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The regulation of indoleamine 2, 3 dioxygenase and its role in a porcine model of acute kidney allograft rejection

In kidney transplantation acute rejection is the most common cause of late allograft loss. Changes in indoleamine 2, 3 dioxygenase (IDO) activity, which catabolizes the degradation of tryptophan to kynurenine, may predict rejection. However, when used therapeutically, IDO is immunosuppressive in rodent kidney transplantation. Thus, the increase in IDO activity observed in acute allograft rejection is insufficient to prevent rejection. To address this question, we assessed the regulation of IDO and its role in acute rejection in a porcine model of kidney transplant. In tissue samples from rejecting kidney allografts we showed a 13 fold increase in IDO gene transcription, and 20 fold increase in IDO enzyme activity when compared to autotransplanted kidneys. Allografts also demonstrated an over 4-fold increase in tissue IFN- γ , with marked increases in TNF- α , TNF- β and IL1- β . Rejecting allografts also showed down regulation of kynurenine 3-monooxygenase (KMO) gene transcription and protein levels. KMO generates the immunosuppressive kynurenine 3-hydroxykynurenine (3-HK) from kynurenine. The results of these studies demonstrate a clear association between rejection and increased allograft IDO expression, likely driven in part by IFN- γ and facilitated by other cytokines of the allogeneic response. Moreover, the loss of downstream enzymatic activity in the IDO metabolic pathway may suggest novel mechanisms for the perpetuation of rejection in the early transplant period.

Biography

Norris Stanely Nahman joined the Faculty of Medicine at Ohio State University College of Medicine after completing his fellowship at the Ohio State University College of Medicine in 1987. In 2004, he became Director of Nephrology division of University of Florida Jacksonville. In 2010, he joined Nephrology division at Medical College of Georgia, where he has directed the Department of Medicine Translational Research Program since 2013, leads a USRDS data mining group, and is PI of a basic research lab studying the tolerogenic properties of enzyme IDO. In 2017, he became Co-chair of American Society of Nephrology in-training exam question writing group.

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