



Metabolomics and genomics of microbial infections and gut microbiome dynamics in patients undergoing allogeneic hematopoietic stem cell transplantation

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Objectives: Use computational systems biology methods to characterise interactions among infective bacteria, microbiome and host, integrating phenotypic, genomic, metabolomic and microbiome dynamic datasets.

Methodology:

Allogeneic hematopoietic stem cell transplantation (allo-HSCT) is a treatment for a range of malignant and nonmalignant disorders. Systemic bacterial infections are frequent during the early transplant period. Patients undergoing allo-HSCT are subjected to chemotherapy, radiation, and antibiotics within a short time frame. Pre-transplant conditioning transiently ablates circulating granulocytes and monocytes and markedly increases susceptibility to disseminated infections. Mucosal barrier injury is also a complication of allo-HSCT and enables commensal microbes to invade underlying tissues and the bloodstream. We have previously observed extreme shifts in the intestinal microbiota during transplant. In many instances, domination by a single bacterial taxon occurred. These perturbations correlated with subsequent development of a corresponding bloodstream infection. Intestinal epithelial cells, underlying immune tissues, and the microbiota establish a state of equilibrium that optimizes resistance to infection and facilitates the absorption of nutrients. Allo-HSCT disrupts this equilibrium, resulting in dramatic compositional fluctuations that can result in domination by bacteria that invade the bloodstream.

At the Memorial Sloan Kettering Cancer Center, the gut microbiome composition of patients undergoing allo-HSCT is monitored by 16S ribosomal RNA sequencing of fecal samples collected from the start of pre-transplant conditioning (up to 15 days before stem cell infusion) and continued at least until 35 days after transplant. Bacteria causing infections in patients undergoing allo-HSCT are also isolated for further study.

Presently, a collection of 25 *Pseudomonas aeruginosa* strains isolated from these patients have already been phenotypically characterized, had their genomes fully sequenced and their metabolome during exponential growth was analyzed by LC-MS.

Within this project, we aim to integrate this detailed genome-wide molecular and genetic characterization of infection causing strains with the underlying microbiome composition dynamics and host clinical data. Systems biology computational methods are required to perform this complex analysis. This approach may shed light on the metabolic or genetic characteristics of infective strains that are determinant for their success in the interactions with other microbiome components and in taking advantage of host weaknesses following the allo-HSCT perturbation.

Type of fellowship: Mixed (Portugal and abroad: MSKCC, NY, USA)