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PURPOSE: Hypoxia-inducible factor (HIF-1α) regulates the balance between effector T cells (Teff) and regulatory T cells (Tregs) by enhancing Th17 development (helper T cell subtype) and attenuating Tregs development via degradation of Foxp3, whose expression defines Tregs. The balance between Tregs and Th17 cells impacts allograft survival. This study investigates the consequence of HIF-1α deficiency on T cell differentiation and vascularized composite allograft (VCA) survival using knockout mice.

METHODS: To assess the effect of HIF-1α deficiency upon T cell subtypes differentiation, naïve CD4+ T cells derived from wild type (WT) and HIF-1α deficient (HIF-1α/−/CD4CreC57BL/6) mice were incubated in 2 types helper T cell subtypes (Th1 and Th17) and Tregs-skewing conditions. Degrees of IFN-γ, IL-17A and Foxp3 expressions were then quantified. Mixed lymphocyte reaction (MLR) was then used to assess effect of HIF-1α deficiency on CD4+ T cell proliferation. To evaluate effect on VCA survival, 13 WT and 15 HIF-1α/−/CD4CreC57BL/6 mice received osteomyocutaneous allografts from Balb/c mice. Immunosuppressive regimen consisted only of co-stimulatory blockade (1 mg anti-CD154 at POD 0, 0.5 mg CTLA4Ig at POD 2). Allograft survival, ratios of Tregs/Teff subpopulations in the periphery and within the allograft were assessed.

RESULTS: Unlike from WT mice, the naïve CD4+ T cells from HIF-1α/−/CD4CreC57BL/6 mice not expressed IFN-γ and IL-17A after incubated in Th1 and Th17-skewing conditions. However, those cells still expressed Foxp3 in Tregs-skewing conditions although the degree of expression was lower than WT mice (p<0.01). HIF-1α deficient CD4+ T cells did not result in T cells proliferation during MLR analysis. In the transplanted mice, a higher ratio of Tregs/Th1 cells and Tregs/Th17 cells in the periphery was observed in tolerant animals and lower ratio of both in graft rejecting animals (p<0.05). With co-stimulatory blockade, improved allograft median survival time (MST) occurred with HIF-1α/−/CD4Cre−/−mice compared to WT mice (MST = 100 vs 36.5 days, p<0.01). Infusion/adoptive transfer of 5x10⁴ Th17 cells at POD 0 in HIF-1α/−/CD4Cre−/−recipients disrupted allograft survival (MST = 60 days).

CONCLUSION: HIF-1α deficiency affects the differentiation of naïve CD4+ T cells, ratio of Tregs/Teff, and improves allograft survival in the setting of co-stimulatory blockade. Targeting potential mechanisms involved in CD4+ T cell differentiation, such as HIF-1α, may be a viable treatment approach in improving allograft tolerance.

QS21
Leadership In Plastic Surgery

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PURPOSE: The pathway to leadership in plastic surgery remains uncertain, but it is thought that exceptional training represents a key to success. Studies have shown that 39% of academic plastic surgeons have been trained by the same 10 programs in the US (Gast, Kuzon, Adelman, & Waljee, 2014), which demonstrates that institutional training is integral to establishing a career in academic plastic surgery. However, the impact of training on the development of leadership skills remains unclear. The present study aims to determine the relationship between training and leadership within the field of plastic surgery.

METHODS: First, a cross-sectional study was conducted in June 2018 to examine the demographics and training background of plastic surgery faculty currently holding leadership positions within academic programs accredited by the Accreditation Council for Graduate Medical Education. The data was gathered from institutional websites. Second, a retrospective review was conducted in July 2018 to examine the demographics and training background of the current and past presidents of leading plastic surgery societies (American Association of Plastic Surgeons, American Society of Plastic Surgeons, Plastic Surgery Foundation, and Plastic Surgery Research Council). The data was gathered from society websites and other electronic media. Frequencies were calculated to determine the number of leaders who trained at each institution during either their plastic surgery residency or fellowships.

RESULTS: Among the 287 institutional leaders (112 chairs or chiefs, 109 residency directors, and 66 fellowship directors) 90 training programs were identified that contributed to their training. However, the top ten training programs
accounted for 41% of the residencies and fellowships individuals received. The top five leadership producing programs among current institutional leaders were University of Pittsburgh, Johns Hopkins University, New York University, University of Pennsylvania, and Harvard Medical School respectively. A similar trend emerged in the second data set of current and past leaders of academic societies. Among the 230 past presidents and chairpersons across all four societies, 51 training programs were identified and of those the top ten accounted for 51% of training received. The top five institutions were Johns Hopkins University, Duke University, Harvard Medical School, Washington University in St. Louis, and University of Pennsylvania respectively.

CONCLUSIONS: This study indicates that a small cohort of institutions produces a large portion of the leaders within the field of plastic surgery. In addition, across the two data sets, the top eight leadership producing institutions remained constant, suggesting that these elite programs have consistently fostered an aptitude for leadership among their trainees.

QS22

A Novel And Unexpected Role Of Donor T Cells In The Efficacy Of Tolerogenic Therapies For Transplant Rejection

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PURPOSE: Costimulation blockade-based regimens are a promising immunomodulatory strategy to prevent transplant rejection and promote lasting tolerance. However, their efficacy is affected by multiple factors, many of which remain unknown. Recently, some reports have highlighted the unexpected capacity of passenger donor lymphocytes to directly fuel the recipient’s anti-graft response. Further studies are then necessary to understand their possible role in settings of regulation of alloreactivity. In this study we aimed to assess if T lymphocytes contained in the donor specific transfusion (DST) inoculum, used as part of a very effective CoB regimen, contribute to the observed limited regulation of skin transplant rejection.

METHODS: Full mismatch skin transplants were performed using dorsal skin from Balb/c into C57BL/6 mice and animals received a peri-transplant regimen based on DST, (10^7 splenocytes; on day 0) and anti-CD154 mAb (MR-1; on day 0, 7, 14). To study the role of donor T cells, DST inocula were depleted in either total T cells, CD8, or CD4 T cell subpopulations by negative-selection. IgG Donor Specific Antibodies (DSA) in serum of transplanted animals was determined by flow cytometry, and T cell-IFNg production to determine the strength of recipients alloresponse, measured by ELISpot.

RESULTS: A peri-transplant regimen based on DST+anti-CD154 (MR-1) has a profound protective effect on mouse skin allotransplantation. However, it does not induce long term survival (MST=58 days). When donor T cells were depleted from the splenocytes used as DST, the beneficial effect was statistically increased (MST=105 days). We studied then the specific role of donor CD4 and CD8 T cell by performing two additional transplant groups receiving DST depleted of CD4 or CD8 T cells respectively. The absence of CD4 abrogated the prolongation of survival observed with the total-T cell depletion in the DST, bringing survival back to a value, MST=64, comparable to that of unmanipulated DST. This suggested a deleterious role for donor CD8 T cells. Unexpectedly, the absence of donor CD8 T lymphocytes induced a remarkable improvement in transplant survival, with 65% of the grafts surviving beyond 180 days. In ongoing experiments, we are aiming to determine the role of donor memory CD4/CD8 T cells in the effect observed and what correlation exists between the presence/absence/type of donor T lymphocytes and the levels of donor specific antibodies, or variations in the strength of the direct and indirect alloresponses.

CONCLUSIONS: Overall, these data reveal the existence of a novel and very important opposing role for donor passenger lymphocytes in the modulation of recipient’s alloimmunity by DST+MR1 based regimens: a deleterious role for donor CD8, and a beneficial one for CD4 T cells. Identification of the specific mechanisms through which these divergent modulations of the anti-donor alloresponse are exerted will be pivotal for the optimization of clinically effective tolerogenic therapies.

QS23

Persistent Disparities in Breast Cancer Surgical Outcomes among Hispanic and African American Patients