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Aya D Pusic, Kae M Pusic & Richard P Kraig

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What are exosomes and how can they be used in multiple sclerosis therapy?

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Aya D Pusic

Department of Neurology, The University of Chicago, Chicago, IL 60637, USA
and
Committee on Neurobiology, The University of Chicago, Chicago, IL 60637, USA

Kae M Pusic

Department of Neurology, The University of Chicago, Chicago, IL 60637, USA

Richard P Kraig

Author for correspondence:
Department of Neurology, The University of Chicago, Chicago, IL 60637, USA
and
Committee on Neurobiology, The University of Chicago, Chicago, IL 60637, USA
Tel.: +1 773 702 0802
Fax: +1 773 702 5175
rkraig@neurology.bsd.uchicago.edu

Current treatment options for multiple sclerosis are limited and consist of immunosuppressors or agents to prevent immune infiltration of the brain. These therapies have potentially harmful side effects and do little to promote myelin repair. Instead, we suggest using exosomes, naturally occurring small vesicles that exert influence through the delivery of mRNA, microRNA and protein. Dendritic cells can be cultured from bone marrow and stimulated to release exosomes. When administered to the brain, these exosomes significantly increase myelination and improve remyelination following injury by prompting preoligodendrocytes to differentiate into myelin producing cells. Additionally, they are non-toxic and can easily cross the blood-brain barrier and, thus, have great potential as a therapeutic.

Multiple sclerosis is an inflammatory disease involving oligodendrocyte loss, demyelination and failure to remyelinate damaged brain areas. Oligodendrocytes produce CNS myelin, the insulation surrounding axons that is necessary for neuronal signaling, including that of learning, memory and cognition. Damage to oligodendrocytes and demyelination, loss of this insulation, can lead to severe neurological disability. Remyelination is a spontaneously occurring repair process mediated by recruitment of oligodendrocyte precursor cells to damaged areas, and their subsequent differentiation into mature oligodendrocytes that are capable of replacing lost myelin. Initially, multiple sclerosis patients follow a relapsing-remitting disease course, characterized by periods of partial recovery associated with incomplete remyelination [1]. However, over time this ability to repair declines and patients develop a secondary-progressive, steadily worsening disease course.

Current therapies for multiple sclerosis are largely directed at reducing demyelination via immune suppression, and often come with an array of harmful immune sequelae [2]. No existing therapies treat progressive multiple sclerosis, and though some agents have minor remyelinating potential, none adequately regenerate damaged myelin sheaths. Thus, we believe in the importance of promoting remyelination as a therapeutic target. We suggest that use of exosomes to stimulate remyelination would be beneficial to multiple sclerosis patients.

Exosomes are small, 30–120 nm diameter membrane vesicles that are secreted by many cell types, and are involved in a multitude of functions, both physiological and pathological [3]. Inward budding of the late endosome leads to the formation of vesicle-containing multivesicular bodies, which then fuse with the plasma membrane to release exosomes. Exosomes do not contain a random sampling of their parent cell's cytoplasm, rather, their specific composition is influenced by disease and/or activation state. Exosomes have the potential for targeting specific cell types to deliver their cargo of protein, mRNA and importantly, miRNA. miRNA are small non-coding RNA molecules that are increasingly recognized for their role in regulating gene expression. A new Common Fund initiative from the NIH Director's Office is designed, in part, to test the clinical utility of extracellular RNA for the development of novel therapeutics.

EXPERT REVIEWS

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There has been significant interest in exploiting these naturally formed vesicles by re-engineering them as specific immunomodulators, or delivery platforms for the development of cancer therapeutics [4] and vaccines [5]. However, much of the current research on exosomes, in the context of multiple sclerosis, has focused on the utility of extracellular miRNAs as prognostic and/or diagnostic biomarkers. While promising, this is an arduous process, with 122 miRNAs currently identified as exclusively associated with multiple sclerosis [6]. Further refinement to determine which subset of these miRNAs are best suited to serve as biomarkers is a valuable pursuit. Nonetheless, we believe that exosomes have great potential not only as multiple sclerosis biomarkers, but for therapeutic purposes as well.

Though, as mentioned above, no current multiple sclerosis therapeutic adequately restores myelin, environmental enrichment is a most opportune means of improving recovery. It is well documented that exposure to environmental enrichment improves outcomes of brain trauma and neurodegenerative disorders, including demyelinating diseases such as multiple sclerosis [7]. Environmental enrichment consists of volitionally increased intellectual (i.e., learning and memory), physical and social activity. When sufficiently robust and followed by adequate periods of rest, these activities stimulate subsequent nutritive adaptation [8,9]. Importantly, environmental enrichment can enhance memory, and increase production of myelin at all ages [10]. We believe that a better understanding of the signaling involved in environmental enrichment-based neuroprotection will allow production of effective mimetics.

In a recent study, we discovered that serum exosomes produced by young or environmental enrichment-exposed rats significantly increased myelin content, oligodendrocyte precursor cell and neural stem cell levels, and reduced oxidative stress in hippocampal slice cultures and when nasally administered to naive rats [11]. These exosomes also improved recovery from lysolecithin-induced demyelination in slice culture, an *in vitro* model of multiple sclerosis. Importantly, we found that exposure of aged animals to environmental enrichment restored their ability to produce these myelination-promoting exosomes. These serum exosomes contain high levels of miR-219, which plays a role in oligodendrocyte maturation and the formation and maintenance of compact myelin [12,13]. miR-219 is necessary and sufficient for oligodendrocyte precursor cell differentiation [14], and is deficient in human multiple sclerosis lesions [15]. These data led to a second project using bone marrow-derived dendritic cell cultures as a scalable, exogenous source for production of similarly pro-myelinating exosomes [16].

To mimic environmental enrichment, we stimulated primary dendritic cell cultures with low-level IFN-γ, a proinflammatory cytokine that is phasically increased during environmental enrichment. Though its role in multiple sclerosis is contested and largely thought to be detrimental, we have recently shown that phasic stimulation with low-level IFN-γ significantly increased myelination in cultured brain slices or when administered nasally to animals. We found that exosomes produced by IFN-γ-stimulated dendritic cells increased myelination and oxidative tolerance *in vitro* and *in vivo*. Like their serum-derived predecessors, these IFN-γ-stimulated dendritic cell-derived exosomes also contain high levels of miR-219, increase oligodendrocyte precursor differentiation and improve recovery from acute experimental demyelination. Additionally, IFN-γ-stimulated dendritic cell-derived exosomes are preferentially taken up by oligodendrocytes, suggesting they directly stimulate these cells.

This work is a first step in proof-of-principal work. However, it shows for the first time that it is feasible to use cells from donors to generate exosomes that effectively remyelinate brain, without adversely impacting endogenous neural stem cells. We suggest that advancement of dendritic cell exosomes as a remyelination therapy may include re-engineering them to contain desired miRNAs, and optimizing *in vivo* targeting methods to direct exosomes to specific cells.

We propose that adjunct use of these exosomes to stimulate remyelination would be beneficial to patients undergoing immunomodulatory therapy for multiple sclerosis. As demonstrated by work done with vaccine development, these exosomes may be additionally altered to reduce inflammation as well. For example, stimulated dendritic cell exosomes contain high levels of specific anti-inflammatory miRNAs that may serve an immunomodulatory role in suppressing development of multiple sclerosis [16]. Indeed, work by the Whitacre group shows that serum exosomes are responsible for pregnancy-induced immunosuppression that ameliorates experimental autoimmune encephalitis, an animal model of multiple sclerosis [17]. Further examination of the immunomodulatory capacity of dendritic cell-derived exosomes, as well as optimization of their ability to stimulate remyelination and stem cell propagation/differentiation may lead to an even more effective therapeutic.

Additionally, it is important to stress that exosomes are non-toxic and can easily cross the blood–brain barrier without use of an additive vehicle [16]. Thus, in addition to the aforementioned positive attributes, exosomes are an ideal delivery platform. Taken together, this supports the importance of continued exosome research for their development as therapeutics for remyelination, and advocates their study for use in other neurodegenerative disorders as well.

Financial & competing interests disclosure

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