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Commentary

The detection of donor-derived cell-free DNA may serve as a biomarker for the early detection of chronic lung allograft dysfunction

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A sobering statistic is that 50% of all lung transplants fail by year 5 due to chronic rejection, also called chronic lung allograft dysfunction (CLAD). Among the subtypes of CLAD, bronchiolitis obliterans syndrome (BOS) is the most common and is the principal factor limiting long-term transplant survival. Research is ongoing for predicting which patients will be at risk for developing BOS and undergo chronic lung transplant rejection. A new study by Agbor-Enoh et al. in *EBioMedicine* [1] addresses a biomarker assay, donor derived cell-free DNA (ddcfDNA) that may provide an early identification of patients at risk for developing BOS. Currently, there is no reliable predictor for patients experiencing BOS and the study by Agbor-Enoh presents a potential predictor for the early detection of BOS. A biomarker that can help predict CLAD has key applications in the clinic as well as to basic scientists who are searching for the immunologic features that initiate and progress to chronic rejection.

Cell-free DNA (cfDNA) is fragmented DNA in the bloodstream that originates from both cell injury and cell death. The authors [1] have taken advantage of detecting this circulating donor DNA as a metric in determining damage to the transplanted lung. When graft injury occurs due to immunologic rejection, donor-derived cell-free-DNA is detectable in the blood of these patients.

cfDNA is not only useful as a biomarker in transplant rejection but also can serve as a potential biomarker in different kinds of disease including stroke, trauma, myocardial infarction, autoimmune disorders, and pregnancy-associated complications. The pattern developing is that there are generally higher concentrations of cfDNA in disease vs healthy individuals. Presence of genetic anomalies including mutations (K-ras, TP53, EGFR etc.), genetic rearrangements, copy number variation, chromosomal rearrangements, methylation changes (APC, ALX4) can be related to cfDNA's in circulation in different kinds of cancers [2–4].

Donor derived cell-free DNA (ddcfDNA) is the terminology for transplant donor DNA and quantification techniques have been employed as an assay for analyzing the presence of donor DNA in plasma. The detection and understanding of ddcfDNA kinetics following transplantation may provide clues for transplant success [5,6]. Alterations in the levels of ddcfDNA during acute/chronic rejection are detectable prior to clinical diagnosis or pathological features of graft rejection, suggesting the utility of ddcfDNA as an early, noninvasive rejection marker [4,7]. Although the precise mechanism of release of cfDNA is unknown, the detection of cfDNA in blood, plasma and urine can be a predictive biomarker [8].

Lung transplantation is the treatment option for organ failure. The current assay described by Agbor-Enoh et al. [1] for ddcfDNA in lung transplant patients will be a powerful tool in identifying patients "at risk" for developing rejection and will be critical in developing treatment strategies that will impact lung transplant outcome. While this assay provides an early detection for BOS, there currently are no therapeutic modalities to prevent or cure chronic lung rejection once it is established. However, this method for early detection of BOS does allow researchers to evaluate changes in immune modulatory molecules and T regulatory cells that may prove to be important in developing novel treatment strategies.

Different research groups have investigated the role of ddcfDNA in a variety of organ transplants including kidney, heart, liver and lung, and have shown that ddcfDNA can be reliably detected and there is a positive correlation to organ rejection. Synder et al. addressed the challenges involved in monitoring the rejection of solid organ transplants (heart transplant) by host immune system [9] and ddcfDNA was found to be significantly elevated in the circulating blood of heart transplant recipients which has been correlated to acute cellular rejection. A research article published by De Vlaminck et al. presented the outcomes and correlation of ddcfDNA post heart transplant [7]. Elevation in the levels of circulatory ddcfDNA occurred prior to the development of rejection on endomyocardial biopsy. This study employed shotgun sequencing of SNP based markers to discriminate between donor recipient pairs and validated their approach to sex matched and mismatched donor-recipient pairs. Zou et al. [10] employed a different platform in which lung transplant donor-recipients genomics-based approach using mismatched HLA allele was employed. They also noted increased levels of donor ddcfDNA in the circulation prior to clinical diagnosis of rejection. However, they pointed out that viral infections can also result in increased levels of circulating ddcfDNA and therefore differential diagnosis is important.

The developing impact of ddcfDNA as a biomarker in monitoring transplant rejection is evident by a recent FDA-approved assay for kidney transplant patients [11]. The assay measures donor-derived cfDNA, as a direct indicator of kidney injury and predictor of rejection. The current article (eBIO) makes a compelling case that ddcfDNA

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measured early after lung transplantation can be a reliable assessment for diagnosis of BOS and chronic lung transplant rejection.

The impact of the current study by Agbor-Enoh et al. [1] established a ready-to-use assay system, the detection of ddcfDNA, that appears to predict chronic graft failure in lung transplant recipients. Early detection of chronic graft rejection will provide a window of opportunity to address immunologic mechanisms that result in BOS and transplant rejection. The Agbor-Enoh et al. study is the first to demonstrate that elevated ddcfDNA in first 3 months after transplant can predict long term outcomes, including progression to chronic rejection. The detection of elevated ddcfDNA in first 3 months after transplant provides a tool to assess efficacy of early treatment with currently available drugs, as well as new targeted therapies as they as developed.

Disclosure

The authors have no conflict of interest to report.

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