Obesity is a worldwide epidemic as well as being a major risk factor for diabetes, cardiovascular diseases and several types of cancers. Obesity is mainly due to the overgrowth of adipose tissue arising from an imbalance between energy intake and energy expenditure. Adipose tissue, primarily composed of adipocytes, plays a key role in maintaining whole body energy homeostasis. In view of the treatment of obesity and obesity-related diseases, it is critical to understand the detailed signal transduction mechanisms of adipogenic differentiation. Adipogenic differentiation is tightly regulated by many key signal cascades, including insulin signaling. These signal cascades generally transfer or amplify the signal by using serial tyrosine phosphorylations. Thus, protein tyrosine kinases and protein tyrosine phosphatases are closely related to adipogenic differentiation. Compared to protein tyrosine kinases, protein tyrosine phosphatases have received little attention in adipogenic differentiation. This review aims to highlight the involvement of protein tyrosine phosphatases in adipogenic differentiation and the possibility of protein tyrosine phosphatases as drugs to target obesity. [BMB Reports 2012; 45(12): 700-706]

INTRODUCTION
The number of obese people is expected to dramatically elevate in both developed and developing countries. Besides the associated increased mortality, obesity has been closely related with a wide spectrum of co-morbidities such as arthritis, cholelithiasis, diabetes, gout and certain types of cancers. Moreover, obesity is at the center of the metabolic syndromes and insulin resistance which predispose patients to enhanced risk of cardiovascular diseases and type II diabetes (1-3). The economical aspect of obesity as well as that which is associated with the multiple related adverse health effects are also of concern.

Obesity is a very complex disease that involves a number of interactions among genetic and environmental factors. In order to treat and overcome obesity, we must develop a deeper understanding of the cellular and molecular basis of adipose tissue growth in physiological and pathophysiological states leading to weight gain. The expansion of adipose tissue results not only from increased adipocyte size (hypertrophy), but also from increased adipocyte numbers (hyperplasia) (Fig. 1). Hyperplasia occurs via de novo differentiation of preadipocytes, which are located in the stromal-vascular fraction (SVF) of adipose tissue (4). Thus, a more detailed understanding of the signal transduction mechanisms of adipogenic differentiation is critical.

Protein tyrosine phosphatases (PTPs) play crucial roles in the regulation of cellular functions, acting in concert with protein tyrosine kinases (PTKs) to control the phosphorylation level of tyrosine residues (5). Reversible tyrosine phosphorylation regulates important signaling pathways involved in the control of adhesion, differentiation, and proliferation. Although equal and balanced activities of PTKs and PTPs have been reported in many physiological processes, the recent findings of several studies contribute to the idea that PTPs have specific, active and even dominant roles in tyrosine phosphorylation (6, 7).
Furthermore, several PTPs seem to act as biochemical "on" or "off" switches and as key regulators in many intracellular signaling pathways (8).

In this review, we briefly introduce PTPs and adipogenic differentiation. We then review the functional roles of PTPs in adipogenic differentiation, and suggest the possibility of PTPs as potential targets for the treatment of obesity.

**Protein tyrosine phosphatase (PTP) superfamily**

The phosphorylation of proteins is a key cellular post-translational modification which occurs during various cellular processes, and mainly occurs in serine and threonine residues, as well as tyrosine to a lesser degree. However, tyrosine phosphorylation occurs specifically in multicellular eukaryotes, and plays important roles in cellular metabolism, growth, signal transduction, differentiation, gene regulation and apoptosis (7).

The equilibrium of protein tyrosine phosphorylation is achieved by the balanced action between PTKs and PTPs (9). It had been considered that PTPs were mainly housekeeping enzymes that merely turned signaling processes off. However, it has been reported that the almost half of PTPs are implicated in human diseases such as cancers and metabolic diseases, indicating the functional importance of PTPs (10). Now, it is generally accepted that PTPs act as both negative and positive regulators of various signaling pathways. The catalytic domain of PTPs contains about 280 residues, and is defined by the conserved active site sequence [I/V] HCXXGXX[R/S][T], which has been termed the PTP signature motif. The human genome encodes a total of 107 PTPs, which are classified into four evolutionary separate subfamilies: class I, II, and Cys-based PTPs (III) and Asp-based phosphatases (class IV) (11, 12). There are 99 PTP members of the class I subfamily in the human genome, and they can be subclassified into the classical PTPs (21 receptor-type and 17 non-receptor type PTPs), and the VH1-like phosphatase group, which contains the eleven MAP kinase phosphatases (MKPs), the 19 atypical dual-specificity phosphatase group, which contains the eleven MAP kinase phosphatases (MKPs), the three singlehot, the three PRLs, the four CDC14s, the PTEN/tensin group, and the 16 myotubularins. Among these, the receptor-type PTPs are found only in multicellular organisms, and additionally, PTPs show delicate substrate and functional specificity (13). Therefore, detailed examinations of the structure, function, and regulation of the PTP superfamily are necessary to understand a wide range of key physiological processes.

**The relationship between adipogenic differentiation and obesity**

Adipose tissue is loose connective tissue which is composed of adipocyte cells, and plays critical roles in maintaining cellular homeostasis as both an energy reservoir and endocrine organ (14). Obesity, or excess body fat, does not depend on, or cannot be determined by body weight, but on the amount of body fat, and more specifically that of adipose tissue. Obesity is a chronic health problem which now affects many people worldwide, and hence, a deeper understanding of the cellular and molecular mechanisms of adipocyte differentiation is necessary to overcome the obesity. There are two types of adipocyte, white adipocyte and brown adipocyte, which have opposite functions in energy balance. White adipocytes store excess energy as triglycerides in lipid droplets, whereas brown adipocytes release energy in the form of heat through thermogenesis (15-17). It has been reported that brown adipose tissue plays an important role in the maintenance of body temperature and energy balance in rodents. In human, it has been considered until recently that brown adipose tissue is present in neonates but disappears early in life. However, the presence of brown adipose tissue in human adults has been verified quite recently (18). Furthermore, there are accumulating reports showing a good correlation between obesity and the amount of brown adipose tissue in the body (19, 20). Thus, the signal mechanisms studies of brown adipogenesis are also very interesting with regard to the treatment and prevention of obesity. The molecular mechanism of brown adipogenic differentiation has not been as extensively investigated as that of white adipogenic differentiation however, due to its only recent identification in adult human (17-20). While further investigation of brown adipose tissue holds significant implications for the future management of this worldwide epidemic, there is a lack of basic genetic and physiological information regarding their formation and propagation, and hence, we cover only white adipogenic differentiation in this review.

**Molecular mechanisms of adipogenic differentiation**

Mesenchymal stem cells (MSCs) are multipotent adult stem cells that can differentiate into a variety of mesodermal-lineage cells, including adipocytes. The cellular and molecular mechanisms of adipocyte differentiation are regulated via fine control of several adipogenic intracellular signaling pathways (Fig. 2).

Many genetic processes have been revealed to be involved in adipogenic differentiation, through the use of either pre-adipocyte cell lines, such as 3T3-L1 or 3T3-F442A, primary SVF, embryonic fibroblasts, or bone marrow stromal cells, all of which can be efficiently differentiated into adipocyte cells in vitro (21). The master adipogenesis regulator is the transcription factor peroxisome proliferator-activated receptor γ (PPARγ), which is mandatory for the adipocyte lineage as well as for the maintenance of the adipocyte phenotype. CCAAT-enhancer binding proteins (C/EBPs) also play important roles in adipogenesis, with C/EBPα and C/EBPδ expressed during early stages of adipogenic differentiation, inducing the expression of PPARγ and C/EBPα (22, 23).

In multipotent cells, it has been known that differentiation into one myogenic, osteogenic or adipogenic lineage reciprocally inhibits differentiation into others (24). The most well-known case is the reciprocal regulation of PPARγ and RUNX2 which determine between adipogenic versus osteogenic fate (25). Besides transcriptional regulation, extracellular signaling is also
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Fig. 2. Regulatory signals of adipocyte differentiation. Several signals act as activators and/or repressors during adipogenesis. They are integrated in the nucleus by transcription factors that directly or indirectly regulate the expression of peroxisome proliferator-activated receptor-γ (PPAR-γ) and CCAAT-enhancer-binding protein-α (C/EBP-α).

an important factor for controlling adipogenesis. Wnt10b, sonic hedgehog (SHH) or TGF-β are the secreted proteins that trigger the inhibitory signaling pathways. On the other hand, extracellular proteins promoting adipogenesis include several members of the bone morphogenic protein (BMP) family (26).

Insulin signaling has profound effects on adipogenesis. The mechanisms of insulin are mediated by a cascade of tyrosine phosphorylation events which are initiated by the binding of insulin to its receptor (27, 28). Insulin binding induces the stimulation of kinase activity of the insulin receptor (IR) and the phosphorylation of IR substrates (IRSs), which lead to the activation of downstream signal molecules, including phosphoinositide 3-kinase (PI3K) and Akt. Then, activated Akt controls the activities of several downstream target proteins involved in gluconeogenesis, lipogenesis and adipogenesis (27, 29, 30). Downstream components of the insulin signal cascade are crucial for adipogenic differentiation. The depletion of individual IRS proteins, including the combined deletion of IRS1 and IRS2, leads to the significant reduction of adipogenesis (31-33). Furthermore, repression of PI3K and the loss of Akt inhibit adipogenesis by the regulation of several adipogenic and anti-adipogenic transcription factors (33-36).

The functional roles of protein tyrosine phosphatases in adipogenic differentiation
A number of growth-factor and hormone receptors belong to the tyrosine kinase receptor family, and undergo phosphorylation and dephosphorylation at tyrosine residues in a concerted manner in response to various stimuli in order to initiate/maintain the signaling cascade pathway (37, 38). Termination of the insulin signal cascade is also accomplished by PTPs, which dephosphorylate and inactivate the IR, inactivating its downstream substrates. PTPs contain a large family of receptor-type or intracellular enzymes that function as either positive or negative regulators of intracellular key signaling pathways (12, 39, 40). Several PTPs, including leukocyte common antigen related (LAR; also known as PTP-RF) phosphatase, PTP-α, PTP-1B and SHPTP2 (also known as Syt), are highly expressed in insulin-sensitive tissues such as liver, skeletal muscle and adipose tissue. These enzymes are determined to be involved in insulin signaling through the use of various experimental approaches.

Our group reported the involvement of several PTPs in adipogenic differentiation of human MSCs (41-43). According to data from PTP profiling analysis during adipogenic differentiation of human MSCs, many PTPs are differentially expressed during adipogenesis, especially during the early phases. PTP-RQ is classified as a receptor-type III PTP with phosphatidylinositol phosphate phosphatase (PIPase) activity, and has been determined to be decreased during the early phase of adipogenesis. This leads to an escalation of the intracellular PIP2 level, resulting in enhanced phosphorylation of Akt/PKB, and consequently, the promotion of adipogenic differentiation (41). LAR phosphatase (also known as PTP-RF) is also im-
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Table 1. Protein tyrosine phosphatases (PTPs) implicated in adipogenesis

| PTP   | Substrate(s)     | Classification         | References |
|-------|------------------|------------------------|------------|
| PTP-RQ| PI(3,4,5)P3      | Class I (Receptor-type PTP) | 41         |
| LAR   | IR, IRS-1        | Class I (Receptor-type PTP) | 42         |
| RPTPμ | p120 catenin     | Class I (Receptor-type PTP) | 43         |
| SHP2  | ND               | Class I (Nonreceptor-type PTP) | 47         |
| MKP-1 | p42/p44 MAPK     | Class I (MKP group)     | 49         |
| PTP-BL| ND               | Class I (Nonreceptor-type PTP) | 50         |

ND: not determined.

Several other groups also reported the involvement of PTPs in adipogenesis. Uehara et al. of the Suzuki group reported that SHP-2 (also known as PTP-N11) phosphatase plays a positive role in adipocyte differentiation of 3T3-L1 preadipocyte cells (47). Although it has been known that SHP-2 binds and dephosphorylates IRS-1 (48), there was no explanation provided as to how SHP-2 regulates adipogenic differentiation. Kasuga group also reported that MKP-1 (also known as DUSP-1) increases during adipogenic differentiation, and that this protein plays an essential role in differentiation by down-regulating the activity of p120 catenin and human MSCs. RPTPμ interacts directly with p120 catenin and controls its tyrosine phosphorylation state. RPTPμ significantly reduced p120 catenin tyrosine phosphorylation at the early phase of adipogenic differentiation. The p120 catenin protein exists in equilibrium between two states - either bound to the membrane-proximal region of E-cadherin or free in the cytoplasm (44, 45). The data clearly indicate that p120 catenin distribution depends on its tyrosine phosphorylation state, which is regulated by RPTPμ phosphatase activity. In adipocytes, insulin increases the levels of glucose transport by stimulating the translocation of Glut-4 from intracellular sites to the plasma membrane (46). Our results clearly show that cytoplasmic p120 catenin suppresses Glut-4 membrane translocation, and represses Glut-4 membrane trafficking by recovering p120 catenin by RPTPμ ectopic overexpression, suggesting that RPTPμ-mediated regulation of adipogenesis functions by increasing the Glut-4 membrane trafficking activity (43). Collectively, our group strongly showed that differentiation into adipocytes can be finely regulated in vitro by controlling the PTPs, supporting the utility of PTPs as novel target proteins for the treatment of obesity.

Fig. 3. Insulin signaling during adipogenesis, showing the potential sites involved by PTPs (red). The agents controlling the activity of these PTPs could be used as anti-obesity drugs in the future.
of p42/p44 MAPK (49). In addition, it was reported that PTP-BL (also known as PTP-N13) represents a novel adipogenic factor that is required for adipocyte differentiation, but is independent of its catalytic activity (50). In the case of PTP-1B, it has been widely accepted that PTP-1B is non-receptor tyrosine phosphatase and a key negative regulator of leptin and insulin signaling (5). However, the functional role of PTP-1B in adipose tissue is less well known. Recently, Owen et al. reported that, surprisingly, PTP-1B does not appear to be the major negative regulator of IR in adipocytes (51). Although PTP-1B may not be a key regulator of insulin signaling in adipocytes, it is obvious that PTP-1B is a useful validated therapeutic target for obesity. Several groups, including our own, have been extensively involved in the investigation of the involvement of PTPs in adipogenic differentiation (Table 1, Fig. 3).

The possibility of novel drug targets of protein tyrosine phosphatases for treatment of obesity

The number of human diseases associated with PTP abnormalities is constantly rising, and thus, small molecules which are able to regulate PTPs hold enormous potential for the treatment of diseases, including many of those associated with obesity. However, the development of molecules regulating PTP activities has been relatively slow compared to those of PTK (52-56). The main bottleneck restricting drug development relating to PTPs is the lack of biologically well-validated targets. Although several PTPs have been proposed as potential drug targets, until now, only PTP-1B has been well-validated as having a significant association with disease (5, 56). As mentioned above, the agents regulating the activity of PTPs involved intimately in adipogenic differentiation could be used as anti-obesity drug targets.

CONCLUSION

The PTP superfamily is an important regulatory component in key signal transduction pathways, cellular functions, apoptosis and insulin signaling. A number of human diseases associated with the malfunction of PTP have provided the motive to recognize PTPs as drug targets. Several PTPs are intimately involved in adipogenesis via modulating the phosphorylation of specific target substrate(s). The regulation of adipogenic differentiation is related to overcoming obesity and thus, PTPs involved in adipogenesis could be used as valuable novel target proteins for the treatment of obesity.

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