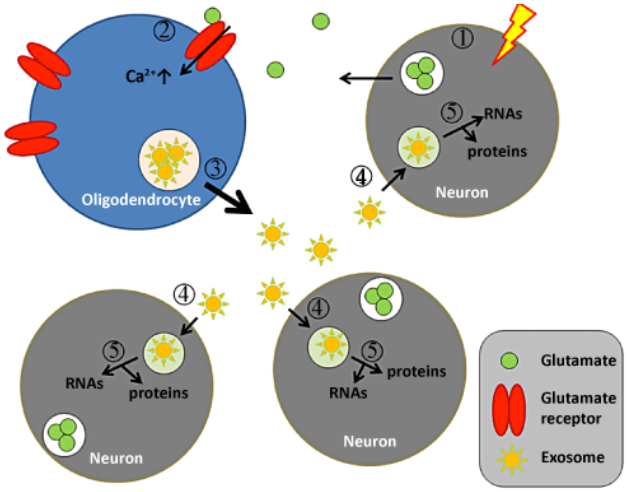

Figure 2: A schematic graph for neuron-guided release of exosomes from oligodendrocytes. **Route 1:** When a neuron is under stress conditions, the neuron releases glutamate. **Route 2:** Glutamate stimulates increases in the intracellular Ca^{2+} levels of oligodendrocytes via NMDA and AMPA receptors. **Route 3:** The stimulated oligodendrocytes release stored exosomes. **Route 4:** The released exosomes are internalized by the stressed neuron and probably by other unstressed neurons. **Route 5:** Presumably, the cargo of exosomes supports normal neuronal physiology and prevents damage of stressed neurons.

While the study was elegantly designed, what remains unclear is how exosomes are delivered to neurons. Experiments were designed to isolate exosomes from the condition media of cultured oligodendrocytes, and the isolated exosomes were added to the neuron culture. Whether exosomes travel through the myelin sheath of oligodendrocytes and are then endocytosed by neurons *in vivo* is not clear. It is reasonable to postulate that neuron picks up exosomes via its soma or myelineated axon.

In summary, many salient features of exosomes have been reported, especially in intercellular signaling and communications and functional supports among cells [1-5]. However, the contents of exosomes are highly complicated. The key components that support signaling and normal cell functions can be subjected to debate and intensive investigations. Nonetheless, once properly designed, exosomes are nice vehicles for targeted drug delivery *in vivo*.

References

1. Johnstone RM (1992) The Jeanne Manery-Fisher Memorial Lecture 1991. Maturation of reticulocytes: formation of exosomes as a mechanism for shedding membrane proteins. Biochem Cell Biol 70: 179-190.
2. Denzer K, Kleijmeer MJ, Heijnen HF, Stoorvogel W, Geuze HJ (2000) Exosome: from internal vesicle of the multivesicular body to intercellular signaling device. J Cell Sci 113 Pt 19: 3365-3374.
3. Nave KA, Trapp BD (2008) Axon-glial signaling and the glial support of axon function. Annu Rev Neurosci 31: 535-561.
4. Raposo G, Stoorvogel W (2013) Extracellular vesicles: exosomes, microvesicles, and friends. J Cell Biol 200: 373-383.
5. Choi DS, Kim DK, Kim YK, Gho YS (2014) Proteomics of extracellular vesicles: Exosomes and ectosomes. Mass Spectrom Rev, in press .

6. Luga V, Zhang L, Viloria-Petit AM, Ogunjimi AA, Inanlou MR, et al. (2012) Exosomes mediate stromal mobilization of autocrine Wnt-PCP signaling in breast cancer cell migration. Cell 151: 1542-1556.

7. Krämer-Albers EM, Bretz N, Tenzer S, Winterstein C, Möbius W, et al. (2007) Oligodendrocytes secrete exosomes containing major myelin and stress-protective proteins: Trophic support for axons? Proteomics Clin Appl 1: 1446-1461.

8. Frühbeis C, Fröhlich D, Kuo WP, Amphornrat J, Thilemann S, et al. (2013) Neurotransmitter-triggered transfer of exosomes mediates oligodendrocyte-neuron communication. PLoS Biol 11: e1001604.

This article was originally published in a special issue, entitled: **"Signaling Pathways in Functional Cells"**, Edited by Li-Na Wei, University of Minnesota, USA