

DANONE
**INTERNATIONAL
PRIZE FOR
NUTRITION**



7TH DANONE INTERNATIONAL PRIZE FOR NUTRITION

An important discovery rewarded

Some foods do more than just nourish our body; they also communicate with our cells, giving orders, for instance, to shed fat from adipose tissue, in similar fashion to certain hormones. This communication system, hitherto unknown, was revealed by Professor Johan Auwerx, thereby opening the way for new preventive and therapeutic strategies to combat obesity and cardiometabolic diseases such as type 2 diabetes and hypertension. The discovery earned him the prestigious *Danone International Prize for Nutrition* worth 120,000 Euros.



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7th Danone International Prize for Nutrition An important discovery rewarded

Bangkok, Thailand. October 6th, 2009 - **Belgian research scientist Johan Auwerx from the Federal Polytechnic School of Lausanne (Switzerland) has just received the *Danone International Prize for Nutrition* for his research in molecular nutrition. "I was delighted to learn that I had been awarded this prize, particularly since I was not expecting it. I am extremely honoured to receive this prestigious prize, following in the footsteps of previous prize winners Professors David Barker and Jeffrey Friedman, two internationally recognised leaders in the field of nutritional research."**

The underlying hypothesis of his research is that the nutrients* in our diet have a direct influence on transcription*. More precisely, the studies by Johan Auwerx focus on the mechanism of shedding of fat from adipose tissue*, thereby paving the way for new preventive and therapeutic strategies to combat obesity and cardiometabolic diseases* such as type 2 diabetes* and hypertension*. "We have discovered for instance that certain fatty acids activate specific nuclear receptors* within the cells of our body known as PPARs* (peroxisome proliferator-activated receptors)," continued the research scientist. "The latter play a major role in fat metabolism and thus offer a new approach to the treatment of insulin resistance* and the metabolic syndrome."

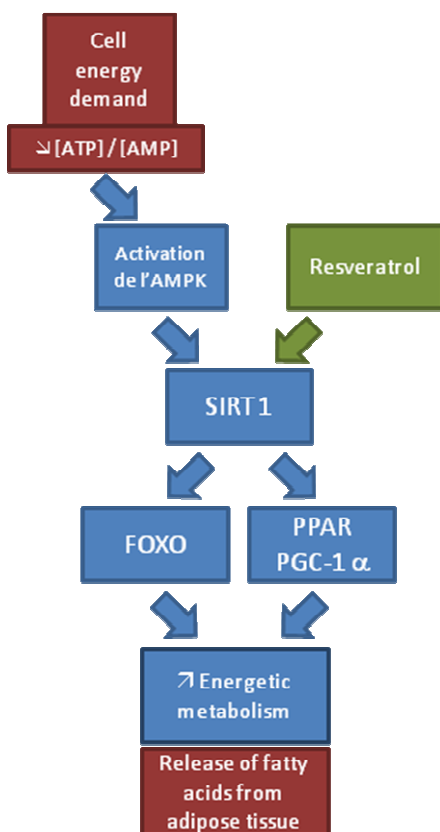


Figure 1: Activation of energy metabolism involving the sirtuin SIRT1. Certain nutrients such as resveratrol stimulate cellular energy demand by directly activating SIRT1.

Studies published in *Nature* and *Cell Metabolism*

Prof. Johan Auwerx is the author of numerous publications in internationally renowned journals, including *Nature* and *Cell Metabolism*. His studies have investigated certain transcription factors (e.g. nuclear factors such as PPARs) and transcription co-factors (e.g. sirtuins* or SIRT) that act as "molecular traps" for nutrients and intracellular metabolites. These proteins in fact play a dual role: they detect changes in concentrations of certain nutrients or metabolites in the environment and they react to this information by modifying transcription of the genes involved in metabolic control, thereby ensuring a suitable response.

In a recent issue of *Nature* in April 2009 [1], he describes the mechanisms by which transcription factors and co-factors allow the body to "sense" an energy deficit following long periods without food or prolonged exercise, before allowing the body to use this information to stimulate the release or production of energy from fat tissue (see diagram). His team showed that AMPK* (AMP-activated protein kinase), an enzyme sensitive to the ratio of ATP* to AMP* and involved in regulation in cellular energy status, controls gene expression involved in energy metabolism by stimulating another metabolic regulator, sirtuin SIRT1 (diagrams from the issue

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of *Nature* appended). The function of this enzyme is to activate the nuclear receptor PPAR PGC-1 α (peroxisome proliferator-activated receptor-gamma co-activator 1 alpha) as well as two Forkhead-type FOXO transcription factors. A few months earlier Prof. Auwerx' team had demonstrated the role of these agents in fatty acid metabolism. This discovery accounts for the numerous similar effects of AMPK and SIRT1 regarding energy metabolism: they enhance metabolic reactions that generate ATP (oxidation of fatty acids and carbohydrates) and reduce biochemical reactions that consume ATP (e.g. lipogenesis).

Specific activation of SIRT1 could thus stimulate fatty acid metabolism by mimicking energy demand, thereby protecting against obesity. Prof. Auwerx and his co-workers showed the ability of certain foods such as resveratrol [2] to specifically activate SIRT1. Other studies involving a synthetic substance were published in *Cell Metabolism* [3]. This molecule, obtained by Prof. Auwerx and his team, noticeably improved endurance in animals and provided considerable protection against obesity and diet-induced insulin resistance by increasing oxidative metabolism in skeletal muscle, liver and brown adipose tissue*. These studies provide an understanding of how to stimulate breakdown of fatty acids stored within the body, thereby preventing obesity and associated cardiometabolic risk.

120 000 € prize

In addition to the renown associated with the prize, currently recognised as the most prestigious in the field of nutrition, the *Danone International Prize for Nutrition* carries a financial reward of 120,000 €. "*This financial prize will allow us to continue our research work,*" explained Professor Auwerx. "*In particular, I will be working on vitamin B3*, which has long been known for its beneficial effects with regard to obesity. I have high hopes for this molecule, which could turn out to be even more interesting than resveratrol since it requires lower concentrations to combat obesity effectively.*"

Now that several years have gone by, previous prize winners such as Prof. David Barker (University of Southampton, UK, prize winner 2005) and Prof. Jeffrey Friedman (Rockefeller University, New York, USA, prize winner 2007), can attest to the research advances resulting from the *Danone International Prize for Nutrition*. "*The 120,000 € prize money allowed me to set up a new research group within Southampton University, in a bid to identify barriers to healthy food choices among young women,*" explained Prof. Barker, the 2005 prize winner. 2007 prize winner Prof. Jeffrey Friedman was equally enthusiastic: "*The Danone International Prize for Nutrition and the prize money of 120,000 € allowed us to begin a number of new research projects which would not have been possible without these funds.*"

“The equivalent of a Nobel Prize for nutrition”

Set up in 1997 by Danone, with the support of the Medical Research Foundation, the *Danone International Prize for Nutrition* forms one of the actions undertaken by the Danone Institute International in support of nutritional research. It should be noted that the Danone Institutes, set up by Danone in 1991, are designed to promote public health by developing and sharing knowledge concerning nutrition, diet and health.

The *Danone International Prize for Nutrition* has been awarded every two years since 1997 to a research scientist or research team conducting outstanding studies in human nutrition. The candidate selection procedure, based on that used for the Nobel Prize, is rigorous, objective and transparent. The *Danone International Prize for Nutrition* committee initially brings together an “electoral college” comprising several

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hundred representatives of leading institutions to promote nutritional research worldwide. Each member of the committee is asked to propose the election of one or two research scientist scientists (or research teams). An independent international jury comprising eight renowned scientists then chooses the prize winner on a majority basis." According to Professor Serrano Rios, President of the Danone Institute International, *"In my view, the Danone International Prize for Nutrition is nothing less than the equivalent of a Nobel Prize for nutrition."* This notion is shared by Danone CEO Franck Riboud: *"Today, we are very proud to see that the Danone International Prize for Nutrition is helping to promote research conducted by the foremost research teams in the fields of health and nutrition, and that it is viewed by scientists as one of the most prestigious awards in existence. This prize and the Danone Institute International offering this reward are both naturally in line with the Group's initiative to provide health through nutrition."*

References:

[1] AMPK regulates energy expenditure by modulating NAD⁺ metabolism and SIRT1 activity. Cantó C, Gerhart-Hines Z, Feige JN, Lagouge M, Noriega L, Milne JC, Elliott PJ, Puigserver P, Auwerx J. *Nature*. 2009 Apr 23;458(7241):1056-60.

[2] Resveratrol improves mitochondrial function and protects against metabolic disease by activating SIRT1 and PGC-1 α . Lagouge M, Argmann C, Gerhart-Hines Z, Meziane H, Lerin C, Daussin F, Messadeq N, Milne J, Lambert P, Elliott P, Geny B, Laakso M, Puigserver P, Auwerx J. *Cell*. 2006 Dec 15;127(6):1109-22.

[3] Specific SIRT1 activation mimics low energy levels and protects against diet-induced metabolic disorders by enhancing fat oxidation. Feige JN, Lagouge M, Canto C, Strehle A, Houten SM, Milne JC, Lambert PD, Matakis C, Elliott PJ, Auwerx J. *Cell Metab*. 2008 Nov;8(5):347-58.

Pr Johan Auwerx interview award of the 7th Danone International Prize for Nutrition



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Prof. Johan Auwerx (Federal Polytechnic School of Lausanne, Switzerland), 2009 winner of the *Danone International Prize for Nutrition*

Belgian research scientist Johan Auwerx from the Federal Polytechnic School of Lausanne (Switzerland) has just received the *Danone International Prize for Nutrition* for his discoveries concerning the mechanisms by which certain nutrients* "communicate" with our cells in similar fashion to hormones by issuing them with orders, for example to shed fat from adipose tissue*. This "weighty" discovery paves the way for new preventive and therapeutic strategies to combat obesity and cardiometabolic diseases* such as type 2 diabetes* and hypertension*.

You have just been awarded the *Danone International Prize for Nutrition*. What was your reaction to the announcement of this prize?

Naturally, I was delighted to learn that I had been awarded this prize, particularly since I was not expecting it. I am extremely honoured to receive this prestigious prize, following in the footsteps of previous prize winners Professors David Barker and Jeffrey Friedman, two internationally recognised leaders in the field of nutritional research. Finally, this recognition by my peers is also reassuring with regard to the research paths I have chosen to follow over the last eight years.

This prize, awarded by your peers on the expert committee set up for the occasion by the Danone Institute International, crowns years of research. Could you outline your main discoveries for us?

I have been working for a number of years on the mechanisms by which cells react to the nutrients present in the cellular environment. My studies show that the effects of these nutrients may in certain cases be more potent than those of hormones. This discovery completely changes our understanding of nutrition since it highlights the degree to which our body in general, and more particularly our cells, are able to adapt to their environment according to what we eat. The nutrients we absorb each day through our diet thus constitute a number of signalling factors able to trigger hormone-like reactions within our bodies.

Pr Johan Auwerx

What applications are there for your studies?

The applications for our studies are based on the hypothesis underlying all of our research, namely that nutrients in the diet have a direct influence on transcription* (the expression of genetic information). In concrete terms, we have been working on the development of foods enriched with certain nutrients, and on capsules containing even higher doses of these nutrients. We have discovered for instance that certain fatty acids* activate specific nuclear receptors within the cells of our body known as PPAR* (peroxisome proliferator-activated receptors). The latter play a major role in metabolism* and thus offer a new approach in the treatment of insulin resistance*.

Following this path, we found that resvératrol*, a polyphenol *found in grapes and wine and involved in the well-known *French Paradox**, also activates a PPAR type nuclear receptor. Resveratrol thus activates the mitochondria*, the cells' energy complex: under the effects of resveratrol, the body starts to burn up its reserves, and thus adipose tissue. However, the concentrations in natural products are extremely low, and in any case too low to produce any visible results on obesity. We therefore began work on developing a synthetic molecule and a capsule containing high concentrations of this substance.

So applications for your studies are mainly pharmaceutical in nature?

For a number of years, our studies effectively applied to the development of drugs. However, for some time now, there has been a clear change: at present, we are working increasingly with food manufacturers. In other words, we are moving from a cure perspective through drugs to one of prevention through nutrition. This is good news given that when obesity has developed, it is generally too late to act. Our current partnerships with the food industry should therefore have a positive impact on public health.

As winner of the *Danone International Prize for Nutrition*, you will receive a cash prize of 120,000 Euros.

Have you decided how this will be used?

This cash prize will allow us to continue our research. In particular, I intend to work on vitamin B3, which has long been known for its beneficial effects regarding obesity. For the moment, our research is limited to *in vitro* studies, i.e. in cultured cells. The 120,000 € prize should allow us to move on to the next stage, namely *in vivo* experimentation, and I have high hopes for vitamin B3*, which could prove more interesting than resveratrol since smaller concentrations are required to fight obesity effectively.

Your peers consider your research as novel and they refer to it as “molecular nutrition*”: are you happy with this definition?

The term “molecular nutrition” strikes me as a perfect description of the area of activity of my research. In addition, the previous winner of the *Danone International Prize for Nutrition*, Prof. Jeffrey Friedman, is a pioneer in the field of research in molecular nutrition. I see nutrition as one of the last pockets of resistance to molecular analysis, although today, many scientists are involved in this field and focusing on this new area of research.

The Danone International Prize for Nutrition, awarded by the Danone Institutes: supporting research since 1997

Every two years, the *Danone International Prize for Nutrition* is awarded to research scientists for their work. In addition to the international stature of the reward, which is currently recognised as one of the most prestigious in the nutrition field, the award carries prize money of 120,000 Euros allowing teams to continue their research. Below are testimonials of two previous prize winners, Prof. David Barker (University of Southampton, UK, prize winner 2005) and Prof. Jeffrey Friedman (Rockefeller University, New York, USA, prize winner 2007).

Every two years since 1997, the Danone Institute International, a non-profit organisation, has awarded the *Danone International Prize for Nutrition* to research scientists or research teams carrying out noteworthy studies in the field of human nutrition. This prize is awarded for innovative concepts and studies expanding the barriers of nutrition science, whether through fundamental or applied research. The candidate selection procedure, based on that used for the Nobel Prize, is rigorous, objective and transparent.

The *Danone International Prize for Nutrition* committee initially brings together a “nomination college” comprising several hundred representatives of leading institutions to promote nutritional research worldwide. Each member of the committee is asked to propose the election of one or two research scientist scientists (or research teams). An independent international jury comprising eight renowned scientists then chooses the prize winner, who will receive 120 000 Euros. “The *Danone International Prize for Nutrition*, with its 120,000 Euro cash award, also provides a formidable stimulus for the prize winners elected every two years since 1997,” indicated Prof. Serrano Rios, President of the Danone Institute International and of the Spanish Danone Institute. “In my view, it is nothing less than the equivalent of a Nobel Prize for nutrition.”

Pr David Barker interview



Prof. David Barker (University of Southampton, UK)

Winner of the 2005 *Danone International Prize for Nutrition*

Prof. David Barker, you were awarded the 2005 *Danone International Prize for Nutrition* for your research work. Could you tell us a few words about your main discoveries?

Twenty years ago I showed for the first time that people who had a low birth weight were at greater risk of developing coronary heart disease, hypertension*, stroke* and diabetes*. This is now widely accepted. It has led to a new understanding that chronic adult diseases are "programmed" by malnutrition in the womb. Malnutrition during development is known to cause life-long changes in the body's structure and physiology. In the Western world many babies are

malnourished because their mothers have unbalanced and monotonous diets, or because their mothers are either overweight or excessively thin. In the Third World many babies are malnourished because their mothers were chronically undernourished when they were young.

As a research scientist, what did you gain from the *Danone Nutrition Prize for International*?

I used the 120 000 € donation to establish a new research group in the University of Southampton whose aim is to determine the barriers to good food choices among young women. The award of this prize was followed by invitations to lecture around the world and this has helped to disseminate the results of my research throughout the nutrition community.

Pr Jeffrey Friedman interview



Prof. Jeffrey Friedman (Howard Hughes Medical Institute and Rockefeller University, USA) is the winner of the 2007 *Danone International Nutrition Prize*

Prof. Jeffrey Friedman, you were awarded the 2007 *Danone International Prize for Nutrition* for your research work. Could you tell us a few words about your main discoveries?

My laboratory identified a new adipocyte hormone that we decided to name leptin*. This discovery has led to the elucidation of a robust physiologic system that maintains fat stores at a relatively constant level. Leptin is a peptide hormone secreted by adipose tissue* in proportion to its mass. This hormone circulates in the blood and acts on the hypothalamus to regulate food intake and energy expenditure.

When fat mass decreases, plasma leptin levels fall stimulating appetite and suppressing energy expenditure until fat mass is restored. When fat mass increases, leptin levels increase, suppressing appetite until weight is lost. It is through this mechanism that total energy stores are stably maintained within a relatively narrow range.

Genetic defects in the leptin gene are associated with massive obesity in mice and some humans. Treatment with recombinant leptin markedly reduces food intake and body weight in these patients. The low leptin levels in patients with leptin mutations are also associated with multiple abnormalities including infertility, diabetes and immune abnormalities all of which are corrected by leptin treatment.

As a research scientist, what did you gain from the *Danone International Prize for Nutrition*?

The Danone Prize [120 000 €] allowed us to begin several novel lines of research that would not have been possible without these funds. In one study, we were able to add a radioactive metal to leptin which allowed us to follow leptin's distribution in the body in rodents and non-human primates. This study allowed us to define the mechanism by which leptin is metabolized in vivo and also revealed a surprising and important avidity of leptin for cells of the human system. This work has recently been accepted for publication.

In other ongoing studies, Danone funds are being used to develop a novel methodology that, if successful, will allow us to non-invasively modulate the activity of specific neurons in awake animals potentially allowing us to assess the effects of activating specific neural populations on feeding behaviour.

On a personal note, the Danone Prize has emerged as the most prestigious prize in the field of nutrition and I feel greatly privileged to have had my name added to the list of distinguished previous recipients.

The Danone International Prize for Nutrition and the Danone Institutes: one of Danone's commitment to health

In the beginning, there was the Danone group, already inherently permeated by the values of nutrition and health. In 1991, Danone decided to promote public health by developing and spreading knowledge about nutrition, diet and health, and set up its first Institute. Eighteen years later, there are now 17 Danone Institutes worldwide operating under the aegis of the Danone Institute International. The latter has been awarding the *Danone International Prize for Nutrition* every two years since 1997 to a research scientist or research team conducting noteworthy studies in human nutrition. This prize is today one of the Institute's key activities but also highlights Danone's long-standing commitment to nutrition and health.

The *Danone International Prize for Nutrition* has been awarded every two years since 1997 by the Danone Institute International. This prize is today one of the Institute's key activities and is completely in line with the Institute's original mission to promote health through the development and spread of knowledge about nutrition, diet and health.

The Danone Institute International: advancing knowledge on nutrition

The first Danone Institute was created in France in 1991 thanks to Danone's desire to go beyond its own products in order to promote health. This was an ambitious project, with the group seeking to create an independent and transparent non-profit association in order to promote public health by developing and spreading knowledge about nutrition, diet and health. To achieve this, Danone brought together eminent members from the scientific community (on the scientific committee), together with nutritional experts and Danone representatives (office), under the presidency of an independent scientist. This organisation is entirely free to use funds provided by the group. Seventeen years later, there are now 17 Danone Institutes worldwide that are funded by local Danone subsidiaries. The Danone Institute International is responsible for steering the network, which provides rich and continual exchange between the different countries. To date, over 900 research projects have been supported (with a global budget of 16 million Euros), dozens of educational programmes have been launched, and close to one hundred symposia organised.

Actions undertaken by the Institute include support for cutting-edge research, as carried out by the group itself, which has always invested heavily in research and development. In this respect, the *Danone International Prize for Nutrition* represents a key activity.



In the words of Prof. Serrano Rios

President of the Danone Institute International and Spanish Danone Institute

“The Danone International Prize for Nutrition is the equivalent of a Nobel Prize for nutrition”

“The Danone Institute actively supports research in health and nutrition, allowing advances to be made in the latter field. This may be seen in my own country, Spain,

where I am president of the national Danone Institute: many research projects are currently being conducted thanks to the financial support provided by the Institute. The Danone International Nutrition Prize, with its 120,000 € cash award, also provides a formidable stimulus for the winner of the prize, awarded every two years since 1997. In my view, it is nothing less than the equivalent of a Nobel Prize for nutrition. Our goal at the Danone Institute International is to create a true nutritional reference centre where all ideas concerning this domain may be freely exchanged and debated.”

Nutrition and health: long-standing Danone values

Since its inception, Danone has always been closely associated with nutrition and health and has always demonstrated complete commitment to these activities at every stage of its history. Already in 1789, the Marquis de Lessert discovered the health benefits of Evian water. In 1881, Joseph Léon Jacquemaire, a pharmacist in Villefranche-sur-Saône, and his associate, Maurice Miguet, founded a laboratory to carry out food research, particularly concerning baby foods, and this resulted in the foundation of Blédina, the infant nutrition department, in France. In 1919, Isaac Carasso supplied pharmacies in Barcelona with the first Danone yoghurts for children with digestive problems. These yoghurts were manufactured using bacteria provided by the Institut Pasteur.

Danone continues to develop health-related products: fresh products (Actimel, Danacol, etc.), mineral waters and products for children (growth milk enriched with iron, cereals, fruit desserts, etc.), as well as clinical nutrition products sold through pharmacies and hospitals for sick, undernourished or elderly patients.

Research is a major pillar of Danone's innovation strategy concentrated within the Danone research centre – Danone Research – with more than 1,200 employees. For example, Danone Research enables the company to identify nutritional deficits in countries in which the group has operations, adapt the nutritional quality of its products accordingly, and offer products tailored to local cultural specificities (taste, circumstances of consumption, portions, etc.), demonstrate the health benefits of its products, etc.

Furthermore, in order to develop scientific knowledge within a specific domain, Danone Research creates partnerships with many internationally renowned institutions (e.g. Institut Pasteur, University of Washington, etc) in areas including probiotics, infant nutrition and medical nutrition.

Danone Institutes

Nutrition and health: at the heart of Danone's corporate governance

Nutrition and health are formally part of Danone's corporate governance as attested by its Food, Nutrition and Health charter based on five fundamental commitments;

- develop products that meet consumers' needs in term of nutritional content, taste and affordability
- strive to develop products with relevant and scientifically proven health benefits, providing consistent nutritional profile,
- inform consumers in a clear and factual manner through nutritional labeling and consumer-friendly claims, as well as to advertize responsibly, especially toward children,
- engage with consumers and local communities, including employees, on nutrition, balanced diets, physical exercise, and healthy lifestyles,
- address major public health and nutrition-related societal challenges through active dialogue with stakeholders , societal innovation and special care to environment.

The Danone Institutes and their projects actively and independently contribute to these commitments through their multiple programmes to support research and provide health care and education professionals with information.



Interview with Franck Riboud
CEO of Groupe Danone

"Health has always been of primordial concern in Danone products"

What is the place of the *Danone International Prize for Nutrition* in the Group's policy?

Health has been historically linked to Danone products. Research has consistently been a major pillar of the Group in meeting its objective to provide consumers with products combining optimal flavour, nutritional benefits and safety guarantee. Beyond our investments to promote research for our own products, it is also essential to support academic research in the field of nutrition, since this activity opens up new avenues for improving health in various populations. For this reason, we actively support the Danone Institutes, one of whose goals is to promote research, and consider the *Danone International Nutrition Prize*, awarded for particularly innovative studies, to be a key initiative.

Other prizes exist for innovative research in the field of nutrition. What sets the *Danone International Prize for Nutrition* apart?

The selection procedure, under the responsibility of renowned scientists, is based on the model of the Nobel Prize, thereby ensuring complete independence, objectivity and transparency. Today, we are proud that through the sizeable cash award, the *Danone International Prize for Nutrition* contributes to the development of novel research among the most innovative teams in the field of nutrition, and that it will helps to highlight the central importance of nutrition, and thus of diet, to health.

Glossary

- **Cerebrovascular Accident (CVA)**

CVA, or stroke, is a deficiency in the oxygenation of the brain due to a blood clot or brain hemorrhage that may be fatal. Hypertension is the principal risk factor for CVA.

- **Fatty acids**

Fatty acids are lipid nutrients more commonly referred to as fats.

- **Adipocytes**

Cells specialized in the storage of fats and localized in fatty tissue. Adipocytes constitute the body's energy reserve.

- **Adenosine monophosphate (AMP)**

AMP is a molecule present in cells and involved in their energy metabolism. Elevation of AMP levels is, in particular, related to the energy requirements of the cell.

- **AMP-activated protein kinase (AMPK)**

AMPK or adenosine monophosphate-activated protein kinase is an enzyme that contributes to the regulation of energy status (via the ATP/AMP ratio). In particular, AMPK controls the expression of genes involved in energy metabolism by stimulating another metabolic regulator, sirtuin (SIRT1).

- **Adenosine triphosphate (ATP)**

ATP is a molecule present in cells and involved in their energy metabolism. The chemical compound contains energy-rich bonds (phosphate bonds) that supply the energy necessary for the cell's numerous chemical reactions.

- **Diabetes, type 2**

Type 2 diabetes (formerly called non-insulin-dependent diabetes mellitus (NIDDM), or adult-onset diabetes) is a disease that affects the regulation of glycemia, the glucose level in the blood, due to insulin resistance or insulin deficiency. Type 2 diabetes is a metabolic disease mainly observed in people above 40 years of age, people who are chronically overweight and/or have pertinent family history. The disease may result in blindness, kidney failure and, if not treated, amputation.

- **French Paradox**

The expression refers to the fact that the French, despite eating a relatively high-fat diet, have an exceptionally low cardiovascular mortality rate. The French diet and, in particular, the consumption of wine, which is rich in antioxidants, have been suggested as a possible explanation for the phenomenon.

- **Energy homeostasis**

Energy homeostasis is an internal equilibrium of the body that enables appropriate energy supply to the cells, thus ensuring that the body functions correctly.

- **Hypertension (HTN)**

Hypertension is high blood pressure in the arteries. The main risks associated with hypertension are cardiac,

Glossary

neurological and renal complications. Hypertension is defined as a blood pressure greater than 140/90 mmHg (or 14/9) when a person has no other co-morbidities such as diabetes.

- **Insulin resistance**

It is thanks to insulin that glucose, the energy required by cells in order to function properly, can enter the cells. Insulin resistance is the resistance of cells to the action of insulin, resulting in accumulation of glucose in the blood. The accumulation is toxic for the body. Insulin resistance is one of the principal causes of type 2 diabetes.

- **Leptin**

Leptin is a hormone secreted by the cells in adipose tissue (adipocytes). The hormone acts on the brain (hypothalamus) and contributes to the regulation of food intake and energy expenditures. Leptin was discovered thanks to the work of Prof. Friedman, who received the Danone International Nutrition Prize in recognition of his body of work in 2007.

- **Cardiometabolic diseases**

The expression, 'cardiometabolic diseases', covers all cardiovascular and metabolic diseases including hypertension, dyslipidemia, type 2 diabetes and obesity.

- **Metabolism**

The term, 'metabolism' covers all the physical, chemical and biological transformations undergone by the compounds taken into or formed in the body in order to ensure that it functions correctly.

- **Mitochondria**

The mitochondria are intracellular structures that enable synthesis of the cell's principal energy source, ATP, from nutrients transported by the blood.

- **Nutrient**

A nutrient is any substance contained in a food and used by the body to cover its physiological needs. Energetic nutrients - lipids, carbohydrates and proteins – are to be distinguished from non-energetic nutrients, such as minerals and antioxidants (e.g., resveratrol).

- **Molecular nutrition**

Molecular nutrition is the science that studies the relationships between nutrients and the variations in the expression of certain genes at cellular level. Molecular nutrition is also called nutrigenomics.

- **Peroxisome Proliferator-Activated Receptors (PPAR)**

Peroxisome proliferator-activated receptors are a series of nuclear receptors that act as transcription factors for energy metabolism genes. The PPAR play a major role in lipid metabolism and are particularly exploited in the treatment of diabetes and metabolic syndrome.

- **Polyphenols**

Polyphenols, organic molecules found in plants, are natural antioxidants that are associated with a reduction in the risk of certain chronic diseases. Polyphenols are attracting particular research interest in the fields of prevention and treatment of certain forms of cancer, as well as inflammatory, cardiovascular and neurodegenerative diseases.

Glossary

- **Nuclear receptors**

Nuclear receptors, proteins present in the cell's nucleus, enable the cell to adapt the expression of target genes, particularly as a function of the nutrients present in the body. PPAR are a well known series of nuclear receptors. They are activated by transcription co-factors such as the sirtuins, which are themselves activated by nutrients such as resveratrol.

- **Resveratrol**

Resveratrol is a polyphenol that occurs naturally in grapes and wine. The hypothesis that a moderate wine intake may have a beneficial effect on human health is based on the effects of resveratrol on cell metabolism.

- **Sirtuin**

The sirtuins are a series of enzymes whose role is to modulate the expression of genes involved in the cell's energy status. Sirtuins are transcription co-factors that act as 'molecular captors' for nutrients and intracellular metabolites. Sirtuins play a dual role: they record the changes in the environmental concentrations of certain nutrients and metabolites, and they translate that information by modifying the transcription of genes involved in metabolic control, thus ensuring appropriate adaptation.

- **Sirtuin 1 (SIRT1)**

The sirtuin enzyme, SIRT1, is an important regulator of metabolic processes, including, in particular, intracellular fatty acid metabolism and energy production. SIRT1 is activated in response to cellular calorie restriction. Recent studies, particularly those conducted by Prof. Auwerx, have shown that SIRT1 is activated by resveratrol.

- **Adipose tissue**

Adipose tissue constitutes the body's fat store and mainly consists of cells specialized in fat storage: adipocytes.

- **Transcription**

Transcription is the mechanism that enables cells to produce RNA from the DNA template contained in the cell nucleus. The mechanism involves numerous enzymes, transcription factors and co-factors. The RNA thus generated is translated into the proteins indispensable for cell life.

- **Vitamin B3 (vitamin PP, niacin or nicotinic acid)**

Vitamin B3 is a water-soluble vitamin necessary for the metabolism of carbohydrates, lipids and proteins. Vitamin B3 plays an important role in the activation of sirtuins, particularly SIRT1. Fish, white meat and liver are the principal food sources of vitamin B3.

Pr Auwerx team's latest publications

AMPK regulates energy expenditure by modulating NAD⁺ metabolism and SIRT1 activity. *Nature*, 2009

AMP-activated protein kinase (AMPK) is a metabolic fuel gauge conserved along the evolutionary scale in eukaryotes that senses changes in the intracellular AMP/ATP ratio¹. Recent evidence indicated an important role for AMPK in the therapeutic benefits of metformin, thiazolidinediones and exercise, which form the cornerstones of the clinical management of type 2 diabetes and associated metabolic disorders. In general, activation of AMPK acts to maintain cellular energy stores, switching on catabolic pathways that produce ATP, mostly by enhancing oxidative metabolism and mitochondrial biogenesis, while switching off anabolic pathways that consume ATP¹. This regulation can take place acutely, through the regulation of fast post-translational events, but also by transcriptionally reprogramming the cell to meet energetic needs. Here we demonstrate that AMPK controls the expression of genes involved in energy metabolism in mouse skeletal muscle by acting in coordination with another metabolic sensor, the NAD⁺-dependent type III deacetylase SIRT1. AMPK enhances SIRT1 activity by increasing cellular NAD⁺ levels, resulting in the deacetylation and modulation of the activity of downstream SIRT1 targets that include the peroxisome proliferator-activated receptor- α coactivator 1 α and the forkhead box O1 (FOXO1) and O3 (FOXO3a) transcription factors. The AMPK-induced SIRT1-mediated deacetylation of these targets explains many of the convergent biological effects of AMPK and SIRT1 on energy metabolism.

To read, double-click on the document below:



Publication Nature
2009

Specific SIRT1 Activation Mimics Low Energy Levels and Protects against Diet-Induced Metabolic Disorders by Enhancing Fat Oxidation, *Cell Metabolism*, 2008

The NAD⁺-dependent deacetylase SIRT1 controls metabolic processes in response to low nutrient availability. We report the metabolic phenotype of mice treated with SRT1720, a specific and potent synthetic activator of SIRT1 that is devoid of direct action on AMPK. SRT1720 administration robustly enhances endurance running performance and strongly protects from diet-induced obesity and insulin resistance by enhancing oxidative metabolism in skeletal muscle, liver, and brown adipose tissue. These metabolic effects of SRT1720 are mediated by the induction of a genetic network controlling fatty acid oxidation through a multifaceted mechanism that involves the direct deacetylation of PGC-1 α , FOXO1, and p53 and the indirect stimulation of AMPK signaling through a global metabolic adaptation mimicking low energy levels. Combined with our previous work on resveratrol, the current study further validates SIRT1 as a target for the treatment of metabolic disorders and characterizes the mechanisms underlying the therapeutic potential of SIRT1 activation.

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Cell Metabolism 2009



The Medical Research Foundation supports French medical research and the Danone International Prize for Nutrition

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