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Mini-review

Involvement of autotaxin/lysophosphatidic acid signaling in obesity and impaired glucose homeostasis

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ABSTRACT

Autotaxin (ATX) is a secreted lysophospholipase D involved in synthesis of lysophosphatidic acid (LPA), a phospholipid growth factor acting via specific receptors (LPA1R to LPA6R) and involved in several pathologies including obesity. ATX is secreted by adipocytes and contributes to circulating LPA. ATX expression is up-regulated in obese patients and mice in relationship with insulin resistance and impaired glucose tolerance. LPA1R is the most abundant subtype in adipose tissue. Its expression is higher in non-adipocyte cells than in adipocytes and is not altered in obesity. ATX increases and LPA1R decreases while preadipocytes differentiate into adipocytes (adipogenesis). LPA inhibits adipogenesis through down-regulation of the pro-adipogenic transcription factor PPARγ2. Adipocyte-specific knockout (FATX-KO) mice or mice treated with the LPAR antagonist Ki16425 gain more weight and accumulate more adipose tissue than wild type or control mice fed a high fat diet (HFD). These observations suggest that LPA (via LPA1R) exerts a tonic inhibitory effect on adipose tissue expansion that could, at least in part, result from the anti-adipogenic activity of LPA. A possible negative impact of LPA on insulin-sensitivity might also be considered. Despite being more sensitive to nutritional obesity, FATX-KO and Ki16425-treated mice fed a HFD show improved glucose tolerance when compared to wild type mice. Moreover, exogenously injected LPA acutely impairs glucose tolerance and insulin secretion. These observations show that LPA exerts a tonic deleterious impact on glucose homeostasis. In conclusion, ATX and LPA1R represent potential interesting pharmacological targets for the treatment of obesity-associated metabolic diseases.

1. Autotaxin/lysophosphadidic acid receptor functions

Autotaxin (ATX) is a glycosylated secreted enzyme of approximately 120 kDa made of several domains, including a catalytic site responsible for lysophospholipase D activity generating lysophosphatidic acid (LPA) from other lysophospholipids such as lysophosphatidylcholine [1]. ATX is expressed in many organs in animals and humans, especially in brain, lymph nodes and adipose tissue. ATX is also present in the blood where it contributes to circulating levels of LPA [2,3]. Complete knockout of ATX in mice is lethal as the result of an impaired neurogenesis and vasculogenesis of the embryo [2–5]. Heterozygous ATX knockout are normal but display 50% reduction in plasma LPA concentration [2].

LPA is a phospholipid growth factor acting through specific G-protein coupled receptors (LPA1R to LPA6R) [1]. LPA elicits a wide range of cell responses (contraction, aggregation, calcium mobilization, chemotaxis, neurotransmitter release, cell proliferation, cell transformation) [6], and has been associated with the etiology of a growing number of disorders including cardiovascular diseases (cardiac ischemia, heart hypertrophy, atherosclerosis, cancer, neuropathies, obesity, and fibrosis [6,7]). LPA1R, LPA2R and LPA3R are members of the endothelial differentiation gene family encompassing the receptors for sphingosine-1-phosphate. LPA4R and LPA6R belong to the purinergic GPCR family, and LPA5R belongs to the GPR family [7]. LPA1R is the most widely distributed subtypes throughout the organism. LPA1R-KO mice [8] have a reduced perinatal survival and exhibit behavioral and developmental alterations such as a reduced body size and alteration of the suckling behavior. The loss of LPA1R *in vivo* modulates several diseases

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including cancer, obesity, neuropathic pain, fibrosis and male infertility [9]. LPA2R-KO mice exhibit no major phenotypic alterations [10]. LPA3R-KO mice exhibit an abnormal embryo implantation in the uterus [11,12]. Whereas LPA4R-KO mice were initially reported to exhibit no major phenotypic alteration [13], a subset of LPA4R-KO embryos display alterations in blood and lymphatic vessel formation [14]. LPA5R-KO mice show no obvious phenotype except that they are protected against neuropathic pain induced by partial sciatic nerve ligation [15].

2. Obesity-associated regulation of the ATX/LPA axis in adipose tissues

ATX is abundantly secreted by adipose tissue where it is 2–3 times more expressed in adipocytes than in the stromal-vascular cells containing, among others, the preadipocytes [16,17]. Conversely to total KO, adipocyte-specific KO mice (FATX-KO) are viable [18]. When fed a normal chow diet, FATX-KO mice show 40% reduction in plasma LPA when compared to wild type mice [18] demonstrating the contribution of adipose tissue in the overall production of LPA in the body. Adipocyte ATX expression and plasma LPA are up-regulated in obese mice fed a high fat diet (HFD) [18]. These increase are suppressed in FATX-KO mice [18]. Adipocyte expression of ATX is also increased in genetically obese diabetic db/db mice in correlation with their insulin resistance state rather than with their fat mass [16,17,19]. In human, ATX expression is higher in subcutaneous than in visceral fat [20]. Whereas obesity has no influence on subcutaneous fat ATX, visceral fat ATX is higher in obese than in non-obese patients and is strongly correlated with leptin expression [20]. ATX expression is also up-regulated in massively obese patients exhibiting diabetes or impaired glucose tolerance when compared to massively obese patients with normal glucose homeostasis [19]. Thus, as in mice, obesity-associated impairment of glucose homeostasis impacts ATX expression in human.

LPARs are expressed in adipose tissue with LPA1R being the most abundant subtypes [21]. LPA1R expression is lower in adipocytes than in the stromal-vascular cells containing, among others, the preadipocytes [22]. In human beings, obesity has no major influence on LPA1R expression in adipose tissue [20]. Above different observations, show that, in adipose tissue, obesity alters LPA synthesis rather than LPA sensitivity.

3. ATX/LPA signaling inhibits adipogenesis *in vitro* and fat mass expansion *in vivo*

In preadipose cell lines (3T3F442A, 3T3-L1) and in primary preadipocytes isolated from adipose tissue adipocytes, ATX expression and secretion increase strongly while preadipocytes differentiate into adipocytes (adipogenesis), and this is associated with a strong accumulation of LPA in the extracellular medium [17,23]. Expression of ATX in differentiated adipocyte in culture is down-regulated by thiazolidinediones [17] or prednisolone [24] and up-regulated by TNFα [17] three compounds known to influence adipocyte insulin sensitivity. Conversely to ATX, LPA1R is more abundant in undifferentiated preadipocytes when compared to differentiated adipocytes [22,25]. LPA increases preadipocyte proliferation [22,25,26] through LPA1R [21] and the activation of the ras/MAPK pathway [22,27,28]. LPA inhibits adipogenesis of preadipose cell lines (3T3F442A and SGBS) and of primary white [21,22] and brown preadipocytes [29]. The anti-adipogenic activity of LPA is mediated by LPA1R since it is lost in preadipocytes from LPA1R-KO mice [21]. The anti-adipogenic activity of LPA results from a down-regulation of the pro-adipogenic transcription factor PPARγ2 [21] via the Rho kinase pathway and delayed activation of the Wnt-signaling [30,31]. Above observations suggest that ATX/LPA signaling could negatively influence adipose tissue development.

Because of their developmental deficiencies [8], LPA1R-KO mice show reduced body size and weight. Despite such phenotype, LPA1R-KO mice under a regular chow diet have a higher fat mass when compared to their wild type counterpart [21]. This is accompanied by larger adipocytes (Daviaud D and Saulnier-Blache, personal results), higher plasma leptin [21] and higher adipocyte expression of leptin and GLUT-4 [32].

FATX-KO mice display no detectable phenotype when fed a normal chow diet, when compared to wild type mice [18]. When fed a high fat diet, FATX-KO mice gain more weight and accumulate more adipose tissue (subcutaneous, perigonadic, perirenal, brown) than wild type mice, whereas the mass of the other organs is not modified. This is associated with higher plasma leptin and adiponectin [18]. Moreover, adipocytes are larger with no change in their number [18]. Similar changes in fat mass expansion are observed after long-term (6 weeks) treatment of HFD-obese mice with a LPA1/3R-antagonist, Ki16425 [33] (Fig. 1A). Above observations suggest that LPA (via LPA1R) exerts a tonic inhibitory effect on adipose tissue expansion. Such conclusion is in agreement with the anti-adipogenic activity of LPA. Nevertheless, regulation of adipogenesis *in vivo* generally leads to increased adipocyte number (hyperplasia) [34]. However, adipocytes from HFD-fed FATX-KO mice, and Ki16425-treated HFD-mice are not hyperplasic but rather hypertrophic [18], and Fig. 1B and C. Thus, the anti-adipogenic activity of LPA is likely not sufficient to explain the tonic inhibitory effect of LPA on adipose tissue expansion.

Adipocyte hypertrophy reflects a better ability of adipocytes to store triglycerides (lipogenesis), a metabolic event that is tightly dependent on insulin sensitivity. Interestingly, adipose tissue from FATX-KO mice exhibit higher expression of the transcription factor PPARγ2 as well as of several of its target genes (adiponectin, FABP4, leptin, glut-1) when compared to wild-type [18]. This is also observed after chronic treatment with Ki16425 (Rancoule and Saulnier-Blache, personal results). Consequently, adipose tissue from FATX-KO mice and Ki16425-treated mice show apparent improvement of its sensitivity to insulin. Thus, the tonic inhibitory effect of LPA on adipose tissue expansion could at least in part be mediated by inhibition insulin sensitivity of adipocytes. Such hypothesis is supported by recent results showing that the refeeding-induction of the insulin-sensitive lipogenic gene fatty acid synthase is stronger in adipose tissue from Ki16425- when compared to control-mice (Fig. 1D).

Beside FATX-KO mice and Ki16425-treated mice, Pamuklar et al. created transgenic mice bearing a liver-specific overexpression of human-ATX using an α1-antitrypsin promoter [35]. When fed a HFD, these mice display increased body weight and increased brown adipose tissue mass when compared to wild type mice [29]. Whether the mass of the other adipose tissue depots is also altered is not precised by the authors. In parallel, the same group demonstrates that LPA inhibited brown adipocyte differentiation *in vitro* [29]. Intriguingly, the phenotype of these mice is accompanied by a down-regulation of brown adipose tissue-related genes (UCP1, Cidea, PGC1a) in white subcutaneous but not in brown adipose tissue itself [29]. The authors conclude to an inhibition of brown adipocyte differentiation in white adipose depots leading to altered « metabolic efficiency and adiposity in the setting of excessive caloric intake ». Whether such phenotype is due to LPA remains unclear since the over-expression strategy of ATX used in this work leads to a modest increase in plasma LPA [35]. Treatment with a LPA receptor antagonist may help to clarify the question in this model. Alternatively ATX released by the liver could also exert LPA-independent pathways through binding to integrins on the cell surface [1].