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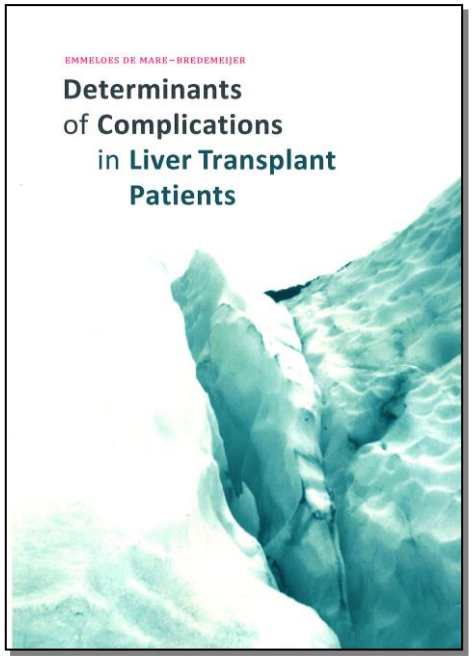

Determinants of complications in liver transplant patientsSamenvatting proef-schrift
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"Determinants of complications in liver transplant patients"

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Liver transplant patients are susceptible to severe complications that strongly affect their survival and quality of life. The aims of this thesis were to identify risk factors for the occurrence of complications in patients with end-stage liver disease (ESLD), both before and after liver transplantation (LTx), and to develop strategies to optimize immunosuppression after LTx in order to reduce immunosuppression-related complications. Important complications in LTx patients are acute rejection and side effects of immunosuppressive drugs, such as infections. For example, up to 80% of LTx patients develop at least one episode of infection during the first year after transplantation, which is the leading cause of death early post-LTx, and about 30% of LTx patients experience one or more episodes of acute rejection. Other factors that influence the occurrence and severity of these complications can be subdivided into different categories, amongst which genetic factors and viral factors. First, we showed that an A allele in TNFA c.238 gene strongly protects ESLD patients before LTx against severe bacterial infections (SBIs) and SBI-related death in two independent cohorts. Second, we found that genetic variants in various innate immunity receptors do not predict risk of infections and acute rejection in patients post-LTx. Third, we showed that CMV infection is associated with donor-specific $CD8^+$ T-cell hypo-responsiveness early post-LTx and that CMV infection protects patients against late acute rejection. We also found that CMV infection induces CD244 expression on $CD8^+$ T cells in patients early and late after LTx, which is associated with $CD8^+$ T-cell hypo-responsiveness to allo-antigen. In the last part, we compared immunosuppressive effects of liver graft-derived mesenchymal stromal cells (L-MSCs) and bone marrow-derived MSCs (BM-MSCs) on allo-responses. We found that L-MSCs suppress proliferation, cytotoxic degranulation and IFN-γ production of allo-reactive T cells better than BM-MSCs, which was partly mediated by PD-L1 and IDO. These findings may lead to cell-based immunosuppressive therapies for LTx patients, in order to reduce complications of currently used immunosuppressive regimens.