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The Revival of Interest in Muscle Energy Metabolism for Human Health Thanks to Genomics and Integrated Biology

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Abstract: Skeletal muscle is a major site of whole-body fat and carbohydrate catabolism due to its mass and its metabolic activity. Among the key biological mechanisms associated with muscle energy metabolism are not only mechanical force and hence physical performances, but also mitochondrial activity and the regulation of muscle insulin sensitivity, for instance. Therefore, muscle energy metabolism plays an important role in human subjects for the apparition of metabolic disorders. It is also important for the production of healthy meat from muscles of farm animals due to its impact on meat quality traits through the regulation of animal physiology. This paper aims to argue that genomics has huge potential to better understand muscle energy metabolism despite some technical limitations. Genome-wide studies of differential expression may help indeed to define gene or protein markers of muscle metabolic properties and hence of metabolic diseases and animal phenotypic traits. However, the vast amount of information derived from expression studies using the new genomics tools remains to be analyzed and combined with physiological data. Indeed, integrated muscle physiology using modeling tools from genes to *in vivo* metabolite levels and fluxes should help to understand the metabolic regulation of fuels at the muscle and whole body levels.

Key words: muscle; metabolism; metabolic disorders; integrated biology; genomics

INTRODUCTION

During the last century, the regulation of muscle energy metabolism has been studied with the ultimate objective to understand how chemical energy from nutrients can be converted into mechanical force. Nowadays, the scientific community recognizes that the regulation of muscle energy metabolism can be associated with metabolic disorders (obesity, diabetes) in humans (Hocquette, 2002) and with the control of body composition and meat quality traits in meat-producing animals (Hocquette *et al*., 1998). Muscle energy metabolism needs oxygen and energy substrates, which are supplied by the diet and through the activities of liver, adipose tissues and the cardiocirculatory system. Muscle metabolism is regulated to a large extent by nutrient supply, i.e. by nutrients supplied by the diet after transformation by the liver in interaction with the other tissues (Hocquette *et al*., 2001). In addition, it is now accepted that nutrients not only meet the quantitative fuel requirements of tissues, but also may themselves have qualitative health benefits. This is the concept of functional foods (Ashwell, 2001). For instance, polyunsaturated fatty acids (as omega-3) are known to reduce the risk of insulino-resistance (Clarke, 2000). This type of nutrients may be provided by animal products, especially fish and to a lesser extent meat.

The challenge of Science in that field is to assess the contribution of muscle energy metabolism to whole-body fuel homeostasis and to understand its regulation. To achieve this goal, scientists nowadays are paying more and more attention to integrated biology of muscle metabolism by combining *in vivo* and *in vitro* approaches at the molecular, cellular, tissue and whole-body levels (Girard *et al*., 1992; Hocquette *et al*., 1998) (Fig. 1). More recently, scientists have created transgenic and knockout mice which over-express or under-express, respectively certain target genes to test hypotheses on the biological functions of the manipulated genes (Chen and Farese, 2002). More recently, scientists are also developing high-throughput technologies to study muscle gene expression on a large scale by using the recent approaches of "functional genomics" (Celis *et al*., 2000; Piétu *et al*., 1999). Genomics is "the study of the functions and interactions of all genes in the genome, including their interactions with environmental factors". The integration of genomics into nutritional sciences has led to nutritional genomics (Stover, 2004). Whereas nutrigenetics is the study of genetic variations and polymorphisms in genes involved in nutrient metabolism, nutrigenomics seeks to

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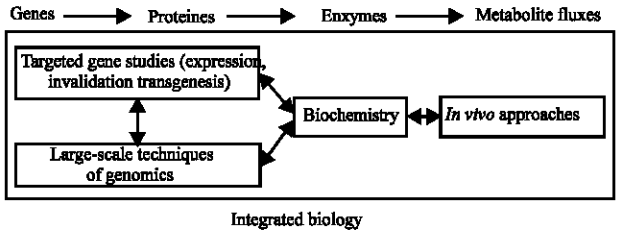

Fig. 1: The defferent approaches to assess muscle energy metabolism

examine and define the effects of small molecules (drugs and nutrients) on the pattern of gene expression in individual cells, organs and tissues (Junien, 2002). Similarly, the integration of genomics into physiology in animal sciences (Eggen and Hocquette, 2004) can be achieved to improve the healthiness of animal products for human consumption. Genomics will indeed assist greatly in the application of integrated biology from genes to metabolic regulation, although integrated biology was developed before the advent of genomics (Fig. 1). These strategies allow a broad picture of muscle biological mechanisms in different physiological and nutritional contexts.

After a recap of muscle biological diversity and physiological functions, we would like to discuss and illustrate by recent papers some "hot topics" concerning the regulation of muscle energy metabolism by nutritional and physiological factors. The main objective of that paper is to argue how genomics can help research in that area in association with classic approaches despite some limitations which will be underlined. In each section, there will be thus a short review of the current knowledge, examples of the new knowledge arising from Genomics and some emerging frontiers for the research which remains to be done using the new biotechnology tools.

DIVERSITY OF MUSCLE FIBER TYPES

The major fiber types: Skeletal muscle is composed of muscle fibers with different functional properties optimized for different tasks. The three major muscle fiber types are called, in humans, type I (slow oxidative), IIA (fast slow oxidative) and IIX (fast glycolytic previously called IIB). The molecular and functional diversity of skeletal muscle fibers arises from (i) the myofibrillar apparatus, for instance the myosin heavy chain isoforms (ii) the sarcolemma and the sarcoplasmic reticulum in which many calcium and ion channels are present (thereby inducing differences in electrical membrane properties) and (iii) the metabolic systems devoted to the production of free energy (i.e. ATP). The existence of the different fiber types based on these three groups of criteria is one of the main determinants of muscle performance *in vivo*. Slow fibers are used for posture control and for slow and repeated contractions, whereas fast fibers are used for powerful and short contractions. During maximal activation, the ranges of variations between muscle fiber types with respect to mechanical power, ATP consumption and energy production are about 10, 7 and 2, respectively. The percentage of fiber volume occupied by mitochondria ranges from 2.3% to 6% in humans depending on the fiber type. This suggests that regulation of muscle fiber performance occurs mainly through energy consumption rather than by energy production as (Bottinelli and Reggiani, 2000). This underlines the importance of physical activity in muscle plasticity.

Knowledge derived from classic approaches: For many years, molecular biologists and biochemists tackled the analysis of one or a few genes, proteins or enzymes at a time. So far, the regulation of muscle properties has indeed been studied by developing studies focused on key proteins or enzymes which control muscle energy metabolism or determine muscle characteristics. They include for instance myosin heavy chain (Picard *et al*., 2002), mitochondrial and glycolytic enzymes (Hocquette *et al*., 1998), insulin-sensitive glucose transporters which control glucose uptake in muscle cells from humans and animals (Hocquette and Abe, 2000), etc. Other studies aimed to understand the activity of ATPases and mitochondria which are key players in fiber type diversity. More recently, some studies have gone further in that direction. It was indeed shown that mitochondria from oxidative muscles have higher ATP synthesis rate, respiratory control ratio and ADP-stimulated respiration than from glycolytic muscles, whereas the inhibitory effect of ATP on respiration is higher in mitochondria from glycolytic muscles (Gueguen *et al*., 2005).

Besides biochemistry, studies focused on key genes were recently developed still further thanks to progress in genome manipulation, namely transgenesis and gene invalidation in mice (Chen and Farese, 2002).

One of the key muscle features being studied at present is the relationship between muscle fiber types, body composition and intramuscular fat content. The latter parameter is indeed of great importance in humans with regard to insulin action (Perseghin *et al*., 1999) and hence obesity and diabetes and also in farm animals with regard to meat flavor and healthiness for human consumption (Hocquette *et al*., 1998). Intramuscular fats which are important for human muscle biology are,

however, located as lipid droplets within muscle fibers, whereas they are mainly located within intramuscular adipocytes in muscles of farm animals. Studies in humans indicated that the percentage of type I fibers (slow oxidative) is negatively correlated with the percentage of body fat (Helge *et al*., 1999) but positively correlated with intramuscular fat content (Gaster *et al*., 2003) whereas the two latter parameters are generally positively correlated. Studies in cattle have also shown that the percentage of oxidative fibers is negatively (comparison of steers and bulls of the same breed) or positively (comparison of different breeds, Hocquette *et al*., 2003) associated with the proportion of fat in the carcass and often positively associated with intramuscular fat. Such conflicting results have also been observed in the rat: rats prone to develop obesity on a high fat diet have a higher proportion of fast glycolytic fibers than obesity-resistant rats (Mrad *et al*., 1992), whereas rats bred to have an increased proportion of fast fibers have been shown resistant to develop obesity even when fed a high fat diet (Suwa *et al*., ???). These discrepancies may be explained by the fact that muscle metabolic properties are not closely related to muscle contractile traits. This is a new idea more and more accepted in the scientific community. Furthermore, intramuscular fat content results from a balance between synthesis and degradation of fats (Fig. 2) within muscles which needs to be assessed by an integrative biological approach as done recently (Gondret *et al*., 2004). This balance depends, however, of the storage site of intramuscular fat (as lipid droplets within fibers or within intramuscular adipocytes). Similarly, body composition results from a balance between fat deposition and catabolism in adipose tissues and muscles, respectively (Fig. 2).

New knowledge from genomics. More recently, the high-throughput technologies of genomic approaches have helped to pinpoint the proteins or the enzymes which clearly differ between muscle types.

In mice, microarray analysis identified 49 mRNA sequences that were differentially expressed between white and red skeletal muscles, including newly identified genes. These genes can be classified into different biological functions: energy metabolism (14 genes out of 49), transcription factors and regulators (10 genes), contractile structure (7 genes), Ca^{2+} homeostasis and signaling (4 genes), etc (Campbell *et al*., 2001). Not surprisingly, the majority of the differentially expressed genes were classified as metabolic genes, which confirms that differences in the ATP-generating process are important between muscle types.

Similarly, studies profiling the differences between red and white muscles were made for pigs. Seventy genes

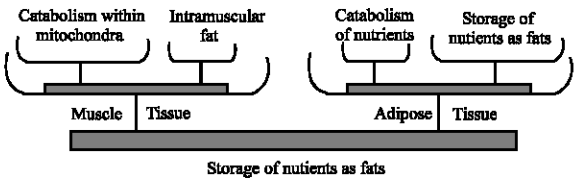

Fig. 2: The complex balance of fats between skeletal muscle and adipose tissue. Excess calorie intake or lack in physical activity may change this balance in a way favorable for the development of obesity

were declared as over-expressed in red muscles and 47 of them were of mitochondrial origin. Among the others, some genes were involved in various cell functions (gluconeogenesis, transcription, translation, signal transduction) or were related to unknown biological functions. On the other hand, 45 clones were over-expressed in white muscles. They concerned fast isoforms of sarcomeric proteins (myosin heavy chain 2a, 2x, 2b, myosin regulatory light chain, fast-troponins C and T3, etc) and genes involved in glycolysis (such as glyceraldehyde 3-phosphate dehydrogenase) (Bai *et al*., 2003).

Recently, differences between bovine muscle types were analyzed using human macroarrays (Sudre *et al*., 2003a, 2003b). However, because these arrays were initially prepared to explore muscular dystrophy in humans, all the expected differences between muscles were not detected, but the authors did detect genes which may be of interest in muscle biology. Some of the detected genes were indeed linked to the contractile (nebulin, actinin-associated LIM protein) or metabolic (ICDH β-subunit precursor) properties of muscles. Two interesting differentially expressed genes were LEU5 and Trip 15. LEU5 is a tumor suppressor gene associated with B-cell chronic lymphocytic leukemia. Trip 15 is a thyroid receptor interacting protein. They are probably involved in muscle development. One important result is that the differences between muscle types depend on the stage of development (Sudre *et al*., 2003a) and the genetic types of animals (Sudre *et al*., 2003b). This confirms previous observations based on biochemical studies (Hocquette *et al*., 2003; Picard *et al*., 2002).

Future trends: This expanding knowledge of the diversity of mRNA expression between muscle types underlines the complex determinism of muscle phenotypes as described above. One important aspect is the global description of new genes potentially involved in the determination of muscle types.

From biochemistry and genomics data, it is clear that one of the major differences between muscle types is

their difference in mitochondria contents. Therefore, mitochondria are attractive targets for proteomics (Heazlewood *et al*., 2003) due to their vital roles in energy production, anabolic and catabolic metabolism and other cell functions. This is one of the reasons why mitochondria are at the forefront of research as predicted five years ago (Kiberstis, 1999). When we compare different animal types (from fish to birds), mitochondrial enzyme levels in muscles vary more than 100-fold (Moyes, 2003). Mitochondrial plasticity may be thus an important factor that regulates muscle properties. However, the molecular mechanisms that control the plasticity of mitochondria are just beginning to unfold (Hoppeler and Martin, 2003). While the transcriptional co-activator PGC-1á (peroxisome proliferator-activated receptor gamma co-activator 1) has emerged as a major player in mitochondrial gene expression, other mechanisms also exist (Moyes, 2003). Mitochondrial biogenesis and remodeling are also important for other tissues such as, surprisingly, adipose tissues (0) although one of the main functions of adipose tissue is to deposit fats rather than to catabolize them. Mitochondria are not only the major site of fatty acid oxidation but may also play an important role in lipogenesis by providing key intermediates for fat synthesis (Owen *et al*., 2002).

PHYSIOLOGICAL FUNCTIONS OF MUSCLE ENERGY METABOLISM

Overview: In the past, most research on muscle biology has been conducted to improve or better understand sport performances. Research was thus focused on muscular contraction which supports posture and allows movements and physical activity. Nowadays, it is recognized that muscle physiological functions attributed to muscle energy metabolism also include (i) the protection of individuals (especially newborn subjects) against any drop in body temperature via muscle shivering or non-shivering thermogenesis, (ii) the partitioning of nutrients between oxidation within lean tissues (such as muscles) and storage within fat tissues and (iii) and the development of certain muscle characteristics linked to meat quality in beef, poultry and pigs (Hocquette *et al*., 1998) (Fig. 3). The regulation of mitochondrial activity is one of the mechanisms which determine non-shivering thermogenesis (Herpin *et al*., 2004). Nutrient partitioning is a key process involved in the control of fuel homeostasis and hence of body composition (Cortright *et al*., 1997). Individuals with a higher proportion of oxidative fibers (with a high mitochondrial content and hence a high capacity to catabolize fat) are likely to be leaner and less likely to have

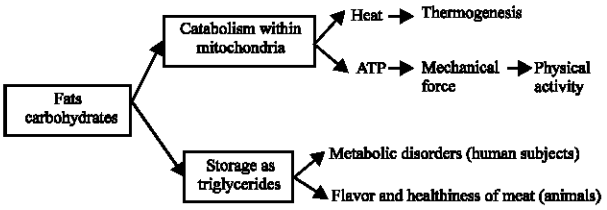

Fig. 3: Partitioning of nutrients between catabolism and storage as fats in relation to the physiological functions of skeletal muscles

metabolic syndromes such as obesity and diabetes (Tanner *et al*., 2002).

Importance of muscle energy metabolism in human subjects and animals. More importantly, it was demonstrated that dysregulations of glucose and lipid metabolism are the primary cause of metabolic disorders, such as obesity. Obesity rates are indeed rising throughout the world to epidemic proportions, especially in North American and European countries and it is a serious risk factor in the development of diabetes and other complications associated with enhanced insulin resistance of the muscle tissue. The worldwide prevalence of diabetes mellitus is expected to double between 1994 and 2010. Type 2 diabetes is the most common and is mostly observed in the elderly population. It is characterized by high blood glucose level resulting from dysfunction of pancreatic cells and peripheral insulin resistance. The latter is associated with alterations in muscle glucose and fat metabolism. Many factors are involved in the etiology of insulin resistance. They include heredity, age, obesity, diet, sex, sedentary life style, etc (Kahn and Safdar, 2003). Impaired glucose transport rate (Shulman, 2004) as well as impaired mitochondrial activity and higher intramyocellular lipid content were showed in the insulin-resistant offspring of patients with type 2 diabetes (Petersen *et al*., 2004). Recently, total muscle fat oxidative capacity was also shown to be positively correlated with insulin sensitivity (Rimbert *et al*., 2004). In addition, insulin-regulated mitochondrial gene expression is positively associated with glucose flux in human skeletal muscle (Huang *et al*., 1999). Mitochondrial markers, but not muscle fiber type *per se*, may indeed be factors predisposing to obesity (Raben *et al*., 1998). The current view is that genetic mutations within metabolic genes explain less than 10% of the occurrence of type 2 diabetes. The most important factors would be regulation of the expression of those genes by physiological and nutritional factors. Nutritional factors (level of dietary energy supply, plasma level of fats, nature of nutrients, type of fatty acids) are indeed able to regulate gene expression and/or activities of

various metabolic pathways depending on the genetic background of the individuals. The key lipid metabolites implicated in the impairment of insulin sensitivity are long-chain acyl-CoA (Yu *et al*., 2002). Thus, any up-regulation of genes which favor the accumulation of fatty-acid derived metabolites may induce insulin resistance. Among those genes, are those involved in fat uptake from circulating blood such as, for instance, lipoprotein lipase (Ferreira *et al*., 2001; Kim *et al*., 2001) or fatty acid transport protein 1 (Kim *et al*., 2001).

Similarly, in Animal Science, the tendency in Europe was to favor the production of lean animals in order to produce more meat and less fat in the carcasses. As a consequence, the meat contains less and less intramuscular fat, which is supposed to be healthier for human consumption. However, meat flavor and tenderness are partly related to muscle metabolic traits, such as glycogen and muscle fat contents (0). It was recently demonstrated in rabbits that muscle fat content can not be explained by the regulation of one specific metabolic pathway, but results from a balance between catabolic and anabolic fatty acid enzyme activities (Gondret *et al*., 2004). It has been speculated that a high fatty acid turnover (which is a characteristic of oxidative muscles) and hence a high level of mitochondrial activity would favor intramuscular fat deposition (Hocquette *et al*., 2003) provided that energy is supplied in excess to the muscle tissues (as in the case of sedentary subjects).

New knowledge from genomics: Thanks to the development of genomics approaches, we are moving towards nutritional genomics, which aims to study the interface between the nutritional environment and cellular/genetic biological and metabolic processes on a large-scale level (Kaput and Rodriguez, 2004). Genome-wide studies of differential expression associated with integrated biology are expected to hasten the discovery of disease-susceptibility genes (McCarthy *et al*., 2003). So far, genomics studies of diabetic-muscle tissue have identified changes in the expression of genes involved in the regulation of oxidative phosphorylation (Toye and Gauthier, 2003). On the other hand, mitochondrial protein leak and the expression of UCP3 correlate with weight loss success in obese diet-resistant subjects (Harper *et al*., 2002). Recent insights derived from knockout mice confirmed that disruptions in the catabolic process of fats within muscles tend to impair insulin action (Chen and Farese, 2002). All these results underline the importance of muscle fat metabolism in the etiology of diabetes and obesity.

Future trends: Generally, gene expression profiling is finding utility in gene discovery, gene regulation and diagnosis. The first aspect is the global description of new genes potentially involved in the occurrence of diabetes and obesity. The second aspect is the regulation of the regulatory networks implicated, for instance, in the accumulation of intramuscular fat and the third aspect is the identification of patterns of gene expression that may represent prognostic indicators of disease states. For instance, some researchers have prepared a Human Insulin Resistance Gene Chip with the aim to investigate regulation in the expression of genes relevant to insulin resistance (Walder *et al*., 2002). The major limitation of these approaches is their ability to generate data in vast amounts ahead of our current ability to make sense of them. It is indeed important to combine expression data with other sources of information to improve the range and quality of biological conclusions. This is why mathematics will nowadays retain a captive audience in biology for analysis gene expression profiling experiments (Friedman, 2004).

REGULATION OF MUSCLE METABOLISM BY NUTRITIONAL AND PHYSIOLOGICAL FACTORS

Current knowledge: Among the factors which regulate muscle energy metabolism are the nutritional level, the nature of the diet and mechanical muscle activity.

Nutrients can affect gene expression and hence muscle metabolism directly or indirectly. Nutrients modify tissue concentrations of substrates and metabolites, act as ligands for transcription factor receptors once they are metabolized and also affect signal pathways (Kaput and Rodriguez, 2004). Nutrients also affect insulin action (Patti, 1999).

Energy restriction was shown to affect muscle characteristics. In rabbits, energy restriction decreases intramuscular fat contents and some lipogenic activities without any change in muscle fiber types (Gondret *et al*., 2000). Similarly, in cattle, muscle metabolism is more affected than any other muscle biochemical characteristic by mild nutritional restriction. In other words, restriction induced a lower glycolytic activity without any significant changes in muscle fiber types. Furthermore, muscles respond differentially to changes in feeding level (Cassar-Malek *et al*., 2004). These results in both rabbits and bovines confirm the general view that mitochondria in skeletal muscles can undergo rapid changes as a consequence of modifications in environmental conditions (Hoppeler and Martin, 2003).

The effect of the nature of the diet has been studied especially at weaning. Indeed, in laboratory rodents,

replacement of the high-fat milk diet by a carbohydrate-rich diet is known to increase expression of insulin-responsive glucose transporters (GLUT4) in both muscles and adipose tissues (Girard *et al*., 1992). By contrast, in ruminant species, fat and carbohydrates present in the milk are replaced at weaning by volatile fatty acids and ketone bodies produced by fermentation of solid foods in the rumen. In this context, GLUT4 expression is not enhanced in muscles and is even decreased in adipose tissues (Hocquette *et al*., 1997) just like lipoprotein-lipase activity and expression (Hocquette *et al*., 2001). This confirms that the regulation of muscle metabolism relies at least in part from dietary nutrients.

The effect of the nature of the diet has also been studied by the replacement of a standard diet by a high-fat diet. A high-fat diet was shown to increase intramyocellular lipid content without any significant change in mitochondrial volume (Hoppeler and Martin, 34). However, a short-term high-fat diet up-regulates the expression of some genes (but not all), which are involved in fatty acid transport across membranes or in fatty acid catabolism in human muscles of well-trained subjects (Cameron-Smith *et al*., 2003). Polyunsaturated fatty acids were generally shown to enhance the transcription of many mitochondrial genes involved in fatty acid oxidation and to reduce the transcription of genes encoding lipogenic enzymes. The consequences are improved energy balance and insulin resistance, enhanced thermogenesis and thereby reduced fat deposition (Clarke, 2000).

It is well known that physical activity affects muscle metabolic properties by shifting them towards the oxidative type. Indeed, endurance training increases muscle fat oxidative capacity and also insulin sensitivity (Rimbert *et al*., 2004) which may have beneficial consequences on health. Intramyocellular lipid content is also increased by endurance exercise training concomitantly to the ability of muscles to catabolize fat (Hoppeler and Martin, 2003). Again, genomic studies have demonstrated the regulation of many genes including metabolic genes in skeletal muscles of exercised- (Zambon *et al*., 2003) or endurance trained humans (Wittwer *et al*., 2004). Other studies have demonstrated the selective increase in mRNA levels of enzymes involved in fat utilization in muscles of endurance-trained human subjects (Schmitt *et al*., 2003). Furthermore, exercise training induces higher fat oxidation by up-regulating the genes involved in the control of fat transport across the plasma and the mitochondrial membranes of muscles (Tunstall *et al*., 2002). This may explain why exercise training increases muscle fat oxidative capacity (Rimbert *et al*., 2004).

Other physiological factors such as sex (Roth *et al*., 2002), age (Gondret *et al*., 2004; Welle *et al*., 2003) and atrophy (Lecker *et al*., 2004) strongly regulate gene expression in skeletal muscles. Increase in fat mass observed in elderly people is also thought to result, at least in part, from defects in the ability of muscles to oxidize fat due to lower physical activity with increasing age (Morio *et al*., 2001; Rimbert *et al*., 2004).

Future trends: One of the principle issues facing biological research is to convert analytical data into knowledge about regulation of biological functions. During the last century, classic biochemistry has efficiently increased (and is still increasing) our knowledge of muscle metabolism as illustrated in this review. More recently, insights into gene function have been provided through conventional and knockout transgenic experiments (Bockamp *et al*., 2002). Nowadays, functional genomics is providing catalogs of muscle genes regulated by various nutritional and physiological factors. Now this vast amount of data needs to be analyzed in order to understand gene functions and interactions. This is currently developed for instance in yeast (Cornell *et al*., 2003). It is starting to be developed for mammalian tissues (Wilson-Fritch *et al*., 2003). Sequence and expression analysis is indeed not enough to understand gene functions. Genomics pinpoints genes which may be coregulated, but this should be coupled with rapid and efficient gene transfer techniques to truly demonstrate the interactions between genes and their biological functions. A more powerful method is to perform large-scale genomics studies on transgenic or knockout mice in which the expression of one target gene was altered. For instance, it was demonstrated that during fasting over-expression of hormone-sensitive lipase in the heart up-regulates the expression of genes involved in fatty acid oxidation (Suzuki *et al*., 2001). The challenge is nowadays to use this new type of information arising from genomics to better understand muscle energy metabolism with the constant help of biochemistry and genome manipulation. This is integrated biology.

CONCLUSIONS

In conclusion, skeletal muscle plays a pivotal role in whole energy metabolism because it is able to transform the biochemical energy of substrates into mechanical work and heat. The former is essential for physical activity and the practice of sports, the latter protects individuals against any drop in body temperature in case of cold exposure. Both processes regulate fuel homeostasis and hence body composition and some metabolic disorders

(obesity, diabetes). Due the increase of metabolic diseases in Western countries, the regulation of gene expression and muscle insulin action by nutritional and physiological factors are nowadays the subjects of active investigation. From the current results, it is clear that the decline in physical activity levels has played a part in the increased prevalence of diabetes and obesity. Physical activity and diet (which produce opposite effects on energy balance) work indeed together for health maintenance and especially are involved in the prevention and treatment of chronic metabolic diseases (obesity, diabetes, etc) in humans. Similar biological mechanisms are observed in farm animals, but, in these species, the balance between energy supply and utilization by the muscle tissue is of interest for body composition and meat quality traits, the latter also being important quantitatively and qualitatively for human health.

Scientists are currently providing catalogs of gene expression patterns in health and disease in humans and animals without any real information about gene function. We hope that seemingly unrelated observations will find their place in an overview of metabolic regulation. The next challenge is indeed the interdisciplinary research approach combining genetics, genomics, metabolite studies (Friedman *et al*., 20040), *in vivo* physiology (Young and Ajami, 2000) and modeling (Fiehn, 2001; van Milgen, 2002) which are all exciting and promising areas of research. In any case, more effective personalized strategies should apply to the prevention of metabolic disorders in humans or the prediction of meat healthiness by animals. In other words, a better knowledge of the genetic characteristics and of the gene expression profile of each individual should provide a prediction of the ability of this individual to become fat or lean.

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