Courting melanocortin

By Lev Osherovich, Senior Writer

A pair of genome-wide association studies makes the case that mutations near the melanocortin 4 receptor locus are common determinants of obesity in humans.^{1,2} The studies may encourage discovery efforts in the obesity space by at least two biotech companies, **Palatin Technologies Inc.** and **Action Pharma A/S**, that focus on targeting melanocortin receptors. However, the specific mutations that underlie the high-risk locus have not yet been identified, leaving the therapeutic path still unmapped.

The G protein-coupled receptor melanocortin 4 receptor (MC4R) is found throughout the nervous system, where it integrates signals from a variety of peptide hormones to regulate feeding behavior and libido. In mice, disruption of MC4R causes severe obesity and metabolic syndrome, whereas humans with rare loss-of-function mutations have hereditary hyperphagia (a propensity to overeat) and early-onset obesity.³

However, the importance of MC4R in body weight and obesity among the overall population was, until now, unknown. “MC4R has a well-established role in hereditary obesity, but until now there has been no association between MC4R and common obesity,” said Inês Barroso, team leader at the **Wellcome Trust Sanger Institute** and an author on one of the two MC4R papers in *Nature Genetics*.

The second study, from a team led by Jaspal Kooner, clinical senior lecturer at **Imperial College London**, found a similar linkage between the MC4R locus and increased waist circumference. Kooner’s study used data from Indian Asian males living in the U.K. and Europe.

SNP to it

Barroso led an international consortium that reported the identification of a SNP in the neighborhood of the MC4R locus associated with elevated body mass index (BMI). BMI is the ratio of weight to the square of height. People with BMI over 25 are considered overweight; a BMI of 30 indicates obesity.

To find the MC4R locus, the team reviewed SNP data from four previously published population studies in a total of 16,876 people. Barroso then replicated the results with data from 16 other population studies and 8 SNP studies of obese patients.

Ultimately, Barroso’s study used SNP data from about 90,000 people. The data pointed to a variant SNP located 188 kilobase pairs

away from the coding region of MC4R, on chromosome 18. Homozygous carriers of the high-risk SNP were on average 1.5 kg heavier and had a 0.1 unit increase in BMI. This compares with an average 3.5 kg increase in weight associated with risky versions of the *FTO* (*Fatso*) gene, according to Barroso.

FTO is another obesity gene that has been identified in genome-wide association studies.⁴ However, that gene encodes a DNA demethylase with poor prospects for druggability.⁵

Barroso told *SciBX* that the modest effect of the MC4R risk allele reflects the multifactorial nature of obesity.

“Common obesity is the result of interactions between many genetic loci and environmental factors. The MC4R variants that we found only explain a very small proportion of the obesity,” she said.

However, this modest effect on average weight correlated with a higher risk of obesity-related pathology than that for noncarriers.

For example, Barroso’s study showed that in children, the MC4R-linked SNP raised the risk of severe obesity and had a more pronounced effect on BMI and body fat than it did in adults. Compared with in adults, the effect of the risky allele on BMI in children aged 7–11 was twice as large. Also, children who were homozygous carriers had a 62% greater likelihood of morbid obesity than noncarriers.

The Kooner study found that a SNP near MC4R gave homozygous carriers a 2 cm greater waistline and a 10% higher score for insulin resistance compared with what was seen in noncarriers. The risky version of the SNP was found more often in Indian Asians

than in a control group of people of European descent.

The physical proximity of the obesity-linked SNPs to the MC4R locus makes it highly probable that MC4R activity is somehow altered in carriers, according to Barroso. However, the specific mutation that is hiding near the risk-associated SNP still needs to be uncovered.

Barroso suspects the culprit is a mutation in the transcriptional regulatory region adjacent to MC4R rather than a mutation in the gene itself. Likewise, the SNP identified by Kooner was near but not within the coding region of the *MC4R* gene. At this point it is unclear whether the mutations identified by the two studies are the same thing or two independent mutations with similar effects.

A wider market

Companies working in the melanocortin receptor space told *SciBX* that the *Nature Genetics* studies support the use of MC4R therapeutics to treat obesity in the general population—not just in people with rare hereditary disorders. However, choosing specific therapeutic strategies will require teasing out the underlying mutations and their effects on MC4R activity.

“You couldn’t get a better assessment of the importance of MC4R in obesity and diabetes” than these two papers, Palatin CEO Carl Spana told *SciBX*. Palatin is developing compounds that modulate

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—Inês Barroso,
Wellcome Trust Sanger Institute

melanocortin receptors to treat obesity, appetite disorders and sexual dysfunction.

The discovery that natural variation in MC4R influences diabetes risk makes it a potential prophylactic target, he added.

Palatin's lead compound is bremelanotide, an agonist of MC4R that completed Phase II testing to treat erectile dysfunction (ED) and was in Phase I testing to treat female sexual dysfunction. On May 13, the company discontinued further development for sexual dysfunction and will instead repurpose bremelanotide for hemorrhagic shock.

Palatin also has several MC4R agonists and antagonists in preclinical development for obesity that are partnered with **AstraZeneca plc**. Spana told *SciBX* that Palatin is "at the final selection of a lead compound" and plans to enter Phase I trials for obesity in early 2009.

Spana also noted that targeting MC4R is on the border between metabolic and psychiatric medicine. He said MC4R differs from most obesity targets in that it affects food craving rather than insulin secretion or energy utilization. Manipulation of melanocortin receptor activity could lead to "behavior modification," according to Spana.

"Whether people want to admit it or not, this is about a behavior problem that develops into a medical problem," he said.

Soren Nielsen, CEO of Action, said the findings "strongly enforce our current strategy to develop compounds targeting MC4R." The challenge, he said, is to develop highly specific, orally available agonists of the receptor.

Action's AP1030, an MC4R agonist, is in Phase I trials to treat type 2 diabetes and obesity.

Barroso and Spana agreed that the next step is to identify the specific

mutation associated with obesity in carriers of the risky SNPs. Although the overwhelming odds are that the obesity-associated SNPs will correlate with lower MC4R activity, this has not been formally proven.

Barroso said the way to resolve the question is to sequence the DNA of selected carriers.

"We're trying to refine the association signals by sequencing to the underlying cause" of the elevated risk, she told *SciBX*.

Because Barroso's study required SNP data from many other independent studies, she said a precondition for using the data was to "agree not to file for IP" protection. The IP status of Kooner's work is undisclosed.

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