CREB: New approach for treating obesity?

A new approach could be on the horizon for treating obesity, diabetes and heart disease based on the binding of a regulatory protein to the DNA in fat cells, according to US researchers[1]. Dwight Klemm, Associate Professor at National Jewish Medical and Research Center, and his colleagues at the Denver Veteran's Affairs Medical Center and the University of Colorado (Denver, CO, USA) have discovered that a single protein, CREB (cAMP response-element binding protein), is crucial to the formation and maintenance of fat cell development.

Energy balance

Excess body fat and obesity are becoming increasingly common in developed nations, with almost one in three Americans and up to one in four Europeans estimated to be overweight and many of these classed as clinically obese by most criteria. The role of obesity in the development of cardiovascular disease, diabetes, pulmonary dysfunction and other disorders is well known, but the crucial factors that lead to such prevalence are not fully understood. It is clear that obesity occurs when energy intake outweighs energy expenditure. However, this does not explain why some people do not gain weight rapidly despite a highly calorific diet and sedentary lifestyle, while other individuals quickly become obese with only a small energy surplus.

The energy balance is determined by various factors, such as dietary composition, exercise levels, physiology and an individuals' particular pattern of biochemical lipid and fat pathways. Some of these factors can be manipulated quite readily, while others are almost beyond control. However, it has been known for some time that obesity can result from an increase in the size of fat cells and, recently, it was discovered that the number of fat cells can also increase. This discovery, coupled with a growing need to overcome the problems of obesity in the developed world, has led to a burgeoning of research in the field[2].

Adipogenesis

Klemm's team has spent the past three years researching adipogenesis (fat cell development), in an attempt to understand how it is controlled and, ultimately, to provide clues for the development of drugs to treat obesity. Most fat cells are an important component in regulating metabolism: for instance, mature fat cells generate the signal that tells the brain that the body does not need food. In some types of obesity, fat cells get 'stuck' in an immature state, so that this message can never be sent, causing the body to increase the rate of fat cell production. This signal is relatively complicated involving numerous proteins to trigger the expression of other proteins that are involved in converting pre-adipocytes into fat cells.

Klemm and his colleagues have hypothesized that the transcription factor (CREB) might be crucial for initiating adipogenesis. This was based on the fact that CREB's phosphorylation and activity are stimulated by other factors, such as insulin, which are known to be involved in adipocyte differentiation. Furthermore, CREB might be involved in nerve growth and fibroblast development. Together with other circumstantial evidence, including the formation of virus-induced tumour growth via CREB activation, this strongly implicates CREB as the regulator of fat and other cell proliferation and differentiation processes[3].

The team began looking more closely at how CREB might function in triggering fat cell proliferation and development, and found that CREB is always expressed in 3T3-L1 fibroblasts prior to adipogenesis. They also showed that treatment of cultured cells with the known differentiation factors, insulin, dibutyryl-cAMP and dexamethasone, leads to rapid phosphorylation and activation of CREB. In addition, differentiation could be induced without the these factors in stable transfected 3T3-L1 cells that had been specifically engineered to always express an active form of CREB called VP16-CREB. Adipogenesis could also be inhibited using dominant-negative KCREB, the 'inverse' factor, which inhibits the activity of CREB already present in the cells.

Thus, Klemm explains that CREB activation is sufficient to initiate the adipocyte differentiation process. This suggests that CREB plays an important role in obesity as, without CREB, fat cells would not develop. Hence, any compound that can inhibit CREB activity might act as an inhibitor of obesity. The gene-promoting proteins to which CREB binds to trigger adipogenesis are now being investigated by the team with a view to unravelling more details of the mechanism underlying fat cell differentiation.

In preliminary experiments, overexpression of KCREB in cultured fat cells triggers the reverse process of differentiation. This might offer a further possibility for novel drugs to reduce obesity and associated disorders by reversing the development of fat cells.

REFERENCES

1 Klemm, D.J. *et al.* (2000) CREB activation induces adipogenesis in 3T3-L1 cells. *Mol. Cell Biol.* 20, 1008–1020

2 Spiegelman, B.M. and Flier, J.S. (1996) Adipogenesis and obesity: Rounding out the big picture. *Cell* 87, 377–389

3 Yarwood, S.J. *et al.* (1998) Cyclic AMP potentiates growth hormone-dependent differentiation of 3T3-F442A pre-adipocytes: Possible involvement of the transcription factor CREB. *Mol. Cell. Endocrinol.* 138, 41–50

David Bradley

URL: http://sciencebase.com

1359-6446/00/$ – see front matter PII: S1359-6446(00)01473-2