Credit: Classen Rafael/EyeEm/Getty

CANCER METABOLISM

In search of the mechanisms of metformin in cancer

Epidemiological studies suggest that treatment with metformin in patients with type 2 diabetes mellitus reduces the incidence of cancer at a number of tumour sites. The mechanism of action of metformin on tumour cells, however, has remained unclear. In addition, much of the preclinical data are limited as studies in some models used doses of metformin many times higher than those used in the clinic. Now, in a clinically relevant study, Simon Lord and colleagues have shown that metformin activates multiple transcriptomic pathways associated with mitochondrial metabolism.

"Key questions remained unanswered regarding the effects of metformin in tumour cells at standard clinical doses," explains Lord. "[Therefore,] we designed an in-depth study to try and answer some of the questions and explored potential biomarkers that could be used to stratify patients in current and future late phase trials."

In the present study, the authors expanded on their previous experience of running clinical studies by integrating novel imaging and transcriptomics, coupled with metabolomic profiling, to investigate the pharmacodynamic effects of metformin in cancer. Lord and colleagues report that metformin increased FDG (a marker of glucose uptake) flux into tumours and altered the concentration of a number of mitochondrial metabolites. Furthermore, an integrated analysis of their data sets demonstrated differential metabolic responses to therapy between patients.

"Drug studies that utilize novel imaging alongside tissue-based assays as a tool for understanding the bioactivity of an anticancer therapy is not routine during drug development," concludes Lord. "Future studies of similar design, if carried out at an early stage of drug development, could optimize late phase trial design and address questions surrounding selection of patients and potential drug combinations."

Alan Morris

ORIGINAL ARTICLE Lord, S. R. et al. Integrated pharmacodynamic analysis identifies two metabolic adaption pathways to metformin in breast cancer. *Cell Metab.* https://doi.org/10.1016/j.cmet.2018.08.021 (2018)

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OBESITY

Mechanisms of leptin resistance revealed

In obesity, leptin resistance is the process by which the body no longer responds to leptin to inhibit energy intake and increase energy expenditure. The mechanisms that contribute to leptin resistance, however, remain unclear. Now, research has reported that a high-fat diet (HFD) in mice increases the concentration of metalloproteinase 2 (MMP2) in the hypothalamus and leptin receptor (ObR) signalling is impaired following the cleavage of the ObR extracellular domain by MMP2.

"The concept of leptin resistance is well established and patients with obesity are characterized by hyperleptinaemia and a diminished response to leptin," explains co-corresponding author Dinorah Friedmann-Morvinski. "[We were intrigued by this as] in most cases of obesity, the [diminished response to leptin] is not associated with genetic defects in leptin or its receptors."

In the present study, Friedmann-Morvinski, Rafi Mazor and colleagues investigated the mechanisms responsible for leptin resistance in obesity by inducing obesity in rats using a HFD and analysing total protease activity in brain lysates. The team found a global increase in the expression and activation of MMP2 in the brains of rats fed a HFD compared with the brains of rats fed a control diet. "Although the activity of MMP2 induced by HFD [was] not restricted to the hypothalamus, we focused our studies on this region as it affects food intake through the action of the leptin receptor," write the authors.

Next, Friedmann-Morvinski and colleagues investigated the effect of incubation with MMP2 on the activity of ObR in hypothalamic cells. After treatment with MMP2, the expression of the ObR extracellular domain in the cells was reduced by >20%. The authors then used *Mmp2*-knockout mice to determine the effect of MMP2 depletion on HFD-induced obesity. The authors showed that MMP2-depleted mice had reduced weight gain when fed a HFD compared with wild-type littermates.

"[Following the *Mmp2*-knockout experiments], we needed a methodology that could show that depletion of MMP2 in the hypothalamus alone could result in reduced weight gain, which is why we adopted the lentiviral injections approach," explains Friedmann-Morvinski. The team used lentiviral vectors to either knock down *Mmp2* in the hypothalamus or to upregulate the expression of a mutant cleavage-resistant form of the ObR. Compared with control mice, mice lacking hypothalamic MMP2 that were fed a HFD gained less weight and had reduced plasma concentrations of leptin.

"I believe we have found a novel target and presented a possible new strategy to develop new treatment approaches to restore leptin sensitivity and hopefully decrease weight gain in people who are obese," concludes Friedmann-Morvinski. "The challenge now is to find the way to deliver MMP2 inhibitors specifically to the hypothalamus."

Alan Morris

ORIGINAL ARTICLE Mazor, R. et al. Cleavage of the leptin receptor by matrix metalloproteinase–2 promotes leptin resistance and obesity in mice. *Sci. Transl Med.* https://doi.org/10.1126/scitranslmed.aah6324 (2018)