Research Theme
Metabolic Disorders

Research Project Title
Muscle Metabolism and Circadian Clock Function

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Project Description
The skeletal muscle is one of the major organs in the human body comprising around 40 per cent of the total body mass. It is also a metabolic organ and is the major site for insulin–stimulated glucose uptake after food intake apart from facilitating locomotion. Reduced muscle mass and strength are commonly associated with many chronic diseases such as obesity and type 2 diabetes. The proteins secreted from skeletal muscle are known as myokines, which play an important role in mediating the beneficial effects of exercise, such as increased insulin responsiveness, glucose uptake and fatty acid oxidation. Myokines are also involved in the metabolic regulation of distant organs through systemic effects in an endocrine fashion, decreasing fat accumulation through lipolysis and fatty acid oxidation.

Nuclear receptors are transcription factors that direct a wide range of genetic programmes, which regulate lipid and carbohydrate metabolism by sensing fat-soluble hormones, vitamins and dietary lipids. The Peroxisome Proliferator-Associated Receptors (PPAR) α, β/δ and γ are ligand-activated nuclear receptors controlling many important physiological processes, including lipid and glucose metabolism, energy homeostasis, inflammation, and adipogenesis. PPARs play a critical role in the enhancement of insulin responsivity. The classical targets of insulin action are skeletal muscle, adipose tissue and liver. In these organs insulin acts to increase glucose metabolism, decrease lipolysis and glucose production. PPARα receptor is predominantly expressed in liver, muscle and...
brow adipose tissue, and is associated with lipid catabolism, reduced inflammation and atherosclerotic plaques. PPARβ/δ is ubiquitously expressed, and is involved in myogenesis, fatty acid oxidation, and tissue repair. PPARγ receptor is widespread throughout the human body but is highly expressed in fat cells and is involved in insulin sensitivity.

With the fervent pursuit of the magic bullet to eradicate the obesity epidemic, special emphasis has been placed on the impacts of PPARs on obesity and its associated diseases. Metabolic processes are also influenced by biological/circadian clocks and feeding rhythms. A circadian rhythm is any biological process that displays an endogenous oscillation of about 24 hours. Circadian rhythms are controlled by clock systems with similar molecular components between the specialized suprachiasmatic neurons in the hypothalamus (central clock) and peripheral tissues, such as gut, liver, muscle, fat and blood vessels (peripheral clocks). Disruption of the core clock genes leads to arrhythmic activity and gut dysbiosis that lead to the development of metabolic syndrome. The central clock is adjustable by external cues called Zeitgebers such as the light/dark cycles, whereas the peripheral clock is entrained by the feeding/fasting or rest/activity cycles, and neuronal and hormonal signals. Recently, all three PPAR isotypes were found to be rhythmically expressed in given mouse tissues, and are direct regulators of core clock components. In skeletal muscle, the circadian rhythm is involved in lipid and protein metabolism, and cytoskeletal organization. We hypothesize that PPARs and the Circadian Clock are tightly intertwined in the regulation of metabolism and energy homeostasis in the peripheral organs such as skeletal muscle, and are influenced by the gut microbiota and involved in organ crosstalk.

Thus the proposed PhD project on muscle metabolism and circadian clock function aims to elucidate the following objectives utilizing available transgenic mouse models and in vitro tissue cultures:

1. Interaction of PPARs and the circadian clock in muscle metabolism
2. Inter-organ signaling of myokines in metabolism
3. Impact of gut microbiota in muscle metabolism and circadian rhythm

**Contact Us**

If you have questions regarding this project, please email the Principal Investigator.

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