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The Alteration of Monocyte Subsets and the Early Acute Rejection After Kidney Transplantation

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Objectives: Despite the use of recent immunosuppressive agents that mainly modulate adaptive immunity, early acute rejection (EAR) in kidney transplantation (KT) remains an unresolved problem. We explored the population and phenotypic changes of circulating monocytes parallel with adaptive immune cells after KT and its association with EAR development.

Methods: We analyzed 35 pairs of pre- and post-KT peripheral blood mononuclear cells from KT recipients and 13 live donor samples by flow cytometry from our prospective KT cohort aligned with the biobank. Monocytes were classified into classical ($CD14^{++}CD16^{-}$), intermediate ($CD14^{++}CD16^{+}$), and non-classical ($CD14^{+}CD16^{++}$) monocyte populations. Post-transplantation samples were collected at the same time as the protocol biopsy between postoperative days 8 and 14. The outcome was defined as biopsy-proven EAR events excluding borderline T-cell mediated rejection.

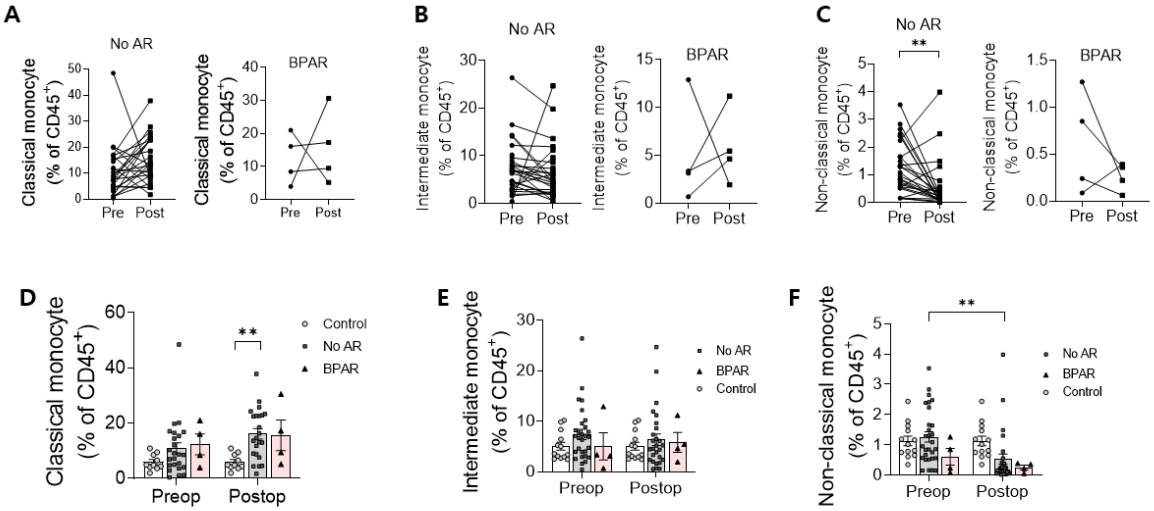
Results: Among 35 KT recipients, 89% received their allograft from living-donor and 10 underwent desensitization for their ABO or HLA incompatibilities. All recipients received basiliximab induction except for one. EAR was diagnosed in 5 (14.2%) of the patients and all of their grafts came from live donors. The composition of preoperative CD4 and CD8 T cells of recipients experiencing EAR was not different from those without EAR or donor controls. However, the proportions of intermediate and non-classical monocytes of EAR patients were not suppressed after KT whereas those of patients without EAR were significantly depressed after KT. Interestingly, the proportion of non-classical monocytes was the lowest in EAR patients in both the pre-and post-KT periods than in KT recipients without rejection or kidney donors (1.26±0.92% vs 0.61±0.55% and 1.13±0.58% at pre-KT ($p=0.294$ and 0.297), 0.53±0.88% vs 0.26±0.15 and 1.13±0.58% at post-KT ($p=0.004$ and 0.300)).

Conclusions: Our findings suggest that changes in monocyte subsets before and after KT are associated with EAR occurrence in KT recipients. Non-classical monocytes, in particular, may play an important role in the development of EAR.

Table 1. Baseline characteristics

	No acute rejection, borderline (n=30)	BPAR (n=5)	P-value
Age – yrs	56.0 [37.0 – 62.0]	44.0 [39.0 – 60.0]	0.396
Male – n (%)	21 (70.0%)	1 (20.0%)	0.052
Cause of ESKD – n (%)			0.447
- DM	6 (20.0%)	1 (20.0%)	
- GN	8 (26.7%)	2 (40.0%)	
- Others	17 (53.3%)	2 (40.0%)	
Pre-emptive KT – n (%)	10 (33.3%)	1 (20.0%)	0.546
RRT duration – mo	21.0 [5.9 – 41.0]	15.2 [14.3 – 20.4]	0.814
Living related donor – n (%)	16 (53.3%)	3 (60.0%)	1.000
Deceased donor – n (%)	4 (13.3%)	0 (0.0%)	
Donor age – yrs	56.0 [47.0 – 61.0]	49.0 [45.0 – 50.0]	0.186
Male donor – n (%)	13 (43.3%)	3 (60.0%)	0.642
Number of HLA-A/B/DR/DQ mismatching – n	4.0 [3.0 – 6.0]	5.0 [4.0 – 8.0]	0.100
Desensitization	9 (30.0%)	1 (20.0%)	1.000
- ABO incompatible	8 (61.5%)	1 (100.0%)	0.614
- HLA incompatible	1 (7.7%)	0 (0.0%)	
Basiliximab induction	29 (96.7%)	5 (100.0%)	1.000
Cold ischemia time – hrs	1.0 [0.7 – 1.3]	0.6 [0.5 – 0.9]	0.207
Warm ischemia time – hrs	0.6 [0.5 – 0.7]	0.5 [0.5 – 0.6]	0.436
Surgery time – hrs	3.5 ± 1.0	3.7 ± 0.7	0.801
Preop creatinine – mg/dL	7.1 [5.5 – 8.3]	10.4 [5.2 – 11.3]	0.732
Postop day 7 creatinine – mg/dL	1.1 [0.9 – 1.4]	1.0 [0.8 – 1.0]	0.150
Last creatinine – mg/dL	1.3 ± 0.4	0.9 ± 0.1	0.000
Slow graft function – n (%)	4 (13.3%)	0 (0.0%)	1.000

Figure 1. Percentage of circulating monocyte subsets before and after kidney transplantation.



Changes of each monocyte subset before and after KT were showed. Analysis of data from flow cytometry was performed by paired t test(A~C) and ANOVA(D~F) with repeated measures and a comparison within three groups (Control, No AR, BPAR) between two time points by contrasts.
(Abbreviations: No AR = No acute rejection, BPAR = biopsy-proven acute rejection)