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Role of Genetic Testing in Lung Transplantation; Prediction of Inflammation

Mohamed SA Mohamed*

University of Cologne, Deutz-Kalker Str, Cologne, Germany

***Corresponding author:** Mohamed SA Mohamed, University of Cologne, Deutz-Kalker Str, Cologne, Germany, Tel: 01625706493; E-mail: Mohammed.shehatta1@gmail.com

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Abstract

While the genetic matching between the donor and the recipient is essential for the success of the transplant procedure, there are other genetic factors that have the potential to significantly influence the clinical outcome. In this paper, the light is shed on this notion from a relatively new point of view.

Keywords: IL6; IL10; Genetic polymorphisms/mutations; Solid organ transplants

Introduction

Due to the increased incidence of end-stage lung diseases that lead to pulmonary failure, lung transplant becomes a frequent life-saving intervention. Unfortunately, there is a high incidence rate of primary graft dysfunction and failure after transplant. Research is progressing strongly in many directions to improve the clinical outcome of lung transplant.

Interleukin-6 (IL-6) is a pro-inflammatory cytokine and an anti-inflammatory myokine. In humans, it is encoded by the IL6 gene [1]. IL-6 is produced mainly by the T cells and the macrophages of the lung, bone marrow, spleen, lymph nodes, brain and skin. Nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) is the main regulator of IL-6 gene expression, which increases in all cases of tissue injury and inflammation [2].

IL-6 is also secreted by the vascular smooth muscles as a pro-inflammatory cytokine, however, IL-6 processes an indirect anti-inflammatory effects through the antagonization of TNF-alpha and IL-1, and the activation of IL-10 [3].

IL-10 is another cytokine, but with anti-inflammatory actions. It down regulates the expression of cytokines in the T helper-1 cells, and the major histocompatibility class II antigens and costimulatory molecules on the surface of macrophages. Moreover, IL-10 antgonizes the activity of NF-κB [4].

Accordingly, the balance between IL-6 and IL-10 can affect the prognosis of any inflammatory condition, including the ischemic reperfusion injury and the graft- host interaction. Hence, the ratio between both cytokines has the potential to predict the prognosis of lung transplant and the incidence of post-transplant graft failure [5]. A high IL-6/IL-10 ratio post-transplant was found to be associated with severe primary graft dysfunction and 20 fold increased relative risk of death [5].

Clinical and experimental implication of the principle

The Torono team for lung transplant, which is one of the leading teams in this regard, has already developed a chip to assess the expression levels of mRNAs of certain genes in graft biopsy, as markers for the prognosis of lung transplant. This includes the expression levels of IL-6 and IL-10. This technology is reliable and takes between 20-30 min, which can be performed while the graft on ex vivo perfusion [6].

As the graft biopsies deal with the graft after death of the donor (pre -implantation), in order to assess the expression levels of the IL-6 and IL-10, in addition to other biomarkers, this might be affected by several variabls, such as the cause of death of the donor and the associated conditions, the degree of the ischemic reperfusion injury, to which the garft has been exposed, and can be also attenuated through the application of graft conditioning techniques, such as preconditioning. This might not be able to reflect the post-transplant *in vivo* graft condition regarding the targeted biomarkers.

Moreover, there are imprinted genetic factors that could be considered earlier, by the time the donor makes his discision for donation. Although such imprinted genetic factors might also be reflected during the pre-implantation assessment, it would be much better to identify these risk factors ealier, so that, the precious time and money could be saved. Some of those genetics imprints lie in the mutations/polymorphisms that result in over expression of IL-6 and or defective IL-10.

There are 5 splice variants of IL-6, the standard is a 212 amino acids (aa) and the others are 252aa, 136aa, 189aa, 198aa and 122aa. Certain polymorphisms, such as the homozygous IL6-174G allele, are associated with decreased function of IL-6, reflected as an increased susceptibility to sepsis [7]. Accordingly, polymorphisms and or mutations, associated with the increased IL-6 expression, will ultimately result in high IL-6/IL-10 ratio and the subsequent primary graft dysfunction, whereas those associated with defective IL-6 expression would have the potential to provide a safer donor graft.

On the other side, loss- or decrease-of-function mutations of the IL-10 gene will lead to similar consequences. IL-10 receptor A polymorphisms, rs2228054 and rs2228055, have been reported to give the upper hand to the development of the inflammatory bowel disease [8]. A similar reaction could be expected in the lung graft.

Following these principles, two polymorphisms of INF-γ and IL-6 genes were reported to be associated with faster development of chronic lung allograft dysfunction (CLAD) following transplant [9,10]. Moreover, genetic polymorphysims/mutations of the Toll-Like Receptor family have a reported impact on the development of inflammation and rejection/CLAD after lung transplant [11-13].

Although some studies failed to correlate CLAD with the known genetic polymorphysims of TNF-α, TGF-β 1, and IL-10, those studies were concentrating on the genetic polymorphisms of the recepients rather than the donor (graft) [14,15].

Conclusion

As the source of the graft cytokines is mainly the resident leukocytes, a preliminary assessment for the increased IL-6 and/or the decreased/defective IL-10 mutations/polymorphisms (in addition to any other relevant genetic markers of inflammation) in the leukocytes of a blood sample can provide a valuable information about the suitability of the potential donor (Figure 1).

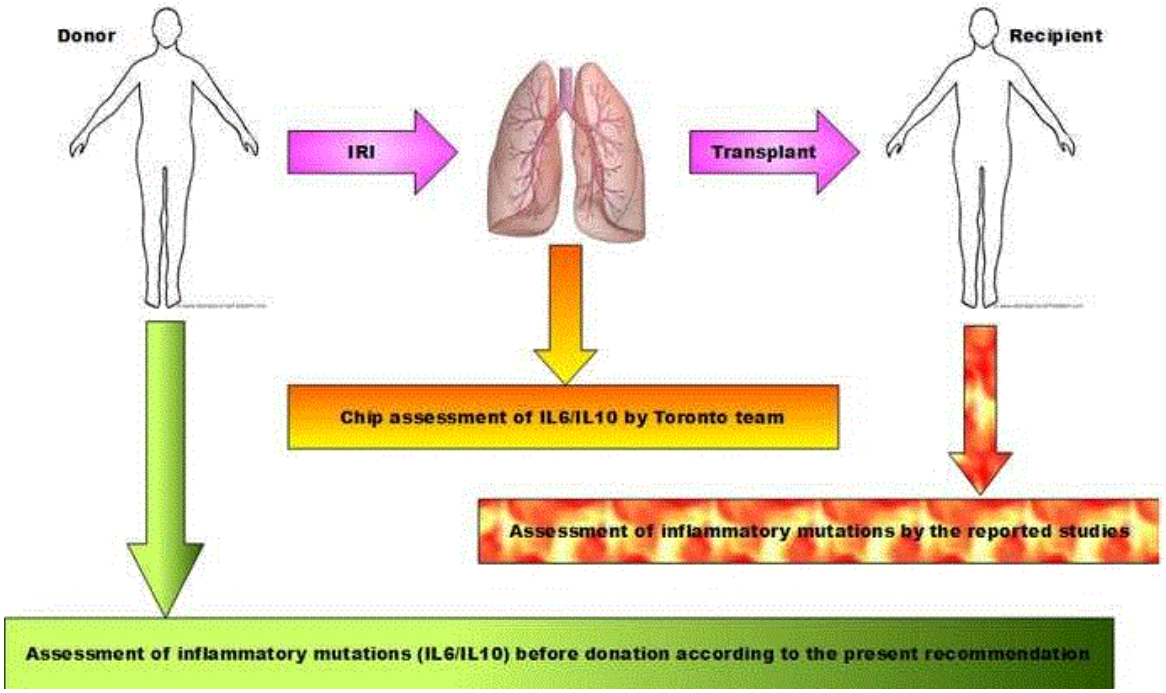

Figure 1: Diagrammatic illustration of the role of the genetic testing of the inflammatory mutations during lung transplant according to the present recommendation and the reported experiences.

This notion is applicable not only for lung transplant, but also for other solid organs transplants. Accordingly, clinical studies to assess the genetic profile of the genes of interest prior to donation, can provide the evidence based association with the rate of success of the transplant procedure and the frequencies of the post-transplant complications. This could be of great value, at least to mark the future grafts as "relatively high risk", which would indicate the application of especial immunomodulatory intervensions during lung transplant according to the present recommendation and the reported experiences.

Conflicts of Interest

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