Editorial

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Signaling, Epigenetic and Transcriptional Regulation of Hepatic Lipogenesis

Derek HH Ho and Roger HF Wong *

Department of Biology, Hong Kong Baptist University, Hong Kong

***Corresponding author:** Roger HF Wong, Hong Kong Baptist University, Department of Biology, Hong Kong, Tel: 852-34117262; E-mail: rogerwong@hkbu.edu.hk

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Editorial

Energy homoeostasis are tightly controlled in living organisms, and there are always Ying and Yang sides. Ying is regarded as lipolysis, fatty acid oxidation, non-shivering thermogenesis in brown adipose tissue (BAT) while Yang is regarded as lipogenesis and triglyceride synthesis in lipogenic tissues.

From the Yang perspective, dysregulation of lipid metabolism such as triglyceride and fatty acid synthesis often is the leading cause of metabolic diseases such as obesity, diabetes, fatty liver disease. Excess synthesis and storage of triglyceride in lipogenic tissues due to overconsumption of calories, that is, overweight and obesity, is a global health epidemic in modern times and is strongly associated with insulin resistance, liver steatosis, dyslipidemia, metabolic syndrome, aging, aging related diseases, cancers and cardiovascular diseases. Paradoxically, the metabolic abnormalities usually found in overweight and obesity are also associated with lipodystrophy which is characterized by selective loss of adipose tissue mass from regions of the body. Although the underlying molecular mechanisms remain to be elucidated, in lipodystrophic patients, metabolic complications may result from ectopic storage of triglyceride in tissues such as liver and muscle. Furthermore, in cancer cells, aerobic glycolysis, instead of oxidative phosphorylation, provides energy (Warburg-effect). Thus, the increase in lipogenic substrate pool facilitates an increase in de novo lipogenesis, providing fatty acid for membrane phospholipid biosynthesis in cancer cells. As a result, lipogenic enzymes not only served as markers for certain types of human cancers, but also are potential anti-cancer targets. Considering the wide range of human diseases from insulin resistance to cancers, it is critical to understand the regulation of lipid metabolism, namely fatty acid and triglyceride synthesis.

Lipogenesis (fatty acid synthesis) and triglyceride synthesis that take place predominantly in lipogenic tissues, namely liver and adipose tissue, must be tightly and dynamically regulated to meet changing nutritional and energy needs. In fasted state, fatty acid and triglyceride synthesis is virtually absent mainly due to the presence of glucagon/cAMP. In contrast, upon feeding, especially of a high carbohydrate fat free diet, fatty acid and triglyceride synthesis are induced dramatically as glucose utilization and glycolysis increase substantially [1]. Many enzymes in the lipogenic pathways are coordinately regulated during this fasting/feeding transition due to changes in transcription. The drastic induction of these enzymes during high carbohydrate feeding has been attributed to either or both high glucose and insulin [1].

Insulin signaling: Upon insulin binding to tis receptor, downstream PI3K is activated and signaling is branched out into three signaling AKT, mTORC2 and aPKC. For the main AKT signaling, PP1 mediates the dephosphorylation aspect of the AKT signaling by activating downstream kinase DNA-PK by dephosphorylation [2]. A battery of transcription factors and coregulators are phosphorylated by these downstream kinases to relay the insulin response to the lipogenic gene transcription.

SREBP-1c: SREBP-1c (Sterol Regulatory Element Binding Protein) belongs to the class C bHLH (basic helix loop helix) transcription factor family and binds to the Sterol Regulatory Element (SRE) for gene promoter activation involved in the synthesis and uptake of lipids. Hepatic overexpression of SREBP-1a in transgenic mice as well as in SREBP-1c knockout mice demonstrated the importance of SREBP-1 in the transcriptional activation of lipogenic genes. SREBP-1c is auto-induced by feeding or insulin treatment. The exact molecular details linking insulin and SREBP-1c transcription are still awaited to be elucidated. The SRE on the SREBP-1c promoter is regulated by SREBP-1c itself. So far, multiple insulin-signaling pathways that can induce SREBP-1c expression have been reported. For example, insulin-mediated activation of atypical PKCλ, PKCζ and AKT via the PI3K pathway induces SREBP-1c transcription and lipogenesis involved SREBP-1c's regulation. Besides transcriptional regulation, insulin was reported to stimulate cleavage processing and nuclear translocation of SREBP-1c, which then initiates a feed-forward auto-regulatory loop.

USF: USF (Upstream Stimulatory Factor) belongs to the same class C basic helix-loop-helix (bHLH) transcription factor family which recognizes the 5'-CANNTG-3', E-box core sequence. Unlike SREBP-1c transcription is regulated, USF is expressed ubiquitously. In transcriptional activation of lipogenesis by feeding/insulin, USF that is constitutively bound to the E-box is required in both metabolic states. The induction of the major lipogenic enzyme fatty acid synthase by high-carbohydrate feeding was severely impaired by 80% in either USF-1 or USF-2 knockout mice, although SREBP-1 expression did not change in these mice. Furthermore, although increased transcription of SREBP-1c to bind the SRE on promoter is critical for feeding/

insulin response, SREBP-1c itself only can bind its SRE through recruitment by USF modifications that are sensitive to changing nutrition needs. During feeding/insulin, USF-1 and its post-translational modifications (PTM) function as a molecular switch to recruit five distinct families of proteins to the lipogenic promoters [2-5].

In the fasted state, HDAC9, the corepressor controlling lipogenic gene transcription, is recruited to USF and triggers the deacetylation of USF. Whereas in the fed state, distinct families of proteins can be recruited to the lipogenic promoters, such as the USF coactivator P/CAF, which promotes transcription activation by acetylation of USF [2,3]. Besides, DNA break/repair machinery, such as Ku70, Ku80, PARP-1, TopoIIB and DNA-PK, can also be recruited to USF promoter, triggering a transient DNA break in the lipogenic gene promoter prior to the transcriptional initiation, probably due to the local changes in chromosome architecture. In the fed state, the downstream signaling molecule of AKT, DNA-PK is activated and phosphorylates USF-1 at S262, allowing recruitment of P/CAF, which concurrently acetylates USF at K237, leading to promoter activation. In contrast, in the fasted state, the attenuated phosphorylation and acetylation of USF blunt the transcriptional activation of FAS and de novo lipogenesis. Identification of DNA-PK as one of the key signaling molecules controlling transcriptional activation of lipogenic genes by insulin helps us better understand how cells regulate metabolic processes in response to insulin. In parallel to the AKT-PP1-DNA-PK insulin signaling, BAF60c is linked to the aPKC insulin signaling [4]. In response to insulin, BAF60c is phosphorylated at S247 by aPKC, which causes translocation of BAF60c to the nucleus and allows a direct interaction of BAF60c with acetylated USF-1. Thus, BAF60c is recruited to form the lipoBAF complex to remodel chromatin structure and to activate lipogenic genes. Consequently, BAF60c promotes lipogenesis in vivo and increases triglyceride levels. Interestingly, the ''dance''-like regulation of the interaction between the phosphorylated BAF60c and acetylated USF might conceptually represent a novel fine tuning in the regulation of protein-protein interaction in general biology.

The latest addition to our understanding of transcriptional regulation of lipogenesis besides coregulators and chromatin remodeling complex is the recruitment of mediator subunit MED17 by USF-1 to the lipogenic gene promoters [5]. Also, in the fed state, CK2 phosphorylates MED17 at S53. However, there is no evidence demonstrating that the recruitment of MED17 by USF is dependent on the insulin mediated phosphorylation or phosphorylation dependent acetylation of USF. It will be interesting to further elucidate how the mediator is linked to the DNA-PK signaling despite CK2 activation is implicated. So far, coregulators, chromatin remodeling complex as well as mediator are identified for transcriptional regulation of lipogenesis. Although histone acetylation has been mapped for lipogenic gene promoters, epigenetic regulation other than histone acetylation such as histone methylation is stilling missing. Histone methylation, epigenetic modifiers that are yet-to-be identified and whether these epigenetic regulations are regulated by DNA-PK signaling or USF modifications need further investigation as histone methylation is a hot topic in all aspects of biology.

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