MEDICINE

Tracking kidney transplant fitness

An implantable bioelectronic device detects the early signs of kidney transplant rejection in rats

By **Mohamad Zaidan**[1,2] *and* **Fadi G. Lakkis**[2]

Kidney transplantation (allograft) is a life-saving treatment for patients with end-stage kidney disease. Despite considerable progress over the past decades, improving long-term kidney allograft survival remains a major challenge with 10-year survival rates in the US of ~55% for deceased donor transplants (*1*). Rejection, arising from the recipient's immune response to the allograft, accounted for ~30% of graft loss (*2*, *3*). Therefore, early detection and management of rejection are crucial to prevent irreversible kidney tissue damage and enhance patient outcomes. On page 1105 of this issue, Madhvapathy *et al.* (*4*) describe a fully implantable, wireless, bioelectronic system to detect subclinical acute rejection. Using rat kidney transplantation models, the authors established that monitoring kidney temperature (T_{kidney}) provides early warning of rejection with greater sensitivity than traditional biomarkers. This approach could uncover medication noncompliance and guide treatment to improve long-term graft outcomes.

Kidney biopsy is the "gold standard" for the diagnosis of transplant rejection. Nevertheless, patients and clinicians are reluctant to repeat such an invasive procedure throughout the transplanted organ's lifetime, hindering the possibility of regular monitoring of graft status. Routine biomarkers from blood and urine samples, such as serum creatinine, blood urea nitrogen, and proteinuria, lack the sensitivity and specificity required for the diagnosis of rejection. Notably, subclinical rejection, which corresponds to kidney allograft rejection with inflammatory lesions but stable renal function, occurs in up to 25% of patients, highlighting the lack of reliability of these markers to guide treatment decisions (*5*, *6*).

Alternative blood or urine biomarkers, including cell-free DNA (*7*), chemokine levels (*8*), and "omics" technologies, such as transcriptomics, proteomics, and metabolomics (*9*, *10*), have been developed to address these issues (*11*). However, these biomarkers still have drawbacks with specificity (positive predictive value), variability among transplant facilities, and the ability to discriminate between rejection types. Moreover, they only provide a snapshot of graft status, and using them to repeatedly monitor the graft over time may not be cost-effective (*12*). Crucially, none were designed to identify nonadherence to immunosuppressive drugs, which occurs in up to one-third of patients, is associated with increased risk of rejection, and is responsible for 15 to 20% of graft loss (*3*, *13*, *14*).

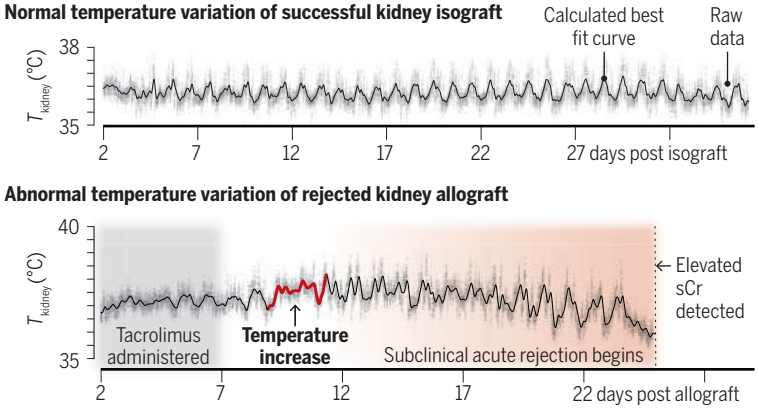
Madhvapathy *et al.* constructed a bioelectronic device that is capable of continuous, real-time, and long-term monitoring of T_{kidney} and thermal conductivity (k_{kidney}), as surrogate markers for kidney inflammation and perfusion, respectively. The device consisted of a mechanically compliant biosensor (probe) connected through wires to an electronic module (receiver). Immediately after transplanting the rat kidney, the receiver was secured to the recipient's abdominal wall adjacent to the graft and the probe was mounted on the surface of the kidney under the kidney capsule. The device had no obvious effect on activity, food and water intake, or sleep-wake cycles. In the native kidney and in isografts (transplants from genetically identical rats), the physiological pattern of T_{kidney} was characterized by a periodic (1-day) circadian rhythm after an initial irregular period corresponding to postoperative recovery (0 to 2 days). Notably, whereas increased activity of the animal induced transient (<1 hour) variations in T_{kidney}, changes in ambient temperature did not. k_{kidney} increased initially after single kidney transplantation, reaching twice the value of an animal with both of its native kidneys intact. This demonstrates that the biosensor successfully detected physiological doubling of renal perfusion in an animal with a single kidney.

Madhvapathy *et al.* identified a distinctive pattern of T_{kidney} that provided a consistent and early warning sign of subclinical acute rejection. Unlike isografts, allografts in nonimmunosuppressed recipients showed an initial rise of T_{kidney}, but not k_{kidney}, followed by a decrease. This pattern was consistent across all rejecting kidney allografts and preceded any change in renal function by 3 days. In rats transiently treated with tacrolimus, a commonly used immunosuppressant, the change in T_{kidney} pattern that is indicative of rejection occurred 2 to 3 weeks before any change in serum biomarkers (see the figure). Moreover, tacrolimus administration was characterized by stabilization of the T_{kidney} fluctuations that no longer exhibited circadian rhythm, suggesting that the biosensor may have the added benefit of detecting whether immunosuppressive drugs are being taken.

The application of such an implantable device to humans would first require experiments in larger animals to ensure safety and adequate function. If successfully translated to humans, the device would represent a

Kidney transplant monitoring

A wireless, bioelectronic device is implanted on transplanted kidneys in rats to continuously monitor kidney temperature (T_{kidney}) in real time. Increased T_{kidney} could be used as an early biomarker of local kidney inflammation, which is potentially related to subclinical acute rejection, before the rise in serum creatinine (sCr) levels.



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[1]Assistance Publique des Hôpitaux de Paris, INSERM, Université Paris-Saclay, Hôpital de Bicêtre, Le Kremlin-Bicêtre, France. [2]Starzl Transplantation Institute, University of Pittsburgh, Pittsburgh, PA, USA. Email: mohamad.zaidan@aphp.fr; lakkisf@upmc.edu

considerable improvement over traditional biomarkers for patient and graft monitoring by allowing timely therapeutic interventions and the recognition of medication noncompliance. Beyond rejection, the recording of biophysical parameters, such as k_{kidney}, may also represent an opportunity to assess situations that affect graft blood flow, including hypovolemia (reduced blood volume) and hypotension (reduced systemic blood pressure), which may also lead to acute kidney injury.

The findings of Madhvapathy *et al.* are promising, but further evaluation is needed. The specificity of the changes observed in T_{kidney} and k_{kidney} for rejection should also be compared with alternative inflammatory conditions affecting the graft, such as pyelonephritis and BK virus–associated nephropathy. Additionally, it will be important to investigate whether continuous monitoring is also suitable for identifying borderline changes in the graft, which correspond to minimal inflammatory changes that may precede the occurrence of full-blown acute rejection or may be detrimental to long-term graft survival (*12*, *15*). Moreover, the ability of such a device to discriminate acute from chronic components of graft injury should also be explored because the models used by the authors are more consistent with acute kidney rejection leading to rapid graft loss. The potential combination of continuous monitoring with additional markers of kidney allograft injury would provide a more comprehensive assessment of the graft status, facilitating clinical decisions. It will also be important to consider the foreign-body response that may accompany the implantation of such a device. Similar to the response to pacemakers, vascular fibrosis and tissue encapsulation may limit the long-term application in humans. Although several hurdles remain to be overcome, the prospect of integrating continuous monitoring into clinical practice could represent a major step toward personalized organ transplant care. ■

REFERENCES AND NOTES

1. S. Hariharan, A. K. Israni, G. Danovitch, *N. Engl. J. Med.* **385**, 729 (2021).
2. Z. M. El-Zoghby *et al.*, *Am. J. Transplant.* **9**, 527 (2009).
3. M. Mayrdorfer *et al.*, *J. Am. Soc. Nephrol.* **32**, 1513 (2021).
4. S. R. Madhvapathy *et al.*, *Science* **381**, 1105 (2023).
5. A. Loupy *et al.*, *J. Am. Soc. Nephrol.* **26**, 1721 (2015).
6. R. B. Mehta *et al.*, *Kidney Int.* **102**, 1371 (2022).
7. L. Bu *et al.*, *Kidney Int.* **101**, 793 (2022).
8. C. Tinel *et al.*, *Am. J. Transplant.* **20**, 3462 (2020).
9. J. J. Friedewald *et al.*, *Am. J. Transplant.* **19**, 98 (2019).
10. W. Zhang *et al.*, *J. Am. Soc. Nephrol.* **30**, 1481 (2019).
11. C. M. Puttarajappa, R. B. Mehta, M. S. Roberts, K. J. Smith, S. Hariharan, *Am. J. Transplant.* **21**, 186 (2021).
12. M. Naesens, J. Friedewald, V. Mas, B. Kaplan, M. M. Abecassis, *Transplantation* **104**, 700 (2020).
13. I. Gandolfini, A. Palmisano, E. Fiaccadori, P. Cravedi, U. Maggiore, *Clin. Kidney J.* **15**, 1253 (2022).
14. A. Cherukuri *et al.*, *Kidney Int.* **96**, 202 (2019).
15. A. Cherukuri *et al.*, *Kidney Int.* **103**, 749 (2023).

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GENOMICS

Chromosomal contacts change with age

The three-dimensional organization of the genome is remodeled throughout life

By **Schahram Akbarian**[1] *and* **Hyejung Won**[2]

Cell-specific transcriptomic and epigenomic programming during human brain development and differentiation are associated with dynamic changes in chromosomal conformations, which provide a structural foundation for a myriad of nuclear functions. These functions include the compartmentalization of the genome into intranuclear environments that are either facilitative (open compartments) or repressive of transcription, as well as the activation or fine-tuning of gene expression through promoter-enhancer looping (*1*, *2*). However, a fine-grained analysis of the three-dimensional (3D) organization of neuronal genomes at the single-cell level and across the life span has been missing, particularly for the human brain. On page 1112 of this issue Tan *et al.* (*3*) report that the chromosomes of some neuronal populations show potentially lifelong progressive changes in conformation in mice and in humans.

The 3D plasticity of the genome is thought to continue after the differentiation of neural progenitors to postmitotic neurons. For example, mapping of chromosomal conformation in neuron-enriched pools of brain nuclei from postnatal and young-adult mouse brain has shown a considerable capacity of the 3D genome to adapt in response to environmental enrichment (*4*) and during learning and memory (*5*, *6*). In addition, estrus cycle–driven chromosomal conformation dynamics have been observed in female mice (*7*).

Tan *et al.* used a DNA-DNA proximity assay called Dip-C and single-nucleus whole-genome amplification to study the dynamic landscape of chromosomal contacts in human and mouse brain. Their primary focus was cerebellar granule cells, which drive excitatory (glutamatergic) signaling in the cerebellum and are the most numerous neuronal subtype in the brain. The authors analyzed 5202 single nuclei from human cerebral and cerebellar cortex from 24 donors ranging in age from 5 weeks to 86 years and collected a similar dataset from mice. In terms of chromosomal conformation mapping, the size of these datasets is impressive. Tan *et al.* also performed standard single-nucleus transcriptome and chromatin accessibility profiling in the same cell type. The results of these analyses showed that cell differentiation–related changes in transcription (such as up-regulation of genes that encode synaptic proteins and ion channels or transcription factors that are critical for neuronal signaling) are, at least from a genome-wide perspective, completed at a relatively early stage in the life of these neurons. In humans, the entire population of cerebellar granule cells showed a mature transcriptome from the second year of postnatal life onward, which remained essentially unchanged thereafter.

By contrast, Tan *et al.* found evidence for an ongoing, perhaps even lifelong, reorganization of the chromosomal contact map, with successively increasing proportions of cerebellar granule cells displaying a fully matured 3D genome as the brain continued to age. This process extended into the seventh decade of life in humans and 12 months in mice. Tan *et al.* identified three specific elements of the 3D genome that seemed to undergo this progressive remodeling. One element was compartmentalization into facilitative and repressive chromosomal environments. Specifically, the authors identified a lifelong, age-progressive increase in open compartment scores (a metric for the degree by which a genomic locus is embedded into a facilitative chromatin environment) that encompass 100 to 200 cerebellar granule cell marker genes (see the figure). Paradoxically, these genes showed stable RNA expression levels from early childhood onward.

3D genome maturation in cerebellar granule cells was also defined by a steady rise in the proportion of intrachromosomal contacts that bypassed 10 to 100 Mb of sequence (ultra-long-range contacts), which increased from 19% at the most immature stage to 33% at the most mature stage in humans. Tan *et al.* also observed an increase in interchromosomal contacts associated with maturation. Therefore, increased compartmentalization in humans and mice could result from many long-range intra- and interchromosomal

[1]Icahn School of Medicine at Mount Sinai, New York, NY, USA. [2]Department of Genetics, University of North Carolina, Chapel Hill, NC, USA. Email: schahram.akbarian@mssm.edu; hyejung_won@med.unc.edu

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Mohamad Zaidan and Fadi G. Lakkis

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