Scientists identify why some kidney transplants don't work

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Scientists have discovered a 'molecular signature' for the allostatic load – or 'wear and tear' of kidneys – which could help clinicians understand why some kidney transplants don't work as well as expected.

The University of Glasgow-led research, published today in *Aging Cell*

and based on a first-of-its-kind study, can now explain why allostatic load develops at a molecular and cellular level, how it affects physiological function and the role of age-related organ capability and resilience.

Allostatic load is the 'wear and tear on the body' that accumulates as an individual is exposed to repeated or chronic stress. It reflects the 'burden of lifestyle and life events."

In the study, the scientists, in collaboration with NHS Great Glasgow & Clyde surgeons and pharmaceutical company GlaxoSmithKline, studied transplanted kidneys which developed delayed graft function, or DGF. DGF is when the organ fails to work after transplantation, and the patient has to be dialysed until the organ starts working or is lost.

The kidneys which displayed impaired function, or DGF, appear to be predisposed to exhibit a greater response to transplant stress and take longer to resolve this.

Previously, the scientists demonstrated that the biological age of transplanted kidneys was important for how well a kidney worked following transplantation, but it was not known why DGF, and the resulting impaired kidney function, occurred.

The scientists now demonstrate that at a molecular level, the kidneys studied displayed a greater magnitude of change in key genes, and elevated expression of features of ageing, consistent with increased allostatic load, or wear and tear.

Paul Shiels, Professor of Geroscience at the University's Institute of Cancer Sciences, said: "We now have strong evidence that an organ's biological age, in combination with physiological stress, plays a major role in DGF, or impaired function, occurring. The findings also suggest

that these effects are driven by donor characteristics, which may be more of a factor than transplant stress itself.

"Our findings are important because, not only have we identified the reason why some kidney transplants don't work when transplanted, we also demonstrate that miles on the biological clock affect the physiological function of organs. This isn't just clinically important, but is also relevant to how we age and how we can maintain good health in old age."

Deaths due to chronic kidney disease (CKD) have increased globally, as well as the number of people reaching old age, bringing with it a major burden of age-related morbidities. An estimated 10-12 percent of the world's adult population is affected by CKD and although a large proportion is distributed among the elderly, CKD occurs across all age groups. Transplantation remains the best option for these individuals as their kidneys eventually fail.

Prof Shiels added: "By using the signature set of genes from this study to identify less resilient organs before they meet a new recipient immune system, transplant stress could be reduced and outcomes improved. Significantly, the study has identified the targets for doing so, which may be applied not only for transplantation, but for other organs as we age, with a view to improving our years of healthy living."

The paper, "A molecular signature for delayed graft function" is published in *Aging Cell*.

More information: Dagmara McGuinness et al. A molecular signature for delayed graft function, *Aging Cell* (2018). DOI: 10.1111/acel.12825

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