Metabolism

A new pathway links iron sensing with histone demethylation and regulation of mTORC1 activity

Various regulatory pathways have evolved to enable cell survival during iron deficiency. However, the mechanisms by which cells sense iron and modulate energy metabolism are unclear. Now, Jason Shapiro and co-authors have identified a new pathway by which eukaryotic cells sense iron and regulate pro-anabolic mTORC1 activity.

The researchers report that in cultured mammalian cells, prolonged iron deficiency results in inhibition of mTORC1 activity, suppression of protein and pyrimidine synthesis, a reduction in the rate of cell proliferation and activation of autophagy. The mechanism by which iron deficiency led to mTORC1 inhibition did not require TSC1–TSC2, HIF or AMPK signalling, but was dependent on leucine sensing. Iron deficiency prevented leucine uptake via repression of the membrane leucine transporter LAT3, which suggests that iron regulates transcription.

Using histone mass spectrometry, the researchers show that iron is required for active histone demethylation and cells regulate chromatin in response to iron availability in the environment. They report that the iron-binding histone-demethylase KDM3B acts as an intrinsic iron sensor that regulates mTORC1 activity by demethylating H3K9me2 at enhancers of *LAT3* and *RPTOR*, which encodes the mTORC1 complex member RAPTOR. Further studies suggested that this pathway is conserved in eukaryotic organisms, including mammals, yeast and plants.

"Overall, our data demonstrate the presence of a sophisticated and evolutionarily conserved iron-sensing mechanism that is engaged to shut down anabolic processes in cases of prolonged [iron deficiency]", conclude the researchers. "This pathway has profound implications for proliferative diseases, which rely heavily on iron and mTORC1-mediated anabolism."

Ellen F. Carney

Original article: Shapiro, J. S. et al. Iron drives anabolic metabolism through active histone demethylation and mTORC1. *Nat. Cell Biol.* **25**, 1478–1494 (2023)

Transplantation

Embryo complementation to generate a humanized mesonephros in pigs

The use of embryo complementation to grow human organs in nonhuman mammals, such as pigs, may represent a future source of organs for human transplantation. Jiaowei Wang and colleagues now demonstrate the potential feasibility of this approach through the generation of humanized mesonephroi in nephric-defective pigs using embryo complementation with pluripotent stem cells (PSCs).

A key obstacle to the generation of viable interspecies chimeras is the poor contribution of human PSCs to host tissues. Wang et al. addressed this barrier through two approaches. First, they optimized the chimeric potential of PSCs by overexpressing the pro-survival genes *MYCN* and *BCL2* and by culturing the PSCs in medium that was previously shown to roll back PSCs to an earlier developmental stage. Second, the researchers injected these PSCs into pig embryos that had been rendered nephric-defective through deletion of the nephrogenic factors SIX1 and SALL1. From 1,820 PSC-injected embryos transferred into 13 surrogates, the researchers obtained two normal embryos at embryonic day (E) 25 and three at E28. Analysis of the injected knockout embryos demonstrated an enrichment of human-derived cells in the mesonephros area, where they accounted for ~50–65% of cells. In the mesonephric tubules, human-derived cells expressed SALL1 or SIX1, as well as PAX2 and WT1, indicative of cell differentiation.

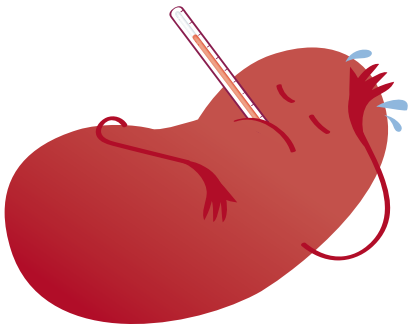
The researchers note that although gestation was terminated prior to development of the metanephros, their findings indicate that further development of the chimeric organs may be feasible. "The results indicate that it might be possible to generate a functional human kidney inside newborn pigs, offering an attractive alternative to overcome the shortage of human organs for transplantation", they say.

Susan J. Allison

Original article: Wang, J. et al. Generation of a humanized mesonephros in pigs from induced pluripotent stem cells via embryo complementation. *Cell Stem Cell* **30**, 1235–1245. e6 (2023)

Bioengineering

Taking kidney temperatures to detect rejection



Early detection of transplant rejection is crucial to prevent graft loss and might be facilitated by wireless implantable bioelectronic systems, according to a new study by John Rogers and colleagues.

In a rat model of kidney transplantation, animals received either an allograft (some were treated with immunosuppressants to model delayed acute rejection) or an isograft (controls). After reperfusion, the researchers implanted a stretchable, flexible and ultrathin bioelectronic system on the surface of the graft. The sensor was connected to an electronics module placed on the adjacent abdominal wall for real-time continuous wireless transfer of kidney temperature and thermal conductivity data (indicators of inflammation and kidney perfusion).

In both rejection models, the sensor revealed a circadian kidney temperature rhythm from 2 days after surgery, which was followed by an increase in graft temperature (midpoint), and then eventually a sharp temperature drop and graft loss (endpoint). The midpoint occurred at ~3 days in the acute model and at ~14 days in the delayed model; the endpoint was observed at ~5–6 days and ~22 days, respectively. Histological evidence showed that the midpoint temperature rise coincided with early graft rejection (necrosis and tubulitis) but preceded changes in blood markers (rise in blood urea nitrogen and creatinine), which only differed from those of controls at the endpoint.

Monica Wang

Original article: Madhvapathy, S. R. et al. Implantable bioelectronic systems for early detection of kidney transplant rejection. *Science* **381**, 1105–1112 (2023)