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Where the chromosome ends: Telomeres and CMV risk in lung transplant recipients

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Prior to the advent of effective cytomegalovirus (CMV)-specific therapy, Henry H. Balfour likened CMV to the troll in the story “Three Billy Goats Gruff,” who threatened to devour patients with organ failure who sought greener pastures across the bridge of transplantation (1). Nearly 40 years later, CMV continues to plague allograft recipients, of whom lung allograft recipients are the most affected (2). This increased CMV burden in lung allograft recipients may result from CMV tropism for lung tissue and relatively more intensive immunosuppression (3). CMV causes morbidity and mortality both directly and indirectly through increased rates of non-CMV infection and chronic lung allograft dysfunction (CLAD) (2). CMV can lead to graft dysfunction through multiple mechanisms, including direct cytotoxicity; CMV-specific T, B, and NK cell targeting of infected cells; and heterologous immune responses promoting allo- or auto-immunity.

Given the burden of CMV disease in lung transplant recipients, consensus guidelines recommend anti-CMV prophylaxis (2). Yet despite 3-6 months of prophylaxis, CMV replication detected in bronchoalveolar lavage fluid is associated with nearly a 2-fold increase in the risk of CLAD (4). A multicenter randomized trial showed decreased frequency and severity of CMV infection in recipients treated with 12-months, as opposed to 3-months, of post-transplant anti-CMV prophylaxis (5). Some centers, including ours, have even advocated for CMV prophylaxis beyond 12 months (6). However, up to half of these lung transplant recipients will require discontinuation of indefinite CMV prophylaxis, mostly due to drug toxicities, which include leukopenia.

Leukopenia requiring medication adjustment is more common in lung allograft recipients with telomere dysfunction (7). Telomere dysfunction is well described as a cause of idiopathic pulmonary fibrosis (IPF), and shortened telomeres have also been linked with other lung transplant indications such as chronic obstructive pulmonary disease (8). It is thus not surprising that telomeropathies are enriched among lung allograft recipients. In this issue of the *Journal*, Popescu *et al.* report that the same lung transplant recipients likely to have CMV prophylaxis discontinued secondary to telomere-related leukopenia may also be at greatest risk for uncontrolled CMV infection (9). In this cohort, IPF patients with short peripheral blood leukocyte telomeres had a 9-fold higher risk of CMV relapse compared to a matched control cohort of non-IPF lung transplant recipients, despite receiving similar durations of CMV prophylaxis. IPF patients with normal telomere length did not appear at increased CMV risk.

The authors hypothesized that the observed increase in CMV disease may reflect defects in T cell-mediated control of CMV replication. Examining lymphocytes isolated from subjects at the time of viremia, they found that T cells from individuals with short telomeres proliferated less, made fewer cytokines, and had less induction of the transcription factor, T-bet, when stimulated with CMV peptides. Such impairments have been previously linked with failure to control CMV infection (9), but exactly how telomere shortening leads to this global T cell impairment remains uncertain. As illustrated in Figure 1, telomere shortening has been linked to the related but distinct processes of T cell exhaustion (loss of functional activity), senescence (cell cycle arrest), and apoptosis (programmed cell death) (10, 11). While this study did not examine markers of T cell senescence, reports that T-bet expression is positively correlated with senescence markers might argue against senescence as the main mechanism linking telomere dysfunction and impaired CMV immunity (12). At the same time, chronic CMV antigen stimulation could directly cause T cell exhaustion with associated decreases in T-bet induction and impairment of telomerase expression.

Figure 1: During initial infection, T cells respond to CMV antigen stimulation by proliferating. Absent defects in telomerase-complex proteins, telomerase may maintain telomere lengths in these T cells. However, T cell proliferation, functional and telomerase activity start to diminish in the face of chronic antigen exposure and T cells progress towards phenotypes of exhaustion, senescence, or apoptosis. These phenotypes can cause or be caused by telomere shortening.

These are interesting findings, which diverge somewhat from prior work. An increased risk of CMV infection was not observed in recipients with short telomeres in the two prior cohort studies (13, 14). At our center, recipients with short telomeres had increased rates of leukopenia requiring medication adjustment again did not have increased rates of CMV infection (7). Indeed, impairment of CLAD-free survival was more associated with short donor, rather than recipient, telomeres. Within the allograft, telomerase activity could be important for regenerating airways damaged by transplant-related injury, and, interestingly, CMV infection increases rates of allograft cell turnover more than other infections in lung allograft recipients (15). Generalizability can be a challenge in interpreting lung transplant studies because recipient populations and treatment protocols vary widely between centers. Such differences may explain discrepancies between the present findings and other cohorts. In this article, 71% of the patients with IPF had telomere lengths below the 10th percentile, which is substantially higher than the 32% of IPF lung transplant recipients in the cohort described at UT Southwestern (14). The high incidence of biopsy-proven end-organ CMV disease in 17 of 84 subjects was also not reported in other cohorts.

The collective experience caring for lung transplant recipients with short telomeres suggests that their clinical courses likely differ from recipients with normal telomere length because of unique telomere-related impacts on an individual's immune system, consistent with the well-established effects of telomeropathies outside of the context of lung transplantation. Measuring telomere length in potential lung transplant candidates has the potential to aid in evaluating candidacy, selecting grafts by CMV serostatus, guiding immunosuppression and CMV prophylaxis choices, and assessing risks for CMV infection, primary graft dysfunction, CLAD, and death. Still, transplant candidates with short telomeres are likely better off getting

a CMV+ graft than no graft because the risk of CMV-related complications remains manageable. At the same time, short telomeres do not account for the entirety of CMV risk, to which impaired antibody, T cell, and NK cell responses are important contributors. In summary, given the variable manifestations of telomere dysfunction observed across centers, further studies will be needed to understand how telomere length measurements should be incorporated into pre- or post-transplant management protocols.

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