



Special Issue: Immunoregulation in regenerative medicine

Brief Review

Immunoregulation in regenerative medicine

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Regenerative medicine field has been booming in recent years, and the invention of induce pluripotent stem cell (iPSC) technology has contributed a lot to this prosperity. One of the biggest advantageous points in the iPSC technology is that iPSCs can be produced from somatic cells of a patient and thus the regenerated cells may not be rejected after transplantation to the patient. Common people therefore seem to think that regenerative medicine is providing the technology to regenerate tissues/organs from their own cells. In medical terminology, this approach represents “autologous transplantation”. However, in reality, regenerative medicine field is taking “allogeneic transplantation” strategy in the approaches using iPSCs, in which regenerated tissues are produced from iPSCs derived from other person. In such allogeneic transplantation, recipients can not be free from the problem that the transplanted tissues will be rejected by recipient’s immune system. Hence it is important to conduct research of transplantation immunology in association with regenerative medicine.

So called “iPSC stock project” is ongoing in Japan,

in which iPSCs are established and stocked from HLA haplotype-homozygous (hereafter referred to as “homo”) donors. Regenerated tissues can be transplanted to not only homo but also HLA haplotype-heterozygous (hereafter referred to as “hetero”) recipients, since recipient T cells can not recognize the graft as non-self. It is said that 140 homo iPSC lines can cover 90 % of Japanese people.

Then, are immunological issues solved by this homo-to-hetero approach? The issues are not that simple. Actually, even in the HLA-fully matched transplantation, the grafts will be finally rejected due to the mismatch in minor histocompatibility antigens. It is probable that NK cells in hetero-recipients also can sense the absence of certain HLA molecules on the homo-graft and may exert immune reaction against grafts. Furthermore, iPSC-derived tissues could have unique immunogenicity, as discussed by R. Araki et al in this issue. Collectively, it would be inevitable that the recipients have to take immunosuppressive drugs for the rest of their life. If people get the fatal disease, it could be acceptable for them to take immunosuppressant to survive, but if it is not the fatal case, then the merit and



demerit of taking such strong drugs should be carefully discussed. It is thus desirable to develop other strategies such as a cell therapy that can induce tolerance to the graft.

In this issue, four articles that concern immune-regulation matter in regenerative medicine field are invited. Y. Matsuzaki introduces pathology of graft-versus-host disease (GVHD) that occurs after bone marrow transplantation, and further proposes a novel model for the cellular mechanisms of chronic GVHD. R. Araki et al argue about their recently

published finding that point mutations take place during iPSC induction process, which may result in immunogenicity of iPSC-derived tissues. H. Wada et al discuss the immunological problems in regenerative medicine and introduce their approach to use immunosuppressive cells that can exert graft-specific immune suppression. We show that T cells with certain antigen specificity can be cloned and regenerated by using the iPSC technology, and that such strategy can be applied to cancer immunotherapy.