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Review

Molecular mechanisms of human lipodystrophies: From adipocyte lipid droplet to oxidative stress and lipotoxicity

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ABSTRACT

Adipose tissue is now recognized for its major role in the control of energy metabolism and insulin sensitivity. We review here the human lipodystrophies, that are rare conditions in which total or partial fat loss is associated with severe lipid and glucose abnormalities leading to diabetes with early cardiovascular and hepatic complications. The genetic origin of a number of human lipodystrophies has been recently unraveled, emphasizing the importance of proteins of previously unknown or unexpected functions. Major adipose functions were also illuminated when studying acquired forms of lipodystrophies linked to human immunodeficiency virus-antiretrovirals. Overall, most of the proteins or functions affected by mutations or antiretrovirals result in altered adipogenesis and insulin sensitivity, triglyceride storage and formation of the unique adipocyte lipid droplet, oxidative stress and fat remodeling. Some mutations or antiretrovirals could affect directly (peroxisome proliferator-activated receptor-γ, Akt2) or indirectly (lamin A/C, human immunodeficiency virus-protease inhibitors) adipogenesis, through the transcription factors peroxisome proliferator-activated receptor gamma-γ or sterol regulatory element binding protein 1c, and insulin signaling through Akt2 that controls adipocyte lipolysis. A number of proteins mutated in genetic lipodystrophies are involved in the control of triglyceride synthesis towards the lipid droplet (1-acylglycerol-3-phosphate-O-acyltransferase 2), or its functions (seipin, cell death-inducing DFF45-like effector C, perilipin, caveolin-1, cavin-1). Decreased triglyceride storage leads to adipocyte lipotoxicity, mitochondrial dysfunction and increased oxidative stress, which could also be induced by some thymidine analogue antiretrovirals. This results in production of inflammatory mediators and deregulated release of free fatty acids. Thus, the impaired ability of adipose tissue to safely store triglycerides inside the lipid droplet results in impaired insulin sensitivity and adverted liver, muscles and heart functions leading to early complications.

Abbreviations: AC, adenyl cyclase; AGPAT2, 1-acylglycerol-3-phosphate-O-acyltransferase 2; AT, adipose tissue; ATGL, adipose triglyceride lipase; BSCL, Berardinelli-Seip congenital lipodystrophy; C/EBP, CCAAT/enhancer binding protein; CGI-58, comparative gene identification-58; CIDEC, cell death-inducing DFF45-like effector C; ER, endoplasmic reticulum; FFA, free fatty acids; FPLD, familial partial lipodystrophy of the Dunnigan type; HIV, human immunodeficiency virus; HSL, hormone-sensitive lipase; IL-6, interleukin-6; LD, lipid droplet; MAD, mandibuloacral dysplasia; MGL, monoglyceride lipase; NFκB, nuclear factor-κB; NRTI, nucleoside analogue reverse transcriptase inhibitors; PI, protease inhibitors; PAT, perilipin, adipophilin, TIP47; PKA, protein kinase c-AMP dependent; PPARγ, peroxisome proliferator-activated receptor gamma; PTRF, polymerase I and transcript release factor; ROS, reactive oxygen species; SREBP1c, Sterol Regulatory Element Binding Protein 1c; TG, triglycerides; TLR-4, Toll-like receptor-4; TNF-α*, tumor-necrosis factor α; tNRTI, thymidine analogue reverse transcriptase inhibitors; TZD, thiazolidinedione; ZMP-STE24, zinc metalloproteinase, STE24 homolog.

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Contents

1. Introduction

In the context of the increasing prevalence of obesity, excess fat is considered as highly deleterious with deregulation of glucose and lipid metabolism leading to increased cardio-vascular risk. However, paucity of fat, due to genetic or acquired causes in the context of human lipodystrophies, also leads to severe metabolic alterations resulting in premature cardiovascular complications. To try to accommodate this apparently conflicting situation, it is important to analyze the pathophysiological mechanisms involved. Human lipodystrophies, in which a number of genes altered by mutations have been recently identified (Barroso et al., 1999; Cao and Hegele, 2000; Agarwal et al., 2002; George et al., 2004; Kim et al., 2008; Hayashi et al., 2009; Rubio-Cabezas et al., 2009; Magré et al., 2001; Gandotra et al., 2011), pointing out their importance in adipose tissue (AT) physiology, are an important model to implement our knowledge by positioning these proteins at key points in the metabolic and signaling pathways and by enlightening unrecognized adipocyte functions.

Lipodystrophies represent a heterogeneous group of diseases all defined by a localized or generalized loss of body fat. If localized, it is often associated with fat hypertrophy in other depots, varying according to the type of lipodystrophy. Lipodystrophy is generally associated with severe metabolic alterations including insulin resistance, dyslipidemia and glucose intolerance, stressing for the importance of fat for the correct regulation of metabolism. Total absence of fat always leads to very severe metabolic disturbances. Partial loss of fat can lead to different phenotypes: if AT is reduced in the lower part of the body and generally increased in the upper part as in the familial partial lipodystrophy of the Dunnigan type (FPLD), severe metabolic alterations are observed (Garg, 2004; Capeau et al., 2005). When fat is reduced with a reverse phenotype, as observed in the Barraquer–Simons syndrome, metabolic alterations are generally mild or absent (Misra et al., 2004). AT has the capacity to buffer excess lipid and protect against its toxicity (Frayn, 2002). In addition, it releases a number of important factors that control insulin sensitivity and energy metabolism including adipokines but also pro-inflammatory cytokines and chemokines, secreted in excess when AT is adversely affected (Rasouli and Kern, 2008). It now appears that maintaining a healthy fat amount and repartition is an essential requirement for the protection of metabolic homeostasis.

We decided in this review to present human lipodystrophies in the light of the major AT functions which are deregulated in these diseases *i.e.* adipogenesis, insulin sensitivity, triglyceride storage, formation of a unique lipid droplet (LD), and the important processes of oxidative stress and fat remodeling. The clinical aspects of each form of lipodystrophy and the treatment options have been detailed previously (Caron-Debarle et al., 2010; Capeau et al., 2005; Garg, 2004; Capeau et al., 2010). This presentation is also complementary to recent excellent reviews on the subject (Jeninga and Kalkhoven, 2010; Rochford, 2010; Huang-Doran et al., 2010).

Studying human lipodystrophies raise important questions on human fat physiology: