GENETICS

Response to antidiabetic drugs affected by SNPs that alter genomic binding of PPARγ

The transcription factor peroxisome proliferator-activated receptor γ (PPARγ) is associated with metabolism and metabolic diseases—it is highly expressed in fat cells and is a target for thiazolidinediones (a class of antidiabetic drugs). Now, new research published in *Cell* shows that single nucleotide polymorphisms (SNPs) can affect the genome-wide binding of PPARγ, which seems to influence the response to thiazolidinediones.

"As PPARγ is a transcription factor that binds to known DNA sequences, we hypothesized that individual differences in the DNA composition, particularly at enhancers, would lead to individual differences in the binding of PPARγ at the genome, which would alter the expression of genes that it normally regulates in fat cells," explains Mitchell Lazar, an author of the study. The researchers thought that the affected genes in fat cells might be those involved in the cell's function or in total-body metabolism, alternatively, genes regulated by thiazolidinediones might be affected. "If a SNP happened to modify PPARγ binding at these sites, the drug response could be changed in a predictable way that could alter the therapeutic benefit of the drug for that individual," says Lazar.

The researchers performed ChIP-sequencing in white adipose tissue from two mouse strains (C57BI/6J [B6] and 129S1/SvlmJ [129]) that differ in their susceptibility to obesity and insulin resistance to identify PPARγ binding sites. The two mouse strains differed by ~5.3 million SNPs and binding sites that were specific to a particular strain were highly enriched for SNPs. Furthermore, the team showed that SNPs affecting the binding of PPARγ were those that directly altered the sequences the transcription factor binds to, or sequences of other transcription factors that are involved in the binding of PPARγ.

Next, Lazar and his co-workers investigated whether the differences in PPARγ binding as a result of SNPs affected the response to antidiabetic drugs. The two strains of mice were treated with rosiglitazone (a thiazolidinedione) for 2 weeks. RNA-sequencing was then performed in white adipose tissue samples from the mice to identify which genes were upregulated or downregulated by the treatment. Genes upregulated by rosiglitazone in B6 mice, but not in 129 mice, were likely to be close to PPARγ binding sites that were specific to the B6 strain; similarly, genes that were only upregulated in 129 mice were located near PPARγ binding sites specific to the 129 strain. "SNPs that alter PPARγ binding control the response to antidiabetic thiazolidinedione drugs," states Lazar.

The investigators went on to validate the findings from mice in humans. ChIP-sequencing was performed on samples of subcutaneous adipose tissue from five individuals. As in the mice, SNPs that changed the binding motifs affected binding of PPARγ in human fat cells. Unfortunately, studies to date have not been sufficiently powered to test whether these SNPs affect drug response in humans. However, an assessment of published meta-analyses of genome-wide association studies revealed that SNPs that changed PPARγ binding motifs were also implicated in dyslipidaemia (that is, altered levels of triglycerides and HDL cholesterol). This finding suggests that SNPs implicated in altered PPARγ binding could modulate the risk of metabolic diseases in humans.

Lazar believes these results demonstrate that an individual's genetic profile can influence how they respond to particular drugs. "A direct benefit of our work could be that some of the PPARγ binding SNPs ... could be correlated with either the efficacy of thiazolidinedione therapy, or one of its adverse effects," explains Lazar. "This information could be used to screen patients to see if their 'personal therapeutic index' would
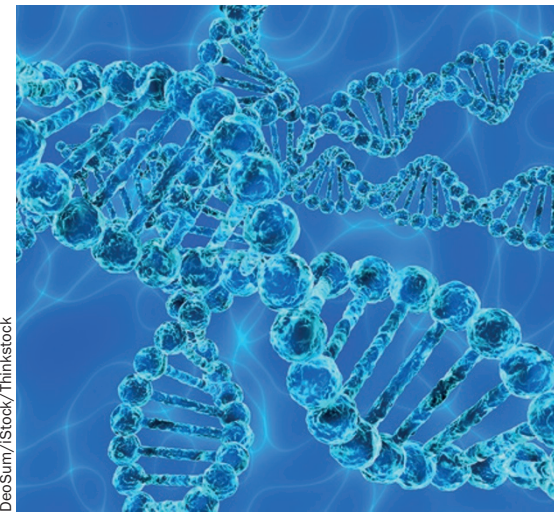
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warrant thiazolidinedione therapy." These findings could also have broader implications for other drugs that target DNA-binding proteins (such as steroid hormones and retinoids). In the future, it might be possible to predict how likely a patient is to benefit from a particular treatment (and, indeed, whether they are at increased risk of adverse effects) simply by analysing their genome. "Taking advantage of this knowledge would be the cornerstone of scientifically based personalized medicine," comments Lazar. While genome sequencing is currently too expensive to be used routinely in the clinic, the cost is decreasing so this application could be viable in the future.

Lazar and colleagues are continuing their search for human studies sufficiently powered to test whether SNPs that alter PPARγ binding affect the response to antidiabetic drugs. They are also looking for additional SNPs that could be implicated in the adverse effects associated with thiazolidinediones.

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