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Precision monitoring of immunotherapies in solid organ and hematopoietic stem cell transplantation☆

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ABSTRACT

Pharmacological immunotherapies are a key component of post-transplant therapy in solid-organ and hematopoietic stem cell transplantation. In current clinical practice, immunotherapies largely follow a one-size fits all approach, leaving a large portion of transplant recipients either over- or under-immunosuppressed, and consequently at risk of infections or immune-mediated complications. Our goal here is to review recent and rapid advances in precision and genomic medicine approaches to monitoring of post-transplant immunotherapies. We will discuss recent advances in precision measurements of pharmacological immunosuppression, measurements of the plasma and gut microbiome, strategies to monitor for allograft injury and post-transplant malignancies via circulating cell-free DNA, and comprehensive measurements of the B and T cell immune cell repertoire.

Contents

1. Introduction

In 2016, 33,599 organs were transplanted from 15,946 donors in the United States alone [1–6] (Fig. 1A). Approximately 120,000 people are currently on waitlists at one or more transplant centers [1–6]. Total Medicare expenditures for solid organ transplants totaled $4.4 billion in 2016 [7]. In 2013, there were 19,220 hematopoietic stem cell (HSC) transplants, including 10,872 autologous, 4991 allogenic from unrelated donors, and 3357 allogenic donations from recipient-related donors [8].

Pharmacological immunosuppression is critical to maintaining graft health [9], in particular for transplants from unrelated donors. In Solid-Organ Transplantation (SOT), the goal is to suppress the main acute response of the adaptive immune system by suppressing the activity of CD8+ cytotoxic T killer cells (T_C), and preventing the activation of CD4+ T helper cells (T_H) [9,10], as well as the concurrent activation of

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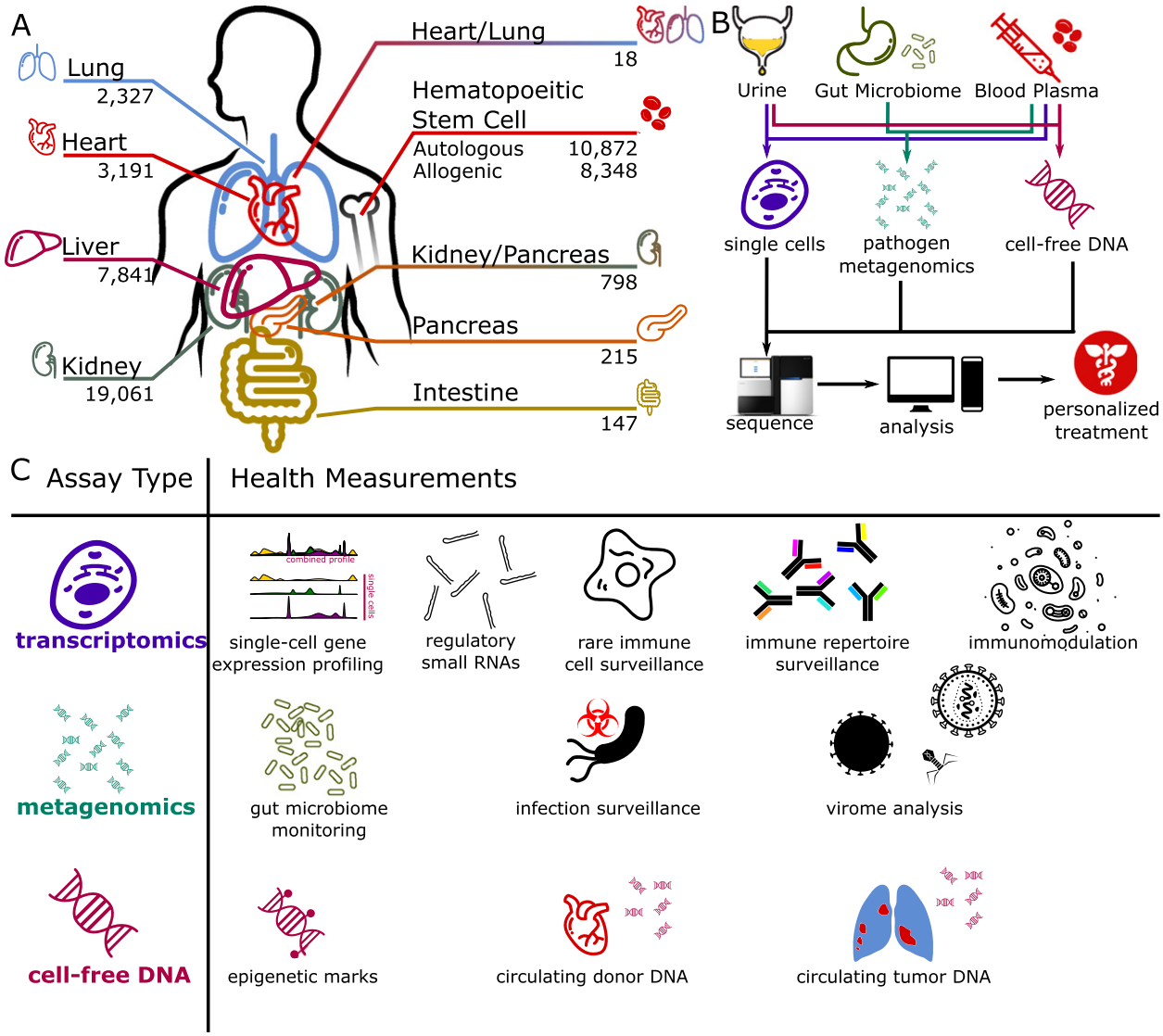

Fig. 1. The promise and need of precision monitoring of immunotherapies in solid-organ and stem cell transplantation. (A) Number of transplants performed in 2016 by organ, and HSCs in 2013, the most recent year for which there is data (B) Precision monitoring strategies involve surveillance of several patient features, and there exist a number of options for analysis which can improve personalized immunotherapy, as outlined in this review. (C) Overview of precision measurements discussed in detail in this review.

antibody producing B lymphocytes by T_H cells [11]. In cases where the T- and B-lymphocyte response to donor tissue is attenuated, and donor specific antibodies (DSAs) do not proliferate, graft survival is improved [9,12,13]. In HSC, pharmacological immunosuppression is critical to prevent Graft-versus-Host Disease (GVHD), a serious and difficult-to-diagnose complication characterized by systemic damage to internal organs [14].

Immunosuppressive therapies largely follow standardized protocols that are not tailored to the needs of individual transplant recipients [10]. This 'one-size fits all' approach to post-transplant therapy leaves a significant portion of transplant patients over- or under-immunosuppressed. Non-personalized therapy is an important factor in many of the complications that frequently arise after transplantation, including immune-mediated complications, viral and bacterial infections and cancer [10,12,15]. While clinicians strive to monitor patients carefully for the onset of these complications, diagnostic options remain limited. Invasive biopsies are still widely used in solid organ transplant (SOT) and hematopoietic stem cell transplant (HST) to diagnose and monitor tissue and organ injury [16–18], although there are concerns within the field over the relative risk versus benefit of long term surveillance biopsy monitoring [17,19,20]. Infectious complications often remain undiagnosed due to limitations of clinical assays that are predominantly limited to testing for one or few pathogens at a time [21–23]. Finally, there is a lack of quantitative measurements of immune system strength. There is thus a critical, unmet need for more informative diagnostic tools in transplantation.

Here, we will review recent and rapid advances in precision and genomic medicine approaches to SOT and HST monitoring. We will discuss precision measurements of the plasma and gut microbiome, non-invasive measurements of organ injury and malignancies via circulating cell-free DNA (cfDNA), technologies for high-throughput profiling of the B cell and T cell immune cell repertoire, and novel approaches to single-cell gene expression analyses (Fig. 1B,C). These advances have the potential to impact patient care in the near term and can ultimately lead to immunotherapies tailored to the needs of the individual patient.

2. Solid organ transplant rejection vs. GVHD – similar but opposite pathologies

Immune reactions to solid organ or HSC transplants have a rich pathobiology, including acute and chronic forms, and a number of causative mechanisms [24–26]. Rejection after solid organ transplantation involves the host immune system reacting to and rejecting the organ, an adverse but manageable complication that can usually be treated