HIGHLIGHT

Pygmy mouse gene mutation protects against obesity

J P Berg

*Hormone and Central Laboratory, Aker University Hospital, Trondheimsveien 235, 0514 Oslo, Norway**(Correspondence should be addressed to J P Berg; Email: j.p.berg@ioks.uio.no)*

Of the four spontaneous mouse mutations resulting in impaired growth, the pygmy mouse is extraordinary because it has no aberrations in pathways involving growth hormone or insulin-like growth factors. The pygmy phenotype is caused by a defect in the *HMGI-C* gene, which is a member of the HMGI family of proteins (1, 2).

HMGI proteins belong to a general class of high mobility group (HMG) DNA binding proteins (reviewed in (3)). These are ubiquitous and abundant non-histone nuclear proteins and are divided into three subfamilies. The HMG-1/-2 subfamily has the HMG-1 box as its major functional motif, which consists of approximately 80 amino acids. The box binds DNA to the minor groove and induces specific DNA deformations. A nucleosomal binding domain is the functional motif in the HMG-14/-17 subfamily. Two molecules of HMG-14 or HMG-17 bind to the nucleosome core, which is the building block of the chromatin fibre, and change the chromatin structure. The HMGI group is the third subfamily and consists of HMG-I and HMG-Y, which are encoded by the same gene and made by alternative splicing, and HMGI-C. The functional domain of these proteins is the AT hook, which is made of nine positively charged amino acids. They bind to the minor groove of DNA with relatively low specificity with regard to the DNA sequence, and preferentially to the sequence AA(T/A)T. The proteins are a part of the structural elements of metaphase chromosomes. HMGI proteins may attenuate the inhibitory effect of the nuclear protein histone H1 on transcription by displacing H1 from DNA. They can also affect embryonic development by interfering with homeodomain binding proteins. In addition, the HMGI proteins can modulate the transcription of several genes. They may enhance or repress transcription by direct DNA interactions or by binding to specific transcription factors. Stimulatory effects of HMG-I/Y on transcription have been studied in detail on the virus-inducible enhancer of the interferon- β gene. Binding of HMG proteins stabilises DNA and specific transcription factors in a higher order nucleoprotein complex called an enhanceosome (reviewed in (4)).

The expression of *HMGI-C* has been studied in detail in mouse embryos (5). At an early embryonic stage *HMGI-C* mRNA is found in all tissues, whereas the pattern of expression is restricted particularly to mesenchymal derivatives, some epithelial cell layers,

and parts of the central nervous system in the second half of embryonic development.

HMGI-C expression is normally not detected in adult tissues from humans or mice (5, 6). However, *HMGI-C* mRNA is frequently found in solid tumours in humans such as lipomas, pleomorphic adenomas of the salivary gland, uterine leiomyomas, and lung hamartomas. It has been shown that these tumours often have chromosome 12 rearrangements, which directly affect the *HMGI-C* gene on this chromosome (7). Expression of *HMGI-C* seems to be linked to proliferation both in normal embryos and in tumour cells.

In a recent paper, Anand & Chada (8) showed that the expression of *HMGI-C* in fat depots from normal mice was detectable after 1 week of a high-fat diet. Expression of the gene was also observed in fat from the genetically obese mouse strains *Lep^{ob}/Lep^{ob}* and *Lepr^{db}/Lepr^{db}*, which lack leptin or its receptor, respectively. Adipose tissue from normal mice on a standard diet did not express the gene. The data indicated a role for *HMGI-C* in obesity. This was further elaborated by feeding a strain of pygmy mouse carrying two non-functional *HMGI-C* alleles (*Hmgic*^{-/-}), heterozygotes (*Hmgic*^{+/-}), and wild-type mice with standard or high-fat diets. Interestingly, both the *Hmgic*^{-/-} and the *Hmgic*^{+/-} mice did not increase in weight on a high-fat diet compared with the controls on a standard diet, whereas the wild-type mice increased in weight compared with their controls as expected. On a standard diet, the weight of the heterozygotes was not significantly different from the wild-type mice. There were no differences in food intake. The observations indicated that lack of one or both of the *HMGI-C* alleles may protect against obesity induced by a high-fat diet and there seemed to be a haploinsufficiency effect of *HMGI-C*.

Anand & Chada (8) also studied effects of *HMGI-C* in the genetically obese *Lep^{ob}/Lep^{ob}* mice, which lack a functional *leptin* gene, by knocking out their *HMGI-C* gene also. Lack of *HMGI-C* resulted in a remarkable resistance against obesity, and the weights of the mice were only 27% of those of the *leptin*-deficient controls by 30 weeks of age. In comparison, the weights of the *Hmgic*^{-/-} mice with a normal *leptin* gene were 47% of those of the wild-type controls. *Leptin*-deficient mice, which were heterozygous for the *HMGI-C* null mutation, had reduced expression of *HMGI-C* and their weights were 72% of those of the *HMGI-C* heterozygotes

with a normal *leptin* gene. Greatest weight reduction was observed in the mesenteric fat pads. Both the appearance of the adipocytes and the expression of genes involved in adipogenesis were similar in *leptin*-deficient mice with or without functional *HMGI-C*. The decrease in fat-pad weight was therefore most likely to have been caused by a reduction in cell number. Although the absence of functional *HMGI-C* attenuated the weight increase in *leptin*-deficient mice, they were still heavier than wild-type mice, indicating that there are pathways for adipocyte proliferation independent of *HMGI-C*.

Absence of *HMGI-C* reduced the accumulation of fat normally observed in the *leptin*-deficient mice, but other phenotypic characteristics of *leptin* deficiency were still present. As evaluated by the concentrations of plasma insulin and glucose, and glucosuria, the relatively lean double-homozygous *HMGI-C* and *leptin*-deficient mice were as insulin resistant as their obese *leptin*-deficient relatives with a normal *HMGI-C* gene. The study by Anand & Chada (8) indicates that insulin resistance in the *Lep^{ob}/Lep^{ob}* mouse is primarily caused by *leptin* deficiency and not by obesity, and indirectly supports the findings of previous studies in which anti-diabetic effects of *leptin* have been demonstrated ((9); reviewed in (10)).

HMGI-C facilitates the interaction between transcription factors and DNA, and seems to determine the growth potential of pre-adipocytes. The absence of *HMGI-C* expression in normal adult tissues, the appearance of *HMGI-C* in adipose tissue in obesity, and

the gene-dosage effect observed in the studies of Anand & Chada (8) makes *HMGI-C* an ideal peripheral target for the treatment of obesity and a complement to interventions aimed at appetite suppression.

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