Klotho and Pulmonary Hypertension
Spinning a Yarn or the Thread of Life?
Margaret R. MacLean

I
n the ancient Greek mythology, Klotho was the youngest of the 3 Fates responsible for spinning the thread of human life. Her sister Lachesis was thought to draw the lots and determine how long one lives by measuring the thread of life, and her other sister Atropos chose how someone dies by cutting the thread of life with her shears. Klotho was the youngest, and she had the power to make major decisions in not only choosing who was born but also deciding if a mortal should be saved or put to death. The 3 Fates (or the Moirai) were believed to appear 3 nights after a child’s birth to determine the course of its life.

When a new gene, thought to be involved in the suppression of ageing, was discovered in 1997,1 it was named Klotho after the youngest sister of these 3 Fates. In their article, Varshney et al2 report that stem cell delivery of secreted Klotho prevented monocrotaline (MCT)-induced endothelial dysfunction and pulmonary arterial remodeling, perhaps by reducing inflammation, restoring levels of SIRT1 (Sir2 family deacetylase 1) and endothelial nitric oxide synthase. The distribution of the transfected gene in the lung was not clear but would be of interest.

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So, does Klotho spin new hope for life after pulmonary arterial hypertension (PAH)? We certainly hope so. It is certainly intriguing as a new potential therapy—but wait—are we not all by now a little wary of the fact that most experimental treatments seem to reverse or prevent vascular pulmonary damage and pulmonary hypertension (PH) in this model? Many agents (over 50) have been reported to prevent or reverse established MCT-induced PH, but only endothelin-1–antagonists,3 PDE5 (phosphodiesterase 5) inhibitors,4,5 and prostacyclin analogues6 have translated into the clinic to date.

Pulmonary vascular endothelial damage occurs within hours after an injection of MCT. Endothelial damage continues to worsen, and inflammation and edema ensue after a week. Two weeks after MCT injection, pulmonary pressures rise, leading to right ventricular hypertrophy. Survival is poor, usually only 5 to 6 weeks. We study this model because it is reproducible and inexpensive and is similar to human PH in terms of hemodynamic and histopathologic severity and high mortality.8 However, MCT-induced PH is not the perfect model because the initial permeability, lung edema, and loss of the endothelial barrier, as well as prominent inflammatory adventitial proliferation, are not typical of PAH.

There is no formation of obstructive intimal lesions in the peripheral pulmonary arteries of the MCT rat, and some consider it to be an acute toxic model characterized by acute/subacute damage of the peripheral vasculature of the lung and other organs.8 Endothelial damage is a hallmark of the MCT model, and it may, therefore, follow that endothelial nitric oxide synthase levels are restored, where endothelial function is restored as demonstrated by Varshney et al.5 So, as a proof of concept, this study is indeed intriguing and exciting and may have great potential. We await The Fate of this potential new therapy, which will now require validation in other models of PH that better recapitulate PAH in humans. This would include the Sugen/hypoxic model of PAH, where PAH is induced by a combination of vascular endothelial growth factor receptor blockade with Sugen 5416 and chronic hypoxic exposure and is progressive even after reexposure of the animals to normoxia. There is also the presentation of occlusive vascular lesions in the Sugen/hypoxic model, and it more closely mimics human severe PAH than either the chronic hypoxic or MCT models.9

Because PAH is well advanced on presentation, we also need to demonstrate that this novel approach reverses established PH in our most refined animal models. Recent research into therapeutic stem/progenitor cell populations for the treatment of PAH have led to the development of other novel cell- and tissue-based regenerative therapies for PAH.10,11 Most of the evidence supporting these therapies have also, however, been based on prevention studies rather than treatment of established PH.10,11 Importantly, we also await confirmation that the Klotho gene is dysfunctional in PAH patients.

So what are The Fates for PAH patients? Survival in patients with PAH is still poor, and so, if you believe in Greek mythology, they may be too well acquainted to Atropos and had too much influence from Lachesis. We hope, however, that the younger sister Klotho will indeed spin the thread of life for PAH patients. Time will tell.
Disclosures
None.

References
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