

# Exploration of late pregnancy extracellular vesicles as regulators of oligodendrocyte biology

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Multiple Sclerosis (MS) is an incurable, debilitating neurological disease that typically strikes young adults, young women in particular, in the prime of their life. The underlying cause of MS remains obscure however disease progression is known to involve immune cells that become activated and infiltrate into the Central Nervous System (CNS) where these cells destroy oligodendrocytes, the specialized support glial cells that ensheath neuronal axons with an insulating membrane termed myelin. Myelin regulates neuronal function and is critical for long-term neuron health, thus myelin destruction leads to dysfunction followed by neurodegeneration. Most types of MS are termed “Relapsing-Remitting” in that periods of disability, or relapses, are characterized by immune activation and CNS damage, and are followed by periods of remission, in which disease activity subsides accompanied by full or partial quelling of symptoms. In the lead up to remission, immature oligodendrocytes, i.e., oligodendrocyte progenitor cells, are known to enter damaged regions, undergo maturation, and, at least in part, restore myelin ensheathment of axons. Despite the remarkable ability of oligodendrocytes to repair and restore axonal function, the disease eventually transitions to a progressive stage in which damage is not countered with repair. Current MS treatments are limited to drugs that suppress immune activity, which are only partly effective at decreasing the frequency and severity of relapses. However these therapies do not halt the transition to the progressive stage that is characterized by permanent disability. Therefore, new knowledge regarding oligodendrocyte regeneration, in particular how to stimulate and perhaps prolong the endogenous oligodendrocyte reparative process during MS, is highly needed.

Clues to factors that influence MS disease activity can be found in pregnancy. MS remission is highly influenced by pregnancy, with disease activity typically being suppressed during late gestation, followed by a spike in disease activity post-partum. While changes in both the immune system and hormone levels are known to occur during pregnancy, attempts to mimic these changes as potential therapies for MS have not been successful. However there is some evidence that pregnancy leads to a change in molecular cargo such as microRNAs (miRNAs) that are packaged within extracellular vesicles in the blood stream. Extracellular vesicles have been demonstrated to cross the blood-brain barrier and enter the brain, where they have the potential to influence oligodendrocytes and other CNS cells. We therefore propose to explore the possibility that circulating extracellular vesicles influence the health and biology of oligodendroglia during pregnancy, and to characterize the molecular factors involved in such a response as potential therapeutic targets. While a handful of studies have suggested that late-pregnancy extracellular vesicles may influence oligodendrocyte function, the precise nature of this influence remains unclear, and the capacity of late-pregnancy extracellular vesicles to treat or prevent oligodendrocyte damage caused by inflammatory stressors has not been explored. Our goal over the next 18 months will be to determine the cellular mechanisms by which circulating and placental extracellular vesicles from late pregnancy dams influence oligodendrocyte progenitor cells and oligodendrocytes *in vitro* and *in vivo*, as well as assess the differential expression of molecular cargo or surface proteins in extracellular vesicles derived from late pregnancy dams compared to those from virgin controls that may underlie altered CNS cell responses. We hypothesize that late-pregnancy extracellular vesicles will have unique biological signatures, such as miRNA content, enabling them to induce the recruitment, proliferation, differentiation, and/or survival of oligodendrocyte progenitor cells, and, possibly, enhance remyelination during MS.