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Spatial mapping of effector T cell profiles in GvHD

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Acute graft-versus-host disease (GVHD) occurs as a result of a tissue-tropic, pathogenic immune response orchestrated by donor T cells following allogeneic hematopoietic stem cell transplantation. Tissue inammation frequently emerges despite the concurrent use of immune suppressive agents targeting systemic T cells; early treatment resistance is common and associated with a high risk of mortality. Although pro-inammatory immune signatures from blood can predict patients likely to develop breakthrough or treatment-resistant acute GVHD, it is currently unclear whether earlier interventions can change the disease course. There is therefore an unmet need to identify targetable pathways that are critical to the initiation and propagation of tissue injury. Following experimental bone marrow transplantation (BMT), allogeneic T cells undergo an initial 3-4 day phase of activation and proliferation in recipient secondary lymphoid organs (SLO), before exit into the blood and subsequent tracking to peripheral tissues where they are rst detectable at day 6-7. Fate mapping of allogeneic T cells in GVHD suggests that early dierentiation programs of eector T cells (TE) are highly plastic leading to a high level of heterogeneity at a population level. Such diversity could potentially arise through either stochastic or instructional mechanisms, the latter reecting responsiveness to environmental cues. Although most studies have focussed upon how such instructions could impact upon early eector programs in SLO, TE will also be subject to a distinct repertoire of signals following their recruitment to non-lymphoid tissues. Indeed, recent studies in healthy volunteers have revealed unexpected diversity in the phenotypic and functional properties of T cells isolated from peripheral tissues compared to blood or lymph node, suggesting that eector programs initiated in lymphoid organs can be over-written when T cells are recruited to other sites. Although dynamic interactions in tissues regulate eector responses to commensal ora or are required for specialized memory dierentiation, the extent to which peripheral tissues directly re-program T cells for pathogenicity has not been explored in GVHD. To investigate the role of GVHD target organs in shaping pathogenic T cell function, we have used a network biological approach to construct an unbiased, high-resolution spatial map of eector CD8+ TE dierentiation at multiple locations during the evolution of GVHD. We have identied wide variation in eector programs in mice and humans according to location, with eector programs in target organs being highly divergent from those primed in lymph nodes. Furthermore, we have found that evidence of TE re-programming through mechanisms that are tissue-autonomous and required for pathogenicity. Our data suggest the need for precision targeting of immune pathological processes that are specic to individual target organs.

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Computational flow cytometry - Helping to make sense of high-dimensional immunology data

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Recent advances in cytometry allow scientists to measure an increasing number of parameters per cell, generating huge and high-dimensional datasets. To analyze, visualize and interpret these data, newly available computational techniques should be adopted, evaluated and improved upon by the broad biomedical community. Computational cytometry is emerging as an important new eld at the intersection of immunology and computational biology; it allows new biological knowledge to be extracted from high-throughput single- cell data. In this talk I will provide a broad and practical overview of the many recent developments in the eld of computational single cell analysis. In addition, some clinical case studies will be presented to showcase the potential of computational methods in cytometry.

CHIP and HSCT : focus on donors

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Purpose - Clonal hematopoiesis of indeterminate potential (CHIP) can be detected in the blood of approximately 20% of the elderly. CHIP is linked to increased risk of hematologic malignancies and all-cause mortality, thereby questioning the eligibility of stem cell donors with CHIP. Thus, we comprehensively investigated how donor CHIP aects outcome of allogeneic hematopoietic stem cell transplantation (HSCT).

Methods - We collected blood samples from 488 healthy, related HSCT donors (aged 55 years) at the time of stem cell donation for targeted sequencing with a 66-gene panel. Clinical data from the 488 recipients were collected using standardized outcome parameters.

Results - A total of 89 clonal mutations with a median variant allele frequency of 6.1% were identied in 77/488 donors (15.8%). CHIP prevalence was higher in donors related to patients with myeloid compared to lymphoid malignancies (18.5% vs. 5.3%, p=0.001). While transplant failure, acute graft versus host disease, and CMV reactivation were not aected, chronic GvHD (cGvHD) was more frequent in HSCT with donor CHIP (54% vs. 39%, p=0.018). In univariate and multivariate analyses, donor CHIP was associated with lower cumulative incidence of relapse/progression (univariate HR=0.58, p=0.022; multivariate HR=0.58, 95%-CI=0.36-0.94, p=0.029) without having impact on non-relapse mortality. Serial quantication of 15 mutations showed engraftment of 14/15 CHIP clones with disproportionate expansion in most recipients. Donor-cell leukemia was observed in two recipients. Overall survival was not aected by donor CHIP status (HR=0.96, 95%-CI=0.7-1.31, p=0.793).

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Conclusions - Allogeneic HSCT from donors with CHIP appears safe and results in similar survival in the setting of elderly related donors. Surprisingly, donor CHIP might increase cGvHD rates and reduce relapse/progression risk. Future studies in younger and unrelated donors are warranted to conrm these results.

Donor selection for natural killer cell receptor genes and relapse/survival after transplantation

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Numerous factors can modify transplant centers' decision-making in choosing donors for allotransplantation. Long accepted are donor age, CMV serology, prior alloimmunization, gender, and above all, HLA matching with the recipient. Novel models of immunogenetic typing have also indicated that killer immunoglobulin-like receptor (KIR) genotyping can inuence natural killer (NK) development and post-transplant contributions to the anti-tumor eect of an allograft. We previously reported retrospective data suggesting that the donor KIR B haplotype favorably reduces risks of relapse for patients with AML after unrelated donor (URD) transplantation and have completed, in part, analysis of a study prospectively testing this strategy for preferred donor selection. Our ndings identied logistical challenges in rapid donor KIR genotyping strategies, integrating this information for donor selection, and disease specic and conditioning intensity inuences of donor KIR genotyping on post-transplant relapse risks and outcome. KIR genotyping of the recipient has little inuence in the donor recipient interaction inuencing NK and potentially T cell development post-transplant. Strategies to capitalize on available options that inuence donor selection can limit relapse risks, at least for patients with AML, and potentially improve the outcomes of transplantation.

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Telomere length and toxicity after HSCT

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Telomeres are highly conserved protective terminal chromosomal structures consisting of hundreds to thousands of tandem TTAGGG hexamers and their associated shelterin proteins. Telomeres shorten with every mitotic cell division, and telomere attrition has a fundamental role in cell senescence. The recent discovery that inherited mutations in genes that encode for proteins that repair or protect telomeres are etiologic in a range of human diseases has disclosed clinical manifestations in diverse tissues, including the bone marrow, lung, and liver, indicating that defects in telomere repair and protection can cause organ failure. Dyskeratosis congenita (DC), an inherited type of aplastic anemia, is caused by mutations in the telomerase complex genes. HSCT is the only curative treatment for bone marrow failure in patients with DC, but case reports and small series of patients have suggested substantial risks of toxicity from radiation and chemotherapy, as well as immune-related complications such as infections. As a result, long-term survival of patients with DC after HSCT has been poor because of TRM, including graft failure, GVHD, sepsis, pulmonary brosis, cirrhosis, and veno-occlusive diseases. HSCT has been considered an experimental opportunity to observe telomere dynamics in a highly proliferative cell environment. The telomere length of marrow cells from HSCT recipients was found considerably shorter than telomere length of donor cells, likely reecting an immediate increased replicative demand after transplantation. The inuence of chemotherapy on telomere length has been demonstrated in breast cancer patients after multiple chemotherapy courses and in lymphoma patients undergoing high-dose chemotherapy courses. Accelerated telo- mere shortening has also been observed after autologous HSCT and appears to persist. Telomere shortening may be related to pretransplantation exposure to multiple courses of chemotherapy in patients before HSCT, as suggested by the association of advanced-stage disease and shorter telomere length. As accelerated telomere loss postautologous HSCT has been implicated as a predictor for the development of therapy-related myelodysplasia and acute myeloid leukemia, this independent association between short telomeres and TRM may be pathophysi- ologic, not simply a biomarker. Patients rated as advanced stage by disease, prior relapses, and remission, or who have equivalent records of chemotherapy or radiation may not have equivalent functional consequences to these exposures, for reasons ranging from variations in medical practice to dierences in drug metabo- lism pathways. Cumulative damage to DNA may be better reected by telomere length than by simple medical history or complex genomic analysis .

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That telomere attrition might have a role in or serve as a marker of long-term outcome after HSCT has been an attractive hypothesis, but data are limited. In our group, we hypothesized that age-adjusted pretransplantation telomere length might predict TRM after HSCT. To determine the eects of telomere attrition on HSCT results, we measured the pretreatment telomere length in 178 consecutive patients who had undergone myeloablative HSCT from a matched related donor, and we analyzed for correlations with outcomes after HSCT. Age-adjusted pretransplantation telomere lengths were analyzed for correlation with clinical outcomes. After age adjustment, patients' telomere-length distribution was similar among all 4 quartiles except for disease stage. There was no correlation between telomere length and engraftment, GVHD, or relapse. Conversely, The TRM rate inversely correlated with telomere length. TRM in patients in the rst (lowest telomere length) quartile was signicantly higher than in patients with longer telomeres (P .017). In multivariate analysis, recipients' age (hazard ratio, 1.1; 95% CI, .0-1.1; P .0001) and age-adjusted telomere length (hazard ratio, 0.4; 95% CI; 0.2-0.8; P .01) were independently associated with TRM. Since then, another group found a correlation between donor telomere length (and not recipient) and TRM in patients with aplastic anemia. The question of the role of pre-transplant telomere length in the predicton of TRM is still open and will be discussed during the talk.

Anti-HLA immunization and outcomes post-HSCT

JL.Taupin, Hôpital Saint-Louis, Paris

Donor-specific anti-HLA antibodies (DSA) can represent an important barrier against engraftment of donor stem cells, with a negative impact on transplant and therefore patient survival. Especially, with the recent development of haploidentical transplantation setting, the likelihood of presence of a (or several) DSA has greatly increased. In addition, new "functional" assays have been recently developed, e.g. to look at DSA ability to activate complement. During this talk, I will try to summarize the current knowledge about the role of DSA in HSCT, and whenever relevant, draw parallels and underline differences that could exist with the current understanding of DSA impact in organ transplantation.

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DNA polymorphism and fungal infection after HSCT

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In recent years, advances in medical care have, paradoxically, promoted an increased prevalence of life-threatening susceptibility to severe forms of fungal disease, such as invasive pulmonary aspergillosis (IPA). There are currently no licensed vaccines, and despite improved diagnosis and therapy, management of IPA remains challenging, leading to unacceptable morbidity and mortality rates among immunocompromised hosts, particularly recipient of allogeneic hematopoietic stem-cell transplantation (HSCT). Since the risk of infection varies considerably even among patients with comparable predisposing clinical factors and microbiological exposure, development of IPA is thought to rely largely on genetic predisposition. Protection against fungi is conferred mainly through phagocytes that recognize pathogen motifs through pattern recognition receptors. The fungal cell wall is the main source of motifs owing to its dynamic composition and structural properties according to morphotype, growth stage and environmental conditions. Over the past years, we have been exploring human genetic variation in innate immune receptors as potentially useful predictive markers for risk of infection in the HSCT setting, and as a tool to dissect the molecular and cellular mechanisms that regulate the activation of antifungal immunity.

Although the overall weight of the antifungal immune response results from adding eects of single genetic factors and their complex interactions with clinical immune dysfunctions, several genetic targets have been recently validated as robust markers of susceptibility to IPA. Relevant examples include the C-type lectin receptor Dectin-1 and the pattern recognition molecule pentraxin-3 (PTX3). The functional dissection of genetic variation in these genes has not only provided crucial insights into the pathogenesis of IPA but has contributed to establish the genetic prole of the host as an important clinical adjuvant for the personalized prognosis, diagnosis and treatment of IPA. Recruitment of larger and carefully controlled cohorts of patients, as well as functional studies dissecting the mechanisms of association with IPA, are ultimately required. This will undoubtedly support the integration of genetic markers into clinically valid processes aimed at the stratication of risk and progression of IPA in HSCT.

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Immune anti-CMV responses and immunosuppression in the context of HSCT

K.Komanduri, Sylvester Cancer Center Adult Stem Cell Transplant Program, Miami

Cytomegalovirus (CMV) remains a major source of morbidity and mortality following allogeneic hematopoietic stem cell transplantation (SCT). This presentation will review the past two decades of work in the Komanduri laboratory performing correlative studies of immune recovery and clinical events in the SCT setting. During this period, methods to assess CMV-specic immunity have signicantly evolved from semi-quantitative approaches to highly sophisticated single cell approaches that can help us understand the phenotype and function of individual T cells within an antigen specic immune response. Our recent studies have rearmed that the numbers of circulating T cells, and even of antigen-specic T cells often do not predict reactivation events; instead, the skewing or distribution of functional subsets within the overall CMV-specic T cell repertoire better predict clinical risk of reactivation. The laboratory and clinical results of these recent studies, and future directions in our approach to correlative studies of immune reconstitution in the SCT setting, will be discussed.