Do donors matter? Short telomeres and survival after lung transplant

Emily S Clausen, Laurie D Snyder

One of the great challenges of lung transplantation is the development of progressive small airway fibrosis leading to pulmonary function decline and allograft loss. Termed as chronic lung allograft dysfunction (CLAD), it is the leading cause of shortened long-term survival among lung transplant recipients and estimated to affect at least half of all recipients within 5 years after transplant.¹ Risk factors for CLAD include type of transplant (single vs bilateral), infections, gastro-oesophageal reflux, graft ischaemic time, ischaemia-reperfusion injury, air pollution exposure, acute cellular rejection (ACR) episodes and specific antibody development.² In this issue of *Thorax*, Faust and colleagues propose a new risk factor for CLAD: short donor telomere length (TL).³

Telomeres consist of repetitive DNA sequences bound to shelterin protein complex at chromosome ends to provide protection from degradation during cell division. Short TL has been identified as a major contributor to lung disease, most notably as a genetic mediator of a subset of patients with idiopathic pulmonary fibrosis (IPF). In particular, mutations in multiple telomere-related genes that code for components of the telomerase enzyme complex are known to be associated with familial idiopathic interstitial pneumonia (IIP), as well as a smaller subset of patients with sporadic IIP without a family history. Telomerase mutations in pulmonary fibrosis can lead to progressive respiratory failure. Since telomerase enzyme activity is required to maintain TL during successive cellular replication, telomerase mutations can trigger replicative senescence and apoptosis to impact on a wide range of cells leading to a spectrum of clinical manifestations. Extrapulmonary disease states associated with telomerase mutations include bone marrow failure and liver disease including cirrhosis and hepatopulmonary syndrome.

IPF and other forms of pulmonary fibrosis now represent the leading

indication for lung transplantation in North America.¹ As telomere-mediated pulmonary fibrosis syndromes have become increasingly recognised, transplant centres are more aware of the complications of short telomere and some centres are now measuring TL in lung transplant candidates with pulmonary fibrosis particularly those patients presenting with a family history, or personal history of cytopenias, hepatic abnormalities and early greying of the hair, another feature of short TL. While observational studies support lung transplantation in patients with telomere-mediated pulmonary fibrosis, several case series reported on post-transplant complications occur at higher rates among these transplant recipients.⁴⁻⁶ In a twist on this TL discussion, Faust and colleagues found that donor allograft TL impacted the development of CLAD.³ In a cohort of 175 recipients, shorter donor TL by quantitative PCR on DNA isolated from donor peripheral blood mononuclear cells (PBMC) was associated with an increased risk of CLAD or death. Importantly, younger donors with shorter TL most strongly demonstrated this effect. Extremes of TL (comparing >80 percentile with <20 percentile) showed an increasing survival difference after 1 year post-transplant up until 5 years post-transplant. No significant association was found between transplant recipient PBMC TL and survival, but short recipient TL was associated with post-transplant leucopenia, as previously been reported.⁴ An ancillary study done along with this analysis included examination of endobronchial TL in patients with either short or long time to onset of CLAD and it was found that those with >8 years until CLAD onset had significantly increased endobronchial TL.³

In contrast to this study, a previous study by Courtwright and colleagues looked at both donor lymphocyte and recipient lung TL and did not find a significant association with survival in their cohort.⁷ Another study since then examined recipient TL specifically in patients with pulmonary fibrosis and divided the cohort into two groups of <10th percentile and ≥10th percentile TL and showed significantly worse survival in the <10th percentile even when controlling for other

factors such as infection rate, ACR and primary graft dysfunction.⁸ Faust's study adds to the field in that it has a longer follow-up and larger study population than previous studies which may account for why the prior studies did not find similar significance.

Notably, in this study and other prior studies, TL was determined by use of PBMC DNA. How TL from PBMC compares to TL in lung tissue remains unknown. In the Faust study, a subset of those with CLAD (n=6) and those without CLAD (n=12) had quantitative fluorescence in situ hybridisation (Q-FISH) performed on endobronchial biopsies. While the authors do not state how this compared with the PBMC TL measurements, short TL were also higher in those with CLAD. A prior study of consistency of TL among various organs on cadaver tissue showed significant variability within the same cadaver among various organs though lung was not included.⁹ It brings to question whether PBMC TL represents an accurate surrogate for lung TL in the donor allograft and further studies are needed to confirm if the PBMC TL of the donor can accurately reflect the allograft TL. An additional consideration is the TL percentile. While earlier studies have considered recipients with very short TL (<1 percentile), more recent studies have considered short TL as <10th percentile. Based on the limited studies available, it is not clear if there are clinically significant differences in recipients with the very short TL versus those with short TL.

The implications of this study are potentially quite important. If donor TL has an impact on CLAD, then measurement of the donor TL prior to transplant may help stratify donors. There are logistical considerations though in performing a highly technical test that is not widely available during the short period of evaluation time that centres typically have to decide on donor suitability. Furthermore, donor shortage is a national problem for all solid organs. Thus, a test that might eliminate more donors needs to be carefully considered. Clearly, further studies in TL are warranted.

Acknowledgements The authors wish to acknowledge Dr Murat Arcasoy's careful review of the manuscript.

Contributors Both authors equally contributed to the design, writing and review of the manuscript.

Funding This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Department of Medicine, Division of Pulmonary and Critical Care, Duke University Medical Center, Durham, North Carolina, USA

Correspondence to Dr Laurie D Snyder, Department of Medicine, Division of Pulmonary and Critical Care, Duke University Medical Center, Durham, NC 27710, USA; laurie.snyder@duke.edu

Provenance and peer review Commissioned; externally peer reviewed.

© Article author(s) (or their employer(s) unless otherwise stated in the text of the article) 2017. All rights reserved. No commercial use is permitted unless otherwise expressly granted.

CrossMark

To cite Clausen ES, Snyder LD. *Thorax* 2017;**72**:965–966.

Published Online First 26 August 2017

► <http://dx.doi.org/10.1136/thoraxjnl-2016-209897>

Thorax 2017;**72**:965–966.
doi:10.1136/thoraxjnl-2017-210363

REFERENCES

- 1 Christie JD, Edwards LB, Kucheryavaya AY, *et al*. The registry of the international society for heart and lung transplantation: 29th adult lung and heart-lung transplant report-2012. *J Heart Lung Transplant* 2012;31:1073–86.
- 2 Royer PJ, Olivera-Botello G, Koutsokera A, *et al*. Chronic lung allograft dysfunction: a systematic review of mechanisms. *Transplantation* 2016;100:1803–14.
- 3 Faust HE, Golden JA, Rajalingam R, *et al*. Short lung transplant donor telomere length is associated with decreased CLAD-free survival. *Thorax* 2017;72:1052–4.
- 4 Silhan LL, Shah PD, Chambers DC, *et al*. Lung transplantation in telomerase mutation carriers with pulmonary fibrosis. *Eur Respir J* 2014;44:178–87.
- 5 Borie R, Kannengiesser C, Hirschi S, *et al*. Severe hematologic complications after lung transplantation in patients with telomerase complex mutations. *J Heart Lung Transplant* 2015;34:538–46.
- 6 Tokman S, Singer JP, Devine MS, *et al*. Clinical outcomes of lung transplant recipients with telomerase mutations. *J Heart Lung Transplant* 2015;34:1318–24.
- 7 Courtwright AM, Fried S, Villalba JA, *et al*. Association of donor and recipient telomere length with clinical outcomes following lung transplantation. *PLoS One* 2016;11:e0162409.
- 8 Newton CA, Kozlitina J, Lines JR, *et al*. Telomere length in patients with pulmonary fibrosis associated with chronic lung allograft dysfunction and post-lung transplantation survival. *J Heart Lung Transplant* 2017;36:845–53.
- 9 Dlouha D, Maluskova J, Kralova Lesna I, *et al*. Comparison of the relative telomere length measured in leukocytes and eleven different human tissues. *Physiol Res* 2014;63(Suppl 3):S343–50.