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Microarray Gene Expression in Immunological conditions

AKADEMISK AVHANDLING

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ABSTRACT

The use of microarray techniques for gene expression analysis provides a global view of the transcriptional activity in a biological sample. In this thesis two conditions accompanied by disturbance in the immune system are addressed following the changes in gene expression. The first condition is hematopoietic stem cell transplantation (HSCT) and the second condition is chronic kidney disease (CKD). A mouse model was used in studies related to HSCT, while human blood samples were used in the CKD study.

In the first project, gene expression profiling in target and non-target organs after HSCT and during early development of acute graft versus host disease (GVHD) was investigated. The results show that both chemotherapy and allogeneicity induce expression of inflammatory genes in target tissues. Furthermore, gene expression in the kidney was similar to that observed in the liver, which is a target for developing GVHD. In conclusion, the kidney could be a possible target organ for GVHD.

In the second project, the role of programmed cell death ligand-1 (PD-L1/CD274) in the development of graft versus host disease was studied. The expression of PD-L1/CD274 was evaluated by PCR, western blot and immunohistochemistry at different time intervals after the development of acute GVHD. A significant up-regulation of PD-L1/CD274 expression was observed in muscle and kidney at days 5 and 7 post allogeneic transplantation. The increase of CD274 expression was paralleled by high serum levels of IFN- γ and TNF- α at corresponding time points. In conclusion, our results confirm that PD-L1/CD274 expression is different after allogeneic and syngeneic transplantation, and that it is more expressed in non-target organs in the early stages of acute GVHD. This further indicates that the higher expression of PD-L1/CD274 in the muscle might have a protective role during acute GVHD.

In the third project, changes in gene expression after two different conditioning regimens used in preparation for HSCT, either single dose or fractionated total body irradiation (TBI), were studied. In the lung, genes belonging to inflammatory and immune responses were intensely under-expressed upon conditioning with single-dose, but slightly increased by treatment with fractionated TBI. These genes remained unchanged in the liver and muscle upon conditioning with either of these regimens. Both the patterns and magnitudes of these effects were changed after 12 and 72 hours. Thus, pathological manifestations observed in the lung after conditioning with single-dose, but not fractionated, TBI can be associated with extensive down regulation of immune and inflammatory gene expression in this organ.

In the fourth project, gene expression profile for monocytes from peripheral blood of chronic kidney disease (CKD) patients was performed. The results demonstrated differences from the gene expression profile of healthy persons. Pathways involved in the inflammatory response were highly expressed in CKD patients, and the Wnt/ β -catenin signaling pathway was the most significant pathway expressed in the patient group. Since this pathway has been attributed to a variety of inflammatory manifestations, the current findings may contribute to dysfunctional monocytes in CKD patients. Strategies for interfering with this pathway may improve host immunity and prevent cardiovascular complications in CKD patients.