토르양 수용체 자극의 이식 면역관용에 대한 영향

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Toll-like receptor (TLR) Stimulation Interferes with Transplantation Tolerance

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Purpose : TLRs recognize pathogen-associated molecular patterns, and play an important role in bridging innate and adaptive immune response. Intrinsic danger signals or environmental antigens may stimulate TLR in the context of transplantation, in association with perioperative tissue damages or postoperative opportunistic infections. Recently, graft survival was shown to be prolonged in MyD88, or Trif knockout donor-recipient pairs. We tried to reevaluate the role of TLR in transplantation by investigating whether TLR stimulation can interfere with tolerance induction.

Methods : We conducted murine skin or cardiac transplantation with or without tolerizing agents, such as CTLA-4Ig, anti-CD40L, and rapamycin. CpG or Poly I:C was injected to these mice once or three times. Overall graft survival was analyzed. To investigate the role of TLR stimulation in alloimmune response on a cellular basis, we used graft versus host disease (GVHD) model, where T cell receptor transgenic cells reactive to I-ABm12 (ABM) were transferred to irradiated Bm12 mice under tolerizing conditions with or without CpG or Poly I:C. Next, the same ABM cells were transferred to C57BL/6 RAG1 knockout mice on the same day of Bm12 skin transplantation, and CpG was injected on day 0, 2, and 4 without any tolerizing agent.

Results : In single injection of CpG or Poly I:C, there was no survival shortening in both skin and cardiac transplantation. However, skin graft survival decreased, and tolerance induction in cardiac graft was broken, when CpG was injected three times with tolerizing agents. Spontaneous tolerance of Bm12 cardiac graft in ABM recipients without any tolerizing agents, was also abrogated by multiple injection of CpG. In GVHD models, single injection of CpG or Poly I:C failed to rescue proliferation or interferon-gamma production, suppressed by CTLA-4Ig and anti-CD40L. In draining lymph nodes on day 10 of skin transplantation, CFSE dilution patterns and apoptosis rates were similar between control and multiple CpG injection group. CpG injection also increased neither the absolute number of total ABM CD4+ T cells nor the proportion of activated T cells (CD44+). Homeostatic proliferation in T cell-deficient recipients might mask the negative impact of TLR stimulation on tolerance induction on a cellular basis.

Conclusion : Repeated, or strong TLR activation can interfere with tolerance induction, and therefore it may be one of important barriers in transplantation tolerance.