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Are Exosomes a Viable Therapy for Pregnancy Complications?

Sharon McCracken*

Division of Perinatal Research, Kolling Institute of Medical Research, Royal North Shore Hospital, Reserve Rd, St Leonards, NSW 2065, Australia

***Corresponding author:** Sharon McCracken, Division of Perinatal Research, Kolling Institute of Medical Research, Royal North Shore Hospital, Reserve Rd, St Leonards, NSW, Australia, Tel: +61 2 9926 4832; Email: Sharon.mccracken@sydney.edu.au**Received date:** January 11, 2017; **Accepted date:** January 13, 2017; **Published date:** January 16, 2017**Citation:** McCracken S (2017) Are Exosomes a viable therapy for pregnancy complications? *Reproductive Immunol Open Acc* 2:27. doi: 10.21767/2476-1974.100027**Copyright:** © 2017 McCracken S. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

Editorial

Exosomes are nano-sized vesicles actively produced and released by all cell types of the body including stem cells. They act as intracellular communicators carrying proteins, mRNA, miRNA and DNA as well as expressing cell surface markers inherent to their parent cell. Exosomes are increasingly emerging as effective therapeutics in immune and regenerative therapy and as such are becoming an effective alternative to stem cell therapy and an adjunct to immunotherapy.

In pregnancy the maternal adaptive immune responses are suppressed throughout gestation [1] with a bias away from Th1/Th17 towards Th2 immunity [2] and a migration of maternal Treg cells to the decidua [3]. In the peripheral circulation the mechanisms that regulate this adaptation are not fully understood. Dr McCracken and colleagues have shown that NF-kappaB is central to the regulation of Th1 immunity [4] and have shown that suppression of NF-kB controls the production of Th1 cytokines thus biasing Th2 cytokine production.

Dr McCracken has shown that the signal that facilitates the suppression of Th1 immunity is derived from pregnancy specific exosomes present in maternal plasma [5]. Placental exosomes possess immune suppressive properties via enhancing lymphocyte apoptosis and suppressing CD3 ζ expression, a signalling moiety required for T-cell receptor activation [5,6]. Exosomes derived specifically from placental cultures express ULBP1-5 and Major histocompatibility complex 1 and 2 on their surface and induced down-regulation of the NKG2D receptor on NK, CD8(+) cells and gamma delta T cells, leading to reduction of their *in vitro* cytotoxicity [7] which *in vivo* would ultimately lead to fetal sparing.

In pregnancy a failure of immune adaptation is associated with complications including recurrent pregnancy loss, pre-eclampsia, preterm delivery [8,9] and intra uterine growth restriction (IUGR) [10]. In addition, inducing Treg function using anti-CD28, rescues the IUGR, but not the pre-clampic symptom in a rat model of preeclampsia and IUGR [11]. This only highlights the importance of maternal immune adaptation in successful fetal growth.

So could we use exosomes derived from the placenta to correct the immunological deficits associated with some or all of

these pregnancy complications? Are all exosomes equal in their function?

Exosome function is dictated by their parent cell type. Not unlike exosomes derived from the placenta, tumour derived (TD) exosomes play a critical role in tumour metastasis by suppressing the function of NK and T-cell through the induction of apoptosis [12,13], thus allowing immune evasion and subsequent tumour growth. In addition however although tumour derived exosomes are predominantly known for their immunosuppressive qualities, they can also enhance immune-stimulation, mainly through antigen presentation of tumour antigens by APCs which in its self incites T-cell responses. This can and has been utilised in clinical trials to assess efficacy in treating cancer with increasing promise [14,15]. In addition, although MSCs are extensively used in regenerative and immunotherapy it is becoming increasingly more evident that the function of many MSCs used in therapy is not due to MSC interactions with affected tissue and cell types, more it is the release and effect of MSC specific exosomes. A realisation Dr Rebecca Lim from the Hudson Institute of Medical Research Australia is investigating with regards to the use of fetally derived amniotic epithelial stem cell exosomes in lung repair both in the adult and the neonate.

Overall the use of exosomes as therapeutic modalities is highly feasible. Their production is cheap and they can be isolated easily by differential ultracentrifugation. In addition they can be purified, frozen, lyophilized, packaged and distributed like any other current drug products, indeed not unlike current FDA-approved liposome therapies. Dr McCracken's group is working towards fully defining the role of placentally derived exosomes in modulating the immune system in pregnancy and determining their potential use in correcting pregnancy complications. If exosomes can be used to correct these maternal complications this will have considerable impact in both short and long term health outcomes and will be of immense benefit for both mothers and their babies.

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