A fine balance: Gene expression and repression in reproduction and energy metabolism

SUMMARY

Control points of gene activity are potential targets for new drugs. Nuclear receptors control many important physiological switches by regulating gene transcription. Research by Malcolm Parker, Professor of Molecular Endocrinology at Imperial College Faculty of Medicine, London, on proteins that regulate nuclear receptor activity is identifying candidates for drug action to control body weight and ovulation.

Background

Obesity is a global problem. The World Health Organization projects that by 2015 approximately 2.3 billion adults will be overweight and more than 700 million will be obese. This epidemic is due both to increased availability of calories in energy-dense, nutrient-poor foods and to sedentary working behaviours that reduce calorie burning.

One approach to this problem is to promote changes in lifestyle – improved diet and increased exercise. Another is to develop drugs that alter appetite, which is controlled by hormones and the nervous system, or to adjust how the calories we eat are used or stored. The latter approach requires a detailed understanding of how the body's energy balance is regulated, and how fats are stored in white adipose tissue and 'burned' in brown adipose tissue to generate heat.

At Imperial College London, Professor Malcolm Parker is investigating the role of nuclear receptor proteins in the body's handling of fats. These proteins are found in many tissues – including fat-storing cells, liver and muscles – where they switch certain metabolic genes on or off depending on whether they bind activating or repressing cofactor proteins.

Advance

Professor Parker and colleagues are studying nuclear receptors that not only affect the balance between the storage and burning of excess fatty acids, but also have a role in the control of reproduction and inflammation. They have discovered two families of proteins that activate and repress nuclear receptors – the RIP160 and RIP140 families of cofactors. These proteins bind to receptors when they bind hormones such as steroids or ligands such as fatty acids.

By studying mice that have had the *RIP140* gene removed, Professor Parker has found that the expression of genes involved in metabolic activity in fat and muscle is increased - suggesting that the normal role of RIP140 is to block the activity of such genes. As a consequence the mice are lean and do not become obese if they eat excessively; their muscle biology is altered and they control their glucose levels more effectively.

Paradoxically RIP140 also seems able to activate certain genes. Thus it seems to promote the expression of cytokines in macrophages and genes required by the ovary for ovulation.

How it's making a difference

Professor Parker's identification of a link between the 'fat-burning' genes and the repressor protein RIP140 suggests a possible target for the therapeutic control of energy metabolism. Such drugs could work by blocking the binding of RIP140 to nuclear receptors, shifting the balance of metabolism away from fat storage to fat burning. They could be used to treat morbid obesity and diabetes. The role of RIP140 in gene control in the ovary also suggests a way to control ovulation therapeutically.

In 2004, patents for the screening of compounds to block ovulation and to modulate fat storage were licensed by Professor Parker to the biopharmaceutical company CytRx in Boston, USA.

Next steps

Professor Parker's group is now investigating the complex fat storage and ovulation pathways that are influenced by RIP140. They are therefore looking for proteins that interact with RIP140, and how they are able to switch off genes in fat and muscle but turn on genes in the ovary.

References

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Timeline of Malcolm Parker