CMV-Specific T Cell Immune Responses in Older Versus Younger Kidney Transplant Recipients

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BACKGROUND

- The numbers of older patients with end-stage organ disease requiring organ transplantation continues to grow as the population ages. Compared to younger transplant recipients, older transplant recipients experience increased rates of infection and death, but decreased rates of rejection. This observation suggests that immune dysfunction in older transplant recipients leads to vulnerability to infection. However, the mechanism behind this vulnerability has yet to be defined.
- Age-related immune dysfunction is associated with deleterious changes in both innate and adaptive immunity, leading to impaired response to vaccination and increased susceptibility to infection. T cell changes include immunosenescence (CD28-, KLRG-1+), chronic activation (CD57+), exhaustion (KLRG-1+, PD-1+), and higher levels of pro-inflammatory cytokines This "inflammaging" is hypothesized to result from recurrent antigen exposure in the setting of acute and chronic viral infections, such as CMV.
- **Hypothesis**: Compared to younger kidney transplant recipients, older kidney transplant recipients will demonstrate impaired immune responses to CMV antigen stimulation.

METHODS

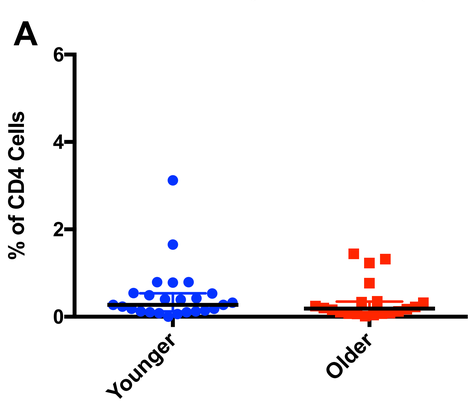
- **Patient characteristics**: Peripheral blood mononuclear cells were isolated from 20 older (≥ age 60) and 25 matched younger (ages 30-59) kidney transplant recipients at 3 months after transplantation. Older versus younger patients were matched on induction type (basiliximab versus lymphocyte depletion with antithymocyte globulin (ATG)) and living versus deceased donor type. All patients were characterized as either high (D+/R-) or intermediate (R+) risk for CMV by donor and recipient serology.
- **Flow cytometry.** Flow cytometry and intracellular cytokine staining were performed using overlapping peptide pools representing the nine most dominant CMV peptides. PBMCs were incubated with CD28-specific antibody, followed by addition of Brefeldin and fluorescent-conjugated antibodies Fluorescence measured by flow cytometry using the LSRFortessa (BD Bioscience). Positive control was Staphylococcal enterotoxin B, and negative control was absence of stimulation.
- **Statistical analysis**: JMP Pro 11 was utilized to calculate nonparametric 2-sample test (Mann-Whitney U Test) for continuous values and Fisher exact test for categorical variables.

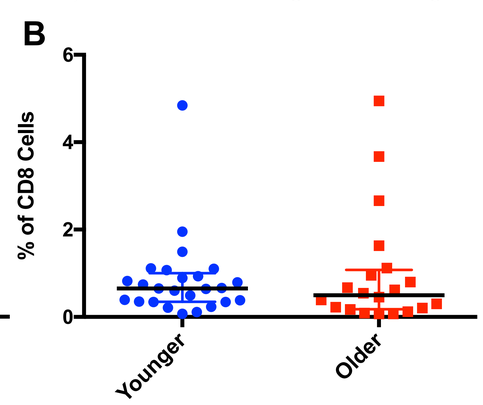
Table 1: Characteristics of older versus younger kidney transplant recipients

	Younger n = 37	Older n = 23	p-value
Age (median, years)	42 (34-51)	67.5 (60-80)	
Male sex	60%	80%	0.202
White race	60%	65%	0.767
Hispanic	36%	35%	1.000
Induction, ATG	32%	25%	0.745
Deceased donor	56%	40%	0.373
Diabetes	36%	55%	0.363
CMV Ab positive	84%	80%	1.000
CMV mismatch (D+/R-)	16%	20%	1.000
CMV viremia	28%	50%	0.216
Invasive infection	12%	15%	1.000
Rejection (ACR or AMR)	12%	15%	1.000

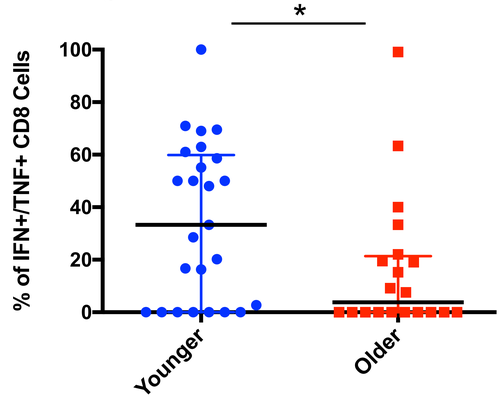
RESULTS

- **CMV-specific T cell response by patient age:** There was no difference between older and younger kidney transplant recipients in release of IFNg, TNFa, or IL-2 from CD4+ or CD8+ T cells in response to CMV antigen stimulation. Older recipients had a decreased frequency of CD8+ terminally differentiated effector memory CD45RA+ (TEMRA) T cells releasing both IFNg and TNFa (p = 0.037).



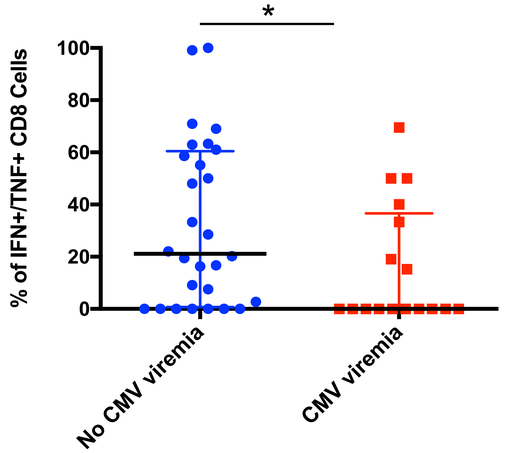


Frequency of **A)** CD4+ and **B)** CD8+ T cells releasing TNFa in response to CMV stimulation by patient age.



Frequency of CD8+ TEMRA cells releasing IFNg and TNFa in response to CMV stimulation by patient age.

- **CMV-specific T cell response by history of viremia:** Patients who developed CMV viremia had a decreased frequency of CD8+ TEMRA cells releasing both IFNg and TNFa (p = 0.041).



CONCLUSIONS

- Older kidney transplant recipients demonstrated a decreased frequency of CMV-specific polyfunctional CD8+ TEMRA T cells. This impaired memory T cell response to CMV suggests a possible mechanism for the increased vulnerability of older recipients to CMV infection or reactivation, which may in turn perpetuate age-related immunologic dysfunction. This impairment may contribute to the increased vulnerability to infection and death in the older transplant recipient transplantation.

Increased age → Decreased CMV immune response → Increased risk of CMV infection

- Patients with subsequent CMV viremia had a decreased frequency of CMV-specific polyfunctional CD8+ TEMRA T cells. This finding may explain patient vulnerability to CMV viremia despite modern protocols for antiviral prophylaxis.

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