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Investigation of the Controversial Immunomodulatory Potential of Trichinella spiralis Excretory-Secretory Products versus Extracellular Vesicles Derived from These Products in vitro

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Abstract : As a very promising candidate for modulation of immune response in the sense of biasing the inflammatory towards an anti-inflammatory type of response, Trichinella spiralis infection was shown to successfully alleviate the severity of experimental autoimmune encephalomyelitis, the animal model of human disease multiple sclerosis. This effect is achieved via its excretory-secretory muscle larvae (ES L1) products which affect the maturation status and function of dendritic cells (DCs) by inducing the tolerogenic status of DCs, which leads to the mitigation of the Th1 type of response and the activation of a regulatory type of immune response both in vitro and in vivo. ES L1 alone or via treated DCs successfully mitigated EAE in the same manner as the infection itself. On the other hand, it has been shown that T. spiralis infection slows down the tumour growth and significantly reduces the tumour size in the model of mouse melanoma, while ES L1 possesses a pro-apoptotic and anti-survival effect on melanoma cells in vitro. Hence, although the mechanisms still need to be revealed, T. spiralis infection and its ES L1 products have a bit of controversial potential to modulate both inflammatory diseases and malignancies. The recent discovery of T. spiralis extracellular vesicles (TsEVs) suggested that the induction of complex regulation of the immune response requires simultaneous delivery of different signals in nano-sized packages. This study aimed to explore whether TsEVs bare the similar potential as ES L1 to influence the status of DCs in initiation, progression and regulation of immune response, but also to investigate the effect of both ES L1 and TsEVs on myeloid derived suppressor cells (MDSC) which present the regular tumour tissue environment. TsEVs were enriched from the conditioned medium of T. spiralis muscle larvae by differential centrifugation and used for the treatment of human monocyte-derived DCs and MDSC. On DCs, TsEVs induced low expression of HLA DR and CD40, moderate CD83 and CD86, and increased expression of ILT3 and CCR7 on treated DCs, i.e., they induced tolerogenic DCs. Such DCs possess the capacity to polarize T cell immune response towards regulatory type, with an increased proportion of IL-10 and TGF-β producing cells, similarly to ES L1. These findings indicated that the ability of TsEVs to induce tolerogenic DCs favoring anti-inflammatory responses may be helpful in coping with diseases that involve Th1/Th17-, but also Th2-mediated inflammation. In MDSC in vitro model, although both ES L1 and TsEVs had the same impact on MDSC phenotype i.e., they acted suppressive, ES L1 treated MDSC, unlike TsEVs treated ones, induced T cell response characterized by the increased RoRγT and IFN-γ, while the proportion of regulatory cells was decreased followed by the decrease in IL-10 and TGF-β positive cells proportion within this population. These findings indicate the interesting ability of ES L1 to modulate T cells response via MDSC towards pro-inflamatory type, suggesting that, unlike TsEVs which consistently demonstrate the suppresive effect on inflammatory response, it could be used also for the development of new approaches aimed for the treatment of malignant diseases. Acknowledgment: This work was funded by the Promis project – Nano-MDCS-Thera, Science Fund, Republic of Serbia.

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