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ORAL ABSTRACTS

701.EXPERIMENTAL TRANSPLANTATION: BASIC AND TRANSLATIONAL

TCF-1is Required By CD8 $^{+}$ T Cells for the Maintenance of Alloimmune Responses in Graft-Vs-Host Disease

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Graft-vs-host disease (GVHD) is a common complication of allogeneic stem cell transplant (alloSCT) wherein donor T cells target alloantigens on recipient tissues. It is unclear how alloimmune responses are maintained in GVHD despite abundant antigen, which causes T cell anergy, deletion and exhaustion. Previously, we identified alloreactive TCF-1 ^{high} T cells arising post-transplant that resemble exhausted progenitors (T $_{EXP}$) capable of propagating immune responses in other chronic antigen models. Here, we sought to further characterize these cells in the B6→129 MHC-matched GVHD mouse model, in which 129 recipients express the immunodominant H-2K ^{b}-restricted minor histocompatibility antigen (miHA) H60. At day +7 post-transplant, alloreactive CD8 $^{+}$ cells specific to H60 (as determined by MHC-I-tetramer staining; Tet $^{H60+}$) were nearly uniformly PD-1 ^{hi}Tox ^{hi} whereas Tet $^{H60-}$ cells displayed a bimodal distribution into discrete PD-1 ^{hi}Tox ^{hi} and PD-1 ^{lo}Tox ^{lo} populations, indicative of more diverse antigen experiences. Among these both Tet $^{H60+}$ and Tet $^{H60-}$ cells were TCF-1 ^{hi} cells. TCF-1 ^{hi} Tet $^{H60+}$ cells were uniformly CD39 ^{lo}Tox ^{hi}PD-1 ^{hi}, which is a canonical T $_{EXP}$ phenotype. In contrast, among activated Tet $^{H60-}$ cells there were TCF-1 ^{hi} cells that were CD39 ^{lo}Tox ^{hi}PD-1 ^{hi} and Tox ^{lo}PD-1 ^{lo}. At later times in spleen and lymph node, and in GVHD target tissues, these populations of TCF-1 $^{+}$ Tet $^{H60+}$ and Tet $^{H60-}$ were found. To test if these CD39 ^{lo}TCF-1 ^{hi} T $_{EXP}$ had proliferative advantages in GVHD, we sorted congenic TCF-1 ^{hi}CD39 ^{lo} and TCF-1 ^{lo}CD39 ^{hi} CD8 $^{+}$ cells from recipient spleens 14-days post-transplant and adoptively transferred them in competition in a 1:1 ratio (of Tet $^{H60+}$ cells) into newly transplanted recipients. Among Tet $^{H60+}$ cells in all tissues at day 14 post-transfer, TCF-1 ^{hi}CD39 ^{lo}-sorted progeny greatly outperformed TCF-1 ^{lo}CD39 ^{hi}-sorted progeny. In line with their role as a source of GVHD effectors, progeny of TCF-1 ^{hi}CD39 ^{lo} cells were mostly TCF-1 ^{lo}CD39 ^{hi}; however, a fraction remained TCF-1 ^{hi} consistent with their being able to undergo self-renewal. Conversely, we observed few if any TCF-1 $^{+}$ progeny of CD39 ^{hi} cells. We next tested whether TCF-1 was an important mediator of T cell fitness or whether it was only a marker for functionality. To do so we competed congenic wild-type (WT) and *Tcf7* $^{p45-/-}$ (p45 $^{-/-}$) donor CD8 cells, which lack the N-terminal β-catenin binding domain of TCF-1, in allogeneic (129) and syngeneic (B6) recipients. Strikingly, p45 $^{-/-}$ CD8 cells were greatly outcompeted by WT CD8 cells in 129 recipients in all tissues and at all times post-transplant, among both Tet $^{H60+}$ and Tet $^{H60-}$ cells. In contrast, in B6 recipients, WT and p45 $^{-/-}$ cells remained evenly matched, suggesting that full-length TCF-1 isoforms are dispensable for lymphopenia-induced T cell expansion. Further, p45 $^{-/-}$ cells were also not disadvantaged when adoptively transferred into B6 mice and acutely challenged with H60 antigen by vaccination. Together these data suggest a model wherein TCF-1 ^{hi} progenitor like T cells are seeded in GVHD target organs where they may serve as a key local source for GVHD effectors, and moreover, full-length TCF-1 is itself critical for alloreactive T cell fitness in GVH responses.

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