論　文　の　内　容　の　要　旨

論文題目：Impact of cryopreservation on anti-infectious properties and indoleamine 2,3-dioxygenase expression of vascular allografts
血管組織の Indoleamine 2,3-dioxygenase (IDO)の抗感染性発現に対する凍結保存の影響

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Background: Bacterial native valve endocarditis (NVE) and prosthetic valve infective endocarditis (PVE) are potentially life-threatening clinical conditions that often associated with poor outcomes. Despite the recent advances in antimicrobial therapies and cardiac surgery techniques, the incidences of left-sided infective endocarditis (IE) and its fatal complications is still significantly high and *Staphylococcus aureus* remains the most common cause of the disease. Viable allografts (homografts) and autografts

(isografts) are believed to maintain resistance to such infections, but the mechanism remains undetermined. In the previous experiments fresh vascular allografts suppressed methicillin-resistant *Staphylococcus aureus* (MRSA) growth by the induction of an immune response and tryptophan metabolism via the indoleamine 2,3-dioxygenase (IDO) pathway. The use of fresh allografts is limited by short storage time and cryopreservation is the method of choice which allows to preserve tissue viability and integrity at good level. We studied both the impact of cryopreservation on the anti-infectious properties (e.g. anti-MRSA) and IDO expression of vascular allografts.

Methods: Brown Norway (BN) and Lewis (LEW) rats were used as allogeneic or syngeneic transplantation models. One centimeter of fresh or cryopreserved thoracic aortas were prepared from donor rats and transplanted into the recipient rats' abdominal aortas, below the kidney level. The grafts were recovered from recipient rats on days 7, 14 and 28 and submitted for gene expression analysis or for MRSA proliferation assay to determine the extent of the local immune-related and IDO gene expression and their bacteriostatic effect. The localization of IDO protein was studied using immunohistochemistry (IHC).

Results: Fresh and cryopreserved allografts significantly suppressed MRSA growth. IFNγ, TNFα gene expression on days 7, 14 and 28 was minimal in cryopreserved syngeneic grafts, and much higher in fresh allografts, but the iNOS gene expression in one week was higher in cryopreserved allografts than in fresh allografts. The expression of IDO on days 7 and 14 was higher in the fresh allografts in comparison to that of cryopreserved allografts, although the difference has diminished on day 28 after transplantation. Inhibition of IDO with 1-methyl-D-tryptophan significantly decreased the

suppressive abilities of allografts. The IDO protein was detected in the intima and adventitia of allografts, where inflammatory cell infiltration was remarkable.

Conclusion: Cryopreservation does not diminish anti-infectious properties of allografts and both fresh and cryopreserved allografts suppressed MRSA proliferation significantly. During first two weeks after transplantation IDO expression in cryopreserved allografts was lower than in fresh allografts, but sufficient to support anti-MRSA resistance of allografts.