
Credit: Jeffrey Coolidge/The Image Bank

PHARMACOLOGY

Unravelling metformin's mechanism of action

Metformin is commonly used in the treatment of patients with type 2 diabetes mellitus (T2DM). Metformin works by inhibiting hepatic gluconeogenesis; however, its precise mechanism of action is widely debated. New research by Gerald Shulman and colleagues provides insight into the mechanism that underlies the glucose-lowering effect of metformin.

Previous work from Shulman and his co-workers demonstrated that metformin reduces hepatic gluconeogenesis by inhibiting mitochondrial glycerol-3-phosphate dehydrogenase (GPD2), which increases the cellular redox state and results in the inhibition of the conversion of some substrates (such as lactate and glycerol) to glucose in vitro. "This current study builds on these previous studies and uses a novel ^{13}C-labelling strategy to demonstrate that this redox-dependent substrate-specific effect is central to metformin's mechanism of action to decrease rates of hepatic glucose production in awake rodent models of T2DM," explains Shulman.

The researchers infused awake unrestrained rats that either did or did not have T2DM with ^{13}C-labelled lactate or alanine and used ^{13}C NMR spectroscopy to trace these molecules as they moved through the gluconeogenic pathway and were scrambled to the 1, 2, 5 or 6 carbon positions on glucose. The rats were also treated with metformin that achieved clinically relevant plasma concentrations. "We found that metformin impedes the hepatic conversion of redox-modulating substrates (lactate and glycerol), but not redox-neutral substrates (alanine and pyruvate) into glucose," says Shulman. "These results would not be predicted to occur with any other proposed mechanism for the glucose-lowering effects of metformin."

> "this redox-dependent substrate-specific effect is central to metformin's mechanism of action"

The investigators are now trying to determine how biguanides (the group of drugs that metformin belongs to) directly or indirectly regulate the activity of GPD2. They are also using similar tracer analyses to see if these findings translate to metformin-treated patients with T2DM. "Our findings also suggest that modulating the liver cytosolic redox state to influence flux through gluconeogenesis might be an effective strategy for developing potent novel therapies to treat T2DM," concludes Shulman.

Claire Greenhill

ORIGINAL ARTICLE Madiraju, A. K. et al. Metformin inhibits gluconeogenesis via a redox-dependent mechanism in vivo. *Nat. Med.* https://doi.org/10.1038/s41591-018-0125-4 (2018)

BONE

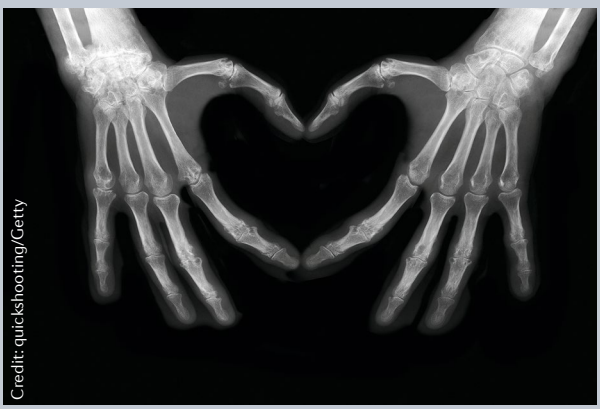
THY1 membrane glycoprotein linked to osteogenesis

Current treatment strategies for osteoporosis are ineffective at reversing the characteristic bone tissue abnormalities associated with increased fragility. Now, new research reports that THY1 membrane glycoprotein is important for osteogenesis promoted by mesenchymal stem cell (MSC) differentiation.

MSCs are thought to have a central role in the development of osteoporosis. Patients with osteoporosis have dramatic bone loss, while bone marrow adiposity is increased — this is caused by an imbalance between osteogenic and adipogenic MSC differentiation. "Studies have shown that THY1, which is expressed on the surface of MSCs, has a regulatory role in mesenchyme-derived fibroblast differentiation," explains corresponding author Anja Saalbach "Therefore, in the present study, we investigated the effect of THY1 expression on the fate of MSCs, with a focus on osteogenic and adipogenic differentiation."

To investigate the effect of THY1 on the balance between osteogenesis and adipogenesis in bone marrow, the authors used micro-computed tomography, histology and biomechanical tests to analyse bone of THY1-deficient and wild-type mice. Samples from these mice were also taken and analysed in vitro. Saalbach and colleagues also measured levels of THY1 in the serum of healthy humans and humans who had disturbed bone formation or obesity.

"We identified THY1 as a critical molecule for MSC differentiation promoting bone formation, while inhibiting adipogenesis and obesity," adds Saalbach. "Furthermore, THY1 levels in the serum indicated that disturbed bone remodelling in osteoporosis or dysregulated adipose tissue accumulation in patients with obesity are mirrored by reduced serum concentrations of THY1".


Credit: quickshooting/Getty

> "We identified THY1 as a critical molecule for MSC differentiation promoting bone formation signalling"

Saalbach writes that future studies should focus on further understanding how THY1 mediates bone mass and concurrently negatively regulates adipose tissue. Targeting the balance between osteogenesis and adipogenesis could be an attractive strategy for novel therapies against osteoporosis.

Alan Morris

ORIGINAL ARTICLE Picke, A.-K. et al. Thy-1 (CD90) promotes bone formation and protects against obesity. *Sci. Transl Med.* **10**, eaao6806 (2018)