MECHANOBIOLOGY

Forcing MT glutamylation

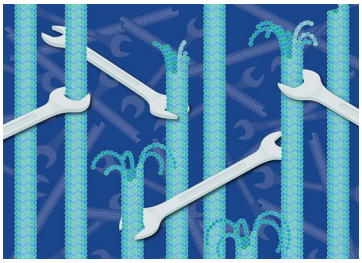
Cells respond to the mechanical properties of their environment, but how mechanical forces control a multitude of cell functions and phenotypes remains poorly understood. Torrino et al. now show that the stiffness of the extracellular matrix (ECM) regulates microtubule (MT) posttranslational modification (PTM) via glutamylation, which impacts MT dynamics and cell invasiveness.

MTs are important force-bearing and force-generating cytoskeletal structures, yet how MT regulation is coupled to cellular mechanotransduction is elusive. Culturing HeLa cells on ECM of increased stiffness suppressed MT dynamics and promoted their stability. This was linked to increased MT glutamylation — a PTM previously shown to regulate MT dynamics in vitro. Increased MT glutamylation, in turn, was associated with changes in cell mechanical properties (shape and compliance) and with increased cell proliferation.

MT glutamylation requires glutamate, which can be derived from glutamine catabolism mediated by glutaminase. Indeed, increased MT glutamylation in HeLa cells grown on stiff ECM relied on glutaminase activity and was regulated by glutamate availability.

As previous work had shown that breast cancer cells respond to stiffness by increasing glutamine catabolism, the authors investigated the relevance of stiffness-mediated MT glutamylation for cancer progression. Like in HeLa cells, MT glutamylation in breast cancer cells was increased by stiffness. Reducing ECM stiffness in a mouse model of metastatic breast cancer lowered glutaminase activity and decreased MT glutamylation, whereas in human breast cancer samples high levels of MT glutamylation correlated with stiff ECM and with high rates of cell proliferation. In line with these findings, decreasing MT glutamylation reduced cell proliferation and pulmonary metastases of breast tumours in mice.

> “high levels of MT glutamylation correlated with stiff ECM and with high rates of cell proliferation”



Credit: V. Summersby/Springer Nature Limited

Overall, this study provides new insights into the interplay between cellular mechanotransduction and metabolism in regulating complex cell behaviours — an emerging area of mechanobiology.

Paulina Strzyz

ORIGINAL ARTICLE Torrino, S. et al. Mechano-induced cell metabolism promotes microtubule glutamylation to force metastasis. *Cell Metab.* https://doi.org/10.1016/j.cmet.2021.05.009 (2021)
RELATED ARTICLES Romani, P. et al. Crosstalk between mechanotransduction and metabolism. *Nat. Rev. Mol. Cell Biol.* **22**, 22–38 (2021) | Janke, C. & Magiera, M. M. The tubulin code and its role in controlling microtubule properties and functions. *Nat. Rev. Mol. Cell Biol.* **21**, 307–326 (2020)

Journal Club

SARS-COV-2

UNCOVERING SARS-COV-2 KIDNEY TROPISM

It is well established that the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) — the cause of the pandemic of coronavirus disease 2019 (COVID-19) — primarily targets cells in the respiratory tract and results in an increased respiratory failure. However, there is mounting evidence that SARS-CoV-2 pathogenicity extends beyond the respiratory tract, affecting multiple organs, including the kidneys, heart, brain and liver. This multi-organ tropism may underlie the high pathogenicity of SARS-CoV-2 and progression to severe COVID-19.

Emerging reports from the review of health records revealed that acute kidney injury frequently occurs in patients hospitalized with COVID-19 and associates with respiratory failure and poor prognosis (see for example Hirsch et al. 2020). Still, it has been unclear whether SARS-CoV-2 can directly infect human kidney cells and if so, whether it employs similar mechanisms for entry and processing (for example, binding to angiotensin-converting enzyme 2 (ACE2)) as during respiratory cell infection.

These questions have not been fully addressed, but a recent publication by Puelles et al. (2020) has helped shed some light on this topic. By analysing viral load in autopsy tissues obtained from patients who had died from COVID-19, the authors showed that the kidneys are among the most common targets of SARS-CoV-2, even in patients without prior history of chronic kidney disease. Intriguingly, SARS-CoV-2 was detectable in multiple kidney compartments (glomeruli, cortex and medulla) of randomized samples from patients with COVID-19, with preferential targeting of glomerular cells. Additional analyses of publicly available data sets from single-cell RNA sequencing revealed that multiple kidney cell types (including podocytes, glomerular endothelium, proximal tubule epithelial cells and collecting duct) express host factor genes such as ACE2, TMPRSS2 and CTSL, which are implicated in SARS-CoV-2 infectivity and pathogenicity, which could underlie SARS-CoV-2 affinity with kidney cells. Based on these findings, the authors speculated that SARS-CoV-2 multi-organ tropism might affect the severity of COVID-19 disease and related health outcomes.

> “the kidneys are among the most common targets of SARS-CoV-2”

Recent advances in human stem cell differentiation into specialized kidney cells and the engineering of in vitro renal tissue models, such as organoids and organ-on-chip cultures, will now be instrumental in experimental investigation of SARS-CoV-2 infections in human kidney cells and in uncovering the mechanism of multi-organ tropism and associated tissue injury in patients with COVID-19 disease.

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ORIGINAL ARTICLE Puelles, V. G. et al. Multiorgan and renal tropism of SARS-CoV-2. *N. Engl. J. Med.* **383**, 590–592 (2020)
RELATED ARTICLE Hirsch, J. S. et al. Acute kidney injury in patients hospitalized with Covid-19. *Kidney Int.* **98**, 209–218 (2020)