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Review

Role of biobanks in transplantation

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ABSTRACT

The establishment of bio-banks together with high throughput technologies, such as genomics, transcriptomics and proteomics has opened new frontiers in biomarker discovery and the development of systems biology approaches to identifying key pathways that could be exploited to improve outcomes of solid organ transplantation. One of the major challenges in organ donation has been the lack of access to large scale well characterised material to facilitate projects that aim to characterise injury to donor organs and identify biomarkers. This may have hampered research in the field of organ donation by not allowing researchers to materials of high quality and lower pre-analytical variability. We describe in this manuscript the need for bio-banks in organ donation, research opportunities and the particular challenges in establishing such an initiative.

1. Introduction

Over the last decade we have seen a multitude of advances in solid organ transplantation including the use of more advanced immunosuppression, novel surgical techniques and the use of *ex-situ* machine perfusion technologies to support and resuscitate organs for transplant [1,2]. Few innovations have been established or rigorously proven in the field of organ donation however, as illustrated by the lack of translational studies that have shown to be of benefit in rodent models of organ transplantation that have progressed into demonstrating efficacy in human clinical trials [3].

This is in part be due to the multi-faceted injury that organs sustain even prior to organ procurement [4]. This is thought to have an impact on the short and long term outcomes of the transplant. Severe and irreversible pathophysiological changes in the donor result in a disturbance of metabolic, immunological, autonomic and haematological homeostasis resulting in injury to donor organs, increasing both their immunogenicity and susceptibility to preservation injury [5]. Overall this leads to the significant variation in the characteristics of donors, complex mechanisms of injury to donor organs and leads to unpredictable variability of transplantation outcomes.

The identification of pathways that are altered during organ donation, potential molecular targets for therapeutics or biomarkers of organ quality is thus extremely challenging. In addition, coordinating large multi-centre clinical trials in organ donation has proven difficult not only due to logistics surrounding national allocation of organs but the legal, ethical, organisational and financial challenges to ensure safety and governance. This may in part be the reason why therapies in the organ donor such as administration of thyroid hormone replacement strategies or steroids, have had conflicting results. There is also a growing body of literature that suggests that there is no 'one size fits all' even for organs within the same donor [6]. Thus there is a need to study both organ and donor types, since one therapeutic intervention for improving kidney transplant outcomes may not necessarily have the same beneficial effects for liver and other forms of transplant.

2. The role of bio banks in organ donation

Bio-banking is not a new phenomenon. For many years researchers and clinicians, usually as part of academic institutions, have held collections of samples from research subjects [7,8]. Over the last 30 years, but particularly since the implementation of legislation such as the Human Tissue Act 2006 in England, this has developed in to a more complex but refined procedure, involving larger collections including national bio-banks, such as the UK bio-bank, or disease and population specific bio-banks, such as that for prostate cancer [9]. An emerging area of science looking into sample quality, specimen handling and biobanking infrastructure has emerged as a consequence [10]. Alongside this a number of important ethical and regulatory issues have emerged, specifically with regards to genetic information, obtaining samples and

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Abbreviations

BCAR	Biopsy confirmed acute rejection
DBD	Donation after brain death
DCD	Donation after circulatory death
ECD	Extended criteria donor
HTA	Human tissue act
QUOD	Quality in Organ Donation
NHSBT	NHS Blood and Transplant
NORS	National organ retrieval service
RCT	Randomised control trial
SNOD	Specialist Nurse in Organ Donation
SORT	Scotland Organ Retrieval Service
SOP	Standard operating procedure

sample storage [11]. Accountability, anonymisation and data protection are also emerging as key areas for consideration for biobanking [12].

The interest in bio-banks has not only been led by the technological revolution of sequencing or large scale –omic studies, but also by the generation of automated systems, robotics and new ways to transport and store samples. In addition the streamlining of data-systems to allow the collection of more accompanying data has meant that bio-banks have become even more powerful for research. Indeed, virtual bio-banks which simply hold clinical data with sequencing or –omic data results are emerging.

In transplantation there are already several bio-banks and many local transplant centre collections of samples facilitating research predominantly in areas concerning the recipient. Our aim was to establish a bio-bank which would open new frontiers of research by looking into the donor, specifically with the aim in improving the quality of donated organs. We outline several areas of research that such a bio-bank could positively contribute to, including biomarker discovery, identification of pathways of injury and repair and clinical trials in organ donation.

2.1. Biomarker discovery

One of the clinical challenges in transplantation remains deciding what constitutes a suitable organ for transplantation. Despite years of experience with offering and allocation, uncertainty still prevails regarding which organ to accept or to decline for a particular recipient. This is increasingly becoming more of a pressing issue, since the transplant community are increasingly having to turn to older and more 'higher risk' donors to address the persistent donor shortage. Exacerbated by the falling rate of death in those aged under 75 years and the associated increase in obesity and other co-morbidities (NHSBT activity report). Demographic factors, such as donor age for example, may provide clues as to short and long term likelihood of outcomes which may affect organs differently, but absolute predictive values of such demographics remains poor. Similarly biochemical/functional measures such as donor serum creatinine are not sensitive enough to make decisions regarding the suitability of an organ.

Composite risk scores, such as a donor risk index, which exists for the kidney, liver and other organs, which take into consideration a number of risk indices, are not sufficiently predictive of the suitability of an organ for transplant. For example the kidney donor risk index (KDRI), is an estimated relative risk of post transplant kidney graft survival based on a score for the deceased donor compared to the median (50th percentile) donor [13]. Such scoring systems are useful tools but generally apply to populations of recipients rather than individual patients, have yet to be validated in large cohorts, and lack the required sensitivity and specificity to enable international adoption as the gold standard assessment criteria for donor kidney selection [14]. In addition, this and other scoring systems are not able to predict other clinically relevant post operative outcomes such as the development of delayed graft function. Other tools which combine recipient information and also histological features may add in more specificity, but are yet to be validated [15].

Many of these risk scores and also biochemical parameters fail to recognise the complexity of the donor. It is becoming increasingly clear that all donor organs do not behave the same either due to the injury encountered following brain death or due to the effects of warm ischemia in DCD donation [16]. Furthermore, such risk scores fail to account for other donor factors, such as risk of disease transmission associated with, for example, social or occupational habits.

Biomarkers may offer a more sensitive way to predict outcomes. The development of next generation proteomics, metabolomics and transcriptomics, together with the development of bioinformatics tools may allow identification of novel biomarkers, or collection of markers referred to as a molecular signature, which can predict outcomes. Combining molecular signatures with demographic information and other donor and recipient factors, obtained from linkage to a transplant registry, will further increase the power of such profiles to predict outcomes. The establishment of a bio-bank facilitates this type of research, which has been successful in other specialities including cardiac research and diabetes [17]. The complexity of biomarker research and the correlation with individual markers and signatures of injury and how they correlate with clinically relevant outcomes is recognised. That said, the advent of data mining, machine learning and artificial intelligence will advance this area of research in the future.

Bio-banks offer standardised procedures for the collection of samples, which allows for minimisation of pre-analytical variability. This is of crucial importance when identifying biomarkers, especially from complex subjects such as organ donors and complex sample types such as serum and tissues. The particular challenge in organ donation, is reducing this pre-analytical variability whilst obtaining samples of high enough quality at times when routine laboratories and research staff are not available [18]. There constantly remains a balance between pragmatism and best practice protocols for sample collection [19].

Sample types, which are easy to obtain and have specific associations with an organ, for example urine for kidney transplantation, may offer specific advantages for biomarker discovery (so called 'proximal samples') [20]. Urinary proteomics has shown some promise in being able to suggest candidate markers for development of acute rejection, chronic allograft nephropathy or BK viral infection [21]. Other markers in serum and plasma have also been identified.

For example Freue et al. used isobaric tagging of relative and absolute protein quantification (iTRAQ) technology to quantitate plasma protein relative concentrations in patients with and without biopsy confirmed acute rejection (BCAR). Plasma samples which were depleted of the 14 most abundant plasma proteins, to increase detection sensitivity, and fold change threshold set at ≥ 1.15 for diagnostic purposes. A range of candidate proteins were identified including titin, lipopolysaccharide-binding protein, peptidase inhibitor 16, amongst others [22]. Few biomarker studies have been performed in the donor however, partly due to the perception of legal constraints and logistical issues in obtaining samples.

A recent review by Sarwal et al. has suggested the potential of such approaches in proteomic biomarker discovery and also personalised medicine [22,23]. The review highlights one of the challenges in proteomics, in handling the complex nature of the protein make-up of samples which increases due to the post-translational modification of proteins and also temporal and dynamic nature of protein turn-over [24].

Other –omic technologies such as lipidomics, metabolomics, micro-RNAs and transcriptomics may provide additional opportunities for biomarker discovery [25]. For example, Verhoeven et al. demonstrated

that analysis of the perfusate collected after flushing a liver following explantation and cold storage from either a DCD (donation after cardiac or circulatory death) or DBD (donation after neurological determination of death/brain stem death) donor showed unique micro-RNA based profiles that were predictive of the length of cold ischemia the allograft was exposed to [26]. The authors argued that perfusate micro-RNA analysis could be another non invasive way to identify markers of organ quality. Metabolomics has similarly been used to identify candidate markers which can predict immediate graft function versus early allograft dysfunction in liver transplantation [27].

The vertical integration of –omic datasets remains a challenging aspect of bioinformatics analysis, but with refinement will offer increased power to detect suitable biomarkers. Mas et al. recently reviewed this area with regards to combining micro-RNA data with mRNA to increase accurate target prediction [28].

Regardless of the platform used, in general biomarker discovery follows a set pattern of discovery, verification, validation and formation of a fast, simplified test for integration into routine clinical practice [29]. Large bio-banks are able to offer unique opportunities to perform an identification phase and then validate the markers in a larger cohort.

2.2. Identification of mechanisms of injury to donor organs

One of the major areas of difficulty in research is developing models of organ donation which truly reflect the complex interplay of homeostatic disturbances that are often seen in the human organ donor. For example in the brain death organ donation, there are disturbances in a multitude of different homeostatic mechanisms including inflammatory cell activation, complement deposition and metabolic disturbance [30,31]. Rodent models are able to some extent to reproduce this injury, however adding in the complexities of age and high-risk behaviours such as smoking are not possible.

Thus rodent models are of some use for mechanistic identification, but studying the cellular, molecular and immunological sequelee in the complex situation of clinical morbidities requires validation in human samples. This will require standardisation of certain factors (e.g. diabetic status), but power calculations are likely to suggest that large numbers of patients will be required to overcome population variability. Bio-banks are uniquely positioned to offer access to such sample sizes not matched by other systems. In addition pre-analytical variability which can profoundly affect outcomes in mechanistic studies can be matched in a well coordinated bio-bank infrastructure.

Systems biology is emerging as the study of multiple systems of biological components. This is in recognition of the fact that biological processes are seldom due to a single process but more due to a complex interplay of multiple interacting systems often with negative and positive feed-back loops [4]. Traditional laboratory approaches are often hypothesis driven, whereas systems biology typically uses unbiased approaches to identify hypotheses which are further validated using more conventional assays or tools. This may involve the vertical and horizontal integration of –omic datasets and use of bioinformatics tools, probability and statistics.

2.3. Association of histological characteristics with outcomes

Histology has for many years been used to attempt to risk stratify the quality of an organ. However pre-implantation biopsy assessment is not routine in all transplant centres. Part of the reason for this is the large scale validation of scoring systems such as the Remuzzi criteria for kidney allografts in subsets of donor types has not been performed and also the validation of such criteria in the era of machine perfusion [32]. Studies have examined the correlation of histologic findings with relation to longer term outcomes; biopsy assessment by institutional kidney transplant histopathologists have been able to predict longer term outcomes based on these in the ECD donor cohort. Correlations of histology, both prospectively and retrospectively with organ outcomes offers a unique opportunity to validate such histology scores. Of course, these approaches are limited by the inevitable necessity to be able to study only those organs that were used and do not give insight into those organs that could have been used and discarded, sometimes inappropriately.

2.4. Platforms for clinical trials and evaluations

In addition to being able to offer retrospective samples for analysis, bio-banks often provide the infrastructure to aid large-scale clinical trials with data and specimen collection. This is of particular importance in organ donation where the allocation of organs can be national. Few national or international trials in donor interventional strategies have successfully been evaluated in randomised controlled trials. Obtaining multiple biopsies from an organ may not be appropriate, and standardised agreed procedures for obtaining biopsies and specimen handling will facilitate clinical trial specimen collection.

For example, in their recent meta-analysis of trials concerning steroid administration to organ donors, Dupuis et al. suggested despite 11 randomised controlled trials (RCTs) and 14 observational studies, the varied methodologies and potential for confounding was too substantial to be able to draw clear benefits from the administration of steroids to donors [33]. The authors argued there is a need for a large RCT to establish the benefit of steroid administration to the donor. Using national data collection infrastructures combined with sample collection would facilitate this type of research identifying clinical benefit but also effects of interventions on molecular and cellular pathways of injury and repair.

3. Conclusion

Development of large-scale bio-banks can help the facilitation of new research and lead to answering some important questions in the field of transplantation. Biomarker discovering and development of an understanding of key pathways of injury and repair in organ donors would be interesting fields for such biobanks to contribute.

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