Cellular and molecular aspects of weight regulation: the adipose tissue

Research into the etiology of obesity may provide novel or better means for treatment or prevention. However, obesity is more complex than originally thought and research might involve various disciplines ranging from genetics, proteomics and metabolomics to public health and social sciences. This thesis provides more insight on how molecular and genetic information may assist the regulation of weight.

Scientific gain of this thesis

In this thesis we have found that:

(1) We found that during weight loss, adipocytes increase their capacity for glucose uptake by reduced GLUT4 scavenging and increase their uptake of fatty acids. In other words, they are preparing themselves to get more energy in and store fat again, which will contribute to weight regain. When we can further prove this hypothesis, such knowledge will enlarge the awareness of people that after weight loss they need to take extra measures to prevent weight regain. “A very low calorie diet makes adipocytes scream for fat”
(2) We have shown that mature adipocytes spend a lot of their energy on sustaining and renewing the extracellular matrix (ECM). When adipocytes lose fat, mechanical stress builds up between the ECM and the cell. Refilling of the adipocytes removes adipocyte cellular stress. Studying the ECM during weight loss may lead to the identification of risk markers for weight regain after weight loss.
(3) Proteomics of adipocytes during weight loss has provided candidates for genetic association studies, which may lead to the identification of genetic risk factors for weight gain and regain.
(4) The investigated single nucleotide polymorphisms or so called SNPs in FTO in men and MMP2 in women are associated with weight gain over a 10 year follow-up period. A genetic risk profile could be generated to select people that are at high risk of weight gain, who can then be given better guidance of weight regulation.

Innovation

The present thesis presents various novel findings and insight. We were able to use proteomics to show the great devotion of adipocytes to maintaining their extracellular matrix, which is in line with an active role of the ECM in the model that proposes adipocyte cellular stress as a driver of weight regain. Further we were able to use a systems proteomics approach to get an overview of the various lipid and glucose handling segments of the adipocyte cellular metabolism. This resulted in the detection of several biomarkers for weight loss-maintenance. Further, the importance of a molecular mechanism of glucose uptake-regulation in the regulation of adipocyte lipid turnover was revealed including the action of aldolase, annexinA2, and tubulinB5. Importantly, our observations showed that during weight loss, adipocytes prepare for uptake of glucose and fatty acids, which provides a risk condition for weight regain after weight loss. It is important that weight loss candidates are aware of this response of their fat tissue. Further, in this thesis we have shown that proteomics analysis can provide candidate proteins/genes for genetic risk assessment via cohort studies. Several genetic biomarkers were found in this thesis with risk alleles for long term weight gain in men and women. These polymorphisms and the found biomarkers could add to a genetic risk profile for weight regulation. A gender difference as observed here is not uncommon for research on weight regulation, but it underscores the importance for setting up sex-specific guidelines for weight loss and maintenance.

Stakeholders in regard to knowledge application

The most important target group is society itself. The scientific gain of this thesis will on the long term help to fight obesity by treating the overweight and obese subjects for weight loss. As such it will contribute to the reduction of the health burden for society. In fact, our knowledge can be incorporated with the current treatment and other new developments to offer a specific, personalized guideline to subjects who aim to lose weight. This will enhance the efficiency of the weight loss treatment and of weight maintenance. For example, subjects with a genetic profile predisposing to long-term weight gain should receive a more stringent and/or frequent guidance than those with a low number of genetic risk polymorphisms. To ultimately achieve this, high quality prediction models are a necessity, because the genetic predisposition of overweight and obesity is extremely complex with a great deal of individual genetic variation. Such models can be more easily worked out by collaborative actions between research groups and companies to explore large-scale genome data.

Dissemination

Knowledge dissemination can be done by delivering prediction models and treatment guidelines to trained dieticians, specialists of hospital and obesity clinics such as Co-Eur (http://co-eur.com). Also it is possible to compose and monitor a complete overview of the health status and personalized guidelines for subjects, for instance in collaboration with companies such as Pre-Scan, a company specialized in preventive medical research (http://www.prescan.nl). Alternatively, the newly gained knowledge can be a starting point of a spin-off company of the university. The goal of such an undertaking would be personalized nutrition, a tailor made nutrition advice, which is based on the genetic, proteomics and metabolomics background of the subject. This tailor made advice can be of interest for health insurance companies. It could reduce the health care costs by combating the obesity epidemic. A good example of the possibilities of personalized nutrition is the use of plant sterol containing food products to lower the plasma cholesterol level [4].
It should be realized that using knowledge from the present thesis in setting up/supplying agencies for personalized advice on weight loss/maintenance that the use of genomic and genetic information is subject to ethical regulation, which may restrict the actual applications. One of the dangers is the chance of unexpected findings such as genetic predisposition to life-threatening conditions in the genetic data. On the other hand, it may be regarded a positive aspect of genetic analysis that such risk can be discovered before actual symptoms occur, but this is only beneficial if treatment is available. Those and other questions have still to be worked out for a complex trait as overweight and obesity. One example is 23andMe, a company giving personalized advice based on genome variation, which last year was severely restricted in their commercial activities because of privacy reasons.

Summary and realization

Valorization requires collaboration among research groups within and outside the university and with the industry, which can form the basis for spin-off companies and knowledge-transfer agencies, in which the social media will play an important role. This collaboration will provide more data and novel ideas, and leads to gain more, better and accurate insight in the health and risk condition of each individual. Our findings are a starting point in this respect, but further research is needed. Newer techniques like detailed proteome quantification and exome sequencing are getting better and cheaper. Nowadays it is possible to get a complete human genome sequenced for 1000 dollar and it will get even more cheaper in the future. Besides ethical consideration in the application of

research findings, the data generated by modern techniques is enormous. Therefore, bioinformatics and biostatistics with a focus on modelling will play a huge role in the process of from data to application.

A reliable individual predictive profile for weight regulation can be available within the next 5 years for society. In the end, however, people should still worry about what they eat and keep sufficient physical activity, because you can't change your genes, but you can change your behavior.

References

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