

1034 IDENTIFICATION OF A POTENTIALLY NOVEL REGULATORY AXIS INVOLVING KIR+CD8+ HLA-E/VL9 TETRAMER+ T CELLS AND HLA-E^{hi} cTFH

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Background T follicular helper cells (TFH) within the tumor microenvironment are associated with good prognosis, and inhibition of regulatory Ly49+CD8 T cells in mice enhances anti-tumor activity via expansion of TFH responses.¹ We investigated whether KIR+CD8+ T cells (the human equivalent of Ly49+CD8+ T cells) may inappropriately regulate TFH activity in colorectal cancer (CRC).

Methods To this end, we characterized KIR+CD8+ T cells and circulating TFH (cTFH; CXCR5+CD4+) cells in PBMCs obtained from normal community donors, untreated colorectal cancer (CRC) patients, Sjogren's disease (SjS) patients, and SjS patients treated with Plaquenil. CRC and SjS were chosen due to evidence for a role of TFH in disease control or autoimmunity, respectively.²⁻³

Results As expected, KIR+CD8+ exhibited a TEMRA phenotype, high cytolytic potential and limited TCR diversity by transcriptional analysis.⁴⁻⁶ Unexpectedly, a significant subset was also positive for HLA-E/VL9 tetramer binding. While total KIR+CD8+ T cells did not vary significantly across the different donor groups, frequencies of HLA-E/VL9 tetramer positive cells were significantly lower in PBMC from untreated SjS patients. Treatment with Plaquenil restored the levels of tetramer positive cells to match healthy controls, consistent with a role for these HLA-E/VL9 targeting cells in regulating the immune response.

Similarly, while total cTFH frequencies did not vary across the donors, the subset of cTFH cells that expressed comparatively high MFI of HLA-E differed across the donor groups. A statistically significant inverse correlation between the frequency of KIR+CD8+ tetramer+ cells and HLA-E^{hi} cTFH cells was identified in PBMC samples from untreated, newly diagnosed SjS patients, and Plaquenil treatment normalized this relationship. Notably, PBMC samples from the CRC patients were found to have very low frequencies of HLA-E^{hi} cTFH cells which may reveal a lack of an appropriate TFH-mediated immune response in the development of CRC.

Conclusions These data suggest that a regulatory relationship may exist between KIR+CD8+tetramer+ T cells and HLA-E^{hi} cTFH in autoimmune SjS patients and that this relationship is modified by Plaquenil treatment. The requirement for tetramer positivity suggests a TCR and/or NKG2C-dependent mechanism. Given the role of TFH in CRC outcomes and the scarcity of HLA-E^{hi} cTFH in these patients with active disease, understanding this regulatory interplay may provide insights to mechanisms of immune suppression in cancer and may help guide development of more effective systemic anti-tumor IO therapies.

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