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Personalized medicine: Incorporating graft versus-host-disease biomarkers and targeted therapy in clinical trials

Sophie Paczesny
Indiana University, USA

Graft-versus-host disease (GVHD) following allogeneic hematopoietic stem cell transplantation (HSCT) is the major cause of non-relapse mortality. A major barrier to GVHD research and treatment is that the diagnosis and prognosis relies almost entirely on the presence or absence of clinical symptoms, which can only be confirmed by biopsy of one of three target organs: the skin, the gastrointestinal (GI) tract, or the liver. Currently, no laboratory tests exist to predict the risk of developing GVHD, the responsiveness to treatment, or patient survival. I will first describe what the large-scale identification of proteins in the plasma of GVHD patients is revealing about candidate biomarkers. Using state-of-the-art antibody arrays, tandem mass-spectrometry as a discovery engine, and ELISA for validation in thousands of samples, we found that biomarkers of disease-related systemic (1) and tissue-specific changes (2) can be detected in the plasma of patients. Second, I will describe how we provided the first demonstration showing that these biomarkers are associated with GVHD clinical outcomes and prognosis, including long-term survival. We showed that plasma elafin levels have significant diagnostic and prognostic power as a biomarker of skin GVHD. Using the same proteomics strategy, we discovered regenerating-islet-derived-3-α (REG3α) as a biomarker of lower GI GVHD and subsequently validated it in two independent sets totaling 1014 patients from three different centers. This marker provides important prognostic information, including response to GVHD treatment and survival. Third, I will describe the shortcomings in the prediction of the response to GVHD therapy. Thus, we further analyzed biomarkers of resistance to GVHD therapy and found that they were different from the biomarkers discovered at GVHD onset. We subsequently identified novel pathways, such as suppressor of tumorigenicity 2 Suppressor (ST2). We are currently validating these candidate biomarkers for response to treatment in approximately 1200 samples. Interestingly, several of these novel biomarkers offer important insights into the biology of GVHD and are potential therapeutic targets. To determine if these biomarkers could also predict GVHD before the appearance of clinical symptoms, we evaluated the most informative biomarker, ST2, in samples from 598 HSCT patients and showed that ST2 predicted mortality early post-transplant. Our next step will be to design a preemptive clinical trial using these results.

Biography

Sophie Paczesny is an Associate Professor of the Blood Marrow and Stem Cell Transplant Program at the Indiana University Medical School. She leads the Blood and Marrow Transplantation Program graft-versus-host disease (GVHD) biomarker discovery and validation research. She received her M.D. and Ph.D. from Paris University, France where she completed her residency and fellowship in Hematology/Oncology and Bone Marrow Transplantation. She joined first the Blood and Marrow Transplantation Program at the University of Michigan in 2006 where she has developed proteomics for the diagnosis of GVHD, a complication that occurs in approximately half of patients following allogeneic hematopoietic cell transplantation. She has recently take on new responsibilities at the Indiana University where she will pursue her research of discovery and validation of biomarkers of complications post-transplantation as well as bring new targeted therapies to the clinic.

sophpacz@iu.edu