Exosomes as a potential biomarker for monitoring and predicting kidney allograft rejection

Kidney transplantation ensures the longest survival and the best quality of life for most patients with end-stage renal disease. However, despite progress made in immunosuppressive treatment, rejection of a transplanted kidney remains a significant clinical problem and one of the main reasons for the failure of this therapy. Apart from kidney dysfunction, mainly characterized by increased concentration of creatinine in serum and/or proteinuria, and in the case of humoral rejection also in the presence of antibodies specific for the donor HLA (human leukocyte antigens) (DSA - donor-specific antibodies), a final diagnosis of rejection requires the presence of lesions in the tissue of a transplanted kidney (interstitial and microvascular inflammation). Analysis of the above-mentioned lesions in the tissue requires a core needle biopsy to be performed for a patient, which is associated with a risk of complications, such as bleeding or damage to adjacent structures. Avoiding this invasive examination and the possibility of monitoring markers of rejection of a transplanted kidney in the blood or urine would be an obvious benefit to a patient.

Exosomes are nanovesicles released by all types of cells. The presence of many components specific for parental cells has been confirmed in the membrane of these vesicles, including key immune-related molecules. Importantly, a repertoire of the major histocompatibility complex (MHC) on the exosome's surface is identical with a one in parental cells. Therefore, in the presented project we hypothesize that after kidney transplantation, in the blood of the recipient two fractions of exosomes coexist with either the MHC profile of the recipient or the MHC profile of the organ's donor. Further, we assumed that the main reason for a transplant rejection is the alloimmune response is initiated in the secondary lymphoid organs by T lymphocytes recognizing the MHC of the donor (allorecognition). Hence, exosomes released by allogeneic transplants that transfer the donor's MHC to the lymphoid organs of the recipient may therefore contribute to the enhancement of the immune response of the recipient against the transplanted organ, leading to its rejection.

The proposed project aims at the identification and functional evaluation of specific components of exosomes released by a transplanted organ and present in the blood of a recipient after transplantation. Owing to the size of the studied vesicles and the amount of material obtained after exosomes isolation, the techniques of mass spectrometry seem to be an ideal tool for qualitative and quantitative analysis of exosomes content. During the realization of the proposed project, we will also monitor immunological parameters of patients, inter alia: subpopulations of T lymphocytes, the profile of interleukins, and the presence of anti-HLA antibodies.

We expect that realization of the proposed project will contribute to gaining knowledge about the role of molecular components of exosomes and will broaden our knowledge about the biology of these structures, especially taking into account their immunomodulatory role in the mechanism leading to rejection of a transplanted kidney. Moreover, a quantitative assessment of donor-specific exosomes and their components in the recipient's blood may coin a principle for a non-invasive method of monitoring the risk of a rejection of a transplanted organ.