Immune Monitoring of Kidney Transplant Recipients with Post-transplant Malignancy

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Chris Hope

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Abstract:

Half of all long-term (>10 years) Australian Kidney Transplant Recipients (KTR) will develop Squamous Cell Carcinoma (SCC) or Solid Organ Cancer (SOC), making cancer the leading cause of death with a functioning kidney graft. Immunosuppressive drugs increase the risk of cancer but prevent rejection. Finding a balance of immunosuppression may decrease cancer incidence without increasing rejection incidence. United Kingdom (UK) KTR with cancer have increased Regulatory T cells (Tregs) and decreased Natural Killer (NK) cells compared to UK KTR without cancer. However, it is not known if these immune cells and their function differ in Australian KTR with SCC or SOC. If so, then these tests will identify patients at risk of developing cancer and may benefit from reduction of immunosuppression. The presence of Donor Specific Antibodies (DSA) and a positive IFN-γ Enzyme Linked Immuno-SPOT (ELISPOT) assay associates with antibody mediated rejection and can predict cell mediated rejection episodes, respectively. It is not known if these differ in KTR with cancer vs KTR with no cancer. An immune phenotype was analysed in 116 KTR and prospectively followed for 3.5 years. The immune function of Tregs and NK cells as well as viral, mitogen and allo-responses were measured in 50/116 (43%) of these KTR.

Summary Table of Results	**No Cancer**	**Cancer**	***P*-value**
Tregs cells/μl	8 (3, 19)	16 (6, 23)	0.016
NK cells/μl	107 (34, 195)	74 (43, 188)	0.980
CFSE 1:4 Treg:Eff. cell ratio, median (Range)	2 (1-7)	9 (3-15)	<0.001
CD154 1:4 Treg:Eff. cell ratio, median (Range)	13 (5-54)	36 (13-73)	0.015
PBMC (NK cell) Lysis, median (Range)	2 (0-11)	0 (0-5)	0.037
Donor Specific Antibodies (DSA)	3 (16%)	3 (10%)	0.661
Mitogen stimulation (PHA), median (Range)	1467(265-2000)	512 (51-1500)	0.002
Alloresponse (PRT), median (Range)	342 (11-1967)	151 (29-765)	0.008

KTR with cancer have different immune phenotype and function compared to KTR with no cancer. Memory B cells and CD8 γδ T cells associated with cancer development (Odds Ratio (95% C.I.); (1.03[1.00-1.06], p=0.038 and 1.01 [1.00-1.02], p=0.080, respectively). Treg numbers associate with SOC (p=0.053), predict SCC that develops (AUC=0.78), and can also predict aggressive lesions (AUC=0.86). Treg numbers are dynamic around cancer diagnosis (p=0.022) and resection (p<0.001). Australian KTR with cancer have increased non-specific Treg function (p<0.05) and decreased NK cell mediated cancer cytolysis (p=0.037), signs of a Treg induced/cancer-permissive immune system. Additionally, KTR have decreased IFN-γ release under allogeneic (p=0.008) and mitogenic stimulation (p=0.002) and similar levels of DSA (p=0.661) than KTR with no cancer.

These data indicate that KTR with cancer who have reduced allo-responses may have the potential to have alterations to their immunosuppressive drug levels. This reduction and its effects on the immune system can be monitored using the assays described in this thesis.

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