Published in final edited form as:

Biochim Biophys Acta. 2012 May ; 1821(5): 778–781. doi:10.1016/j.bbalip.2012.02.001.

The degradation of apolipoprotein B100: multiple opportunities to regulate VLDL triglyceride production by different proteolytic pathways

Edward A. Fisher

The Department of Medicine (Cardiology) and the Marc and Ruti Bell Program in Vascular Biology, New York University School of Medicine, Smilow 7, 522 First Avenue, New York, NY 10016; 212-263-6631 (Voice), 212-263-6632 (FAX), edward.fisher@nyumc.org

Abstract

Very low density lipoproteins (VLDL) are a major secretory product of the liver. They serve to transport endogenously synthesized lipids, mainly triglycerides (but also some cholesterol and cholesteryl esters) to peripheral tissues. VLDL is also the precursor of LDL. ApoB100 is absolutely required for VLDL assembly and secretion. The amount of VLDL triglycerides secreted by the liver depends on the amount loaded onto each lipoprotein particle, as well as the number of particles. Each VLDL has one apoB100 molecule, making apoB100 availability a key determinant of the number of VLDL particles, and hence, triglycerides, that can be secreted by hepatic cells. Surprisingly, the pool of apoB100 in the liver is typically regulated not by its level of synthesis, which is relatively constant, but by its level of degradation. It is now recognized that there are multiple opportunities for the hepatic cell to intercept apoB100 molecules and to direct them to distinct degradative processes. This mini-review will summarize progress in understanding these processes, with an emphasis on autophagy, the most recently described pathway of apoB100 degradation, and the one with possibly the most physiologic relevance to common metabolic perturbations affecting VLDL production.

INTRODUCTION

Very low density lipoproteins (VLDL) are a major secretory product of the liver. They serve to transport endogenously synthesized lipids, mainly triglycerides (TG), but also some cholesterol and cholesteryl esters, to peripheral tissues. VLDL is also the precursor of LDL and both are well known atherogenic lipoproteins and risk factors for coronary artery disease. Apolipoprotein B100 (apoB100) is absolutely required for VLDL assembly and secretion. The amount of VLDL TG secreted by the liver depends on the amount of TG loaded onto each lipoprotein particle, as well as the number of particles. Each VLDL has one apoB100 molecule, making its availability a key determinant of the number of VLDL particles, and hence TG, that can be secreted by hepatic cells [1].

Given the importance of understanding apoB100's contribution to the basic science of VLDL and LDL production and its relevance to a major disease, its metabolism has been of long standing interest in both academia and the pharmaceutical industry. As molecular biological approaches informed studies of apoB100, it was rapidly determined that

© 2012 Elsevier B.V. All rights reserved.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

transcriptional regulation of its gene was primarily of importance in the developmental and tissue-specific regulation of expression. In the fully differentiated hepatocyte, it was found that variations in the secretion of apoB100 associated with VLDL were mainly controlled by processes beyond the transcriptional level (e.g., [2]). The story of VLDL regulation by the degradation of apolipoprotein B100 (apoB100) began in the mid-80's. Ground breaking studies from the laboratories of Roger Davis and Sven Olof-Olofsson focused on the turnover of newly synthesized apoB100 in rat primary hepatocytes [3] and in human HepG2 cells [4]. The prevailing paradigm then was that the level of synthesis of a secretory protein was the major, if not sole, driver of the amount that was secreted. In contrast, Davis and Olofsson showed that a large amount of newly synthesized apoB100 in hepatic cells could be degraded under certain conditions. Subsequent studies by many investigators have gone on to show that variations in the rate of apoB100 degradation was the underlying explanation for differences in the hepatic secretion of apoB100 and apoB100-containing lipoproteins after a variety of metabolic perturbations (for a recent review, see [5]).

OVERVIEW OF THE PATHWAYS OF APOB100 DEGRADATION IN THE LIVER

Broadly speaking, 3 major sites of apoB100 degradation have been described in vitro (reviewed in [6]). The first to be reported is a re-uptake pathway in which newly synthesized apoB100, when it reaches the cell surface, can encounter an LDL receptor or heparin sulfate proteoglycans, be internalized, and undergo lysosomal degradation [7]. The second was the diversion of apoB100 that failed to be lipidated during its translocation into the ER to the ubiquitin-proteasome system in a process that involved Hsp70, and subsequently shown to involve a number of factors, such as Hsp90, P58^{IPK}, Hsp110, p97, and BiP [8-14]. While there are many proteins that fail to fold properly in the ER and are similarly diverted to proteasome-mediated ER-associated degradation (ERAD), almost all are structural mutants with changes in their primary amino acid sequences, whereas the failure of apoB100, a wild-type protein, to assume a native conformation is a consequence of inadequate lipidation.

The third site is a post-endoplasmic reticulum, pre-secretory proteolytic process ("PERPP") that was originally reported in connection with the ability of fish oil fatty acids (DHA, EPA) to decrease apoB100 and VLDL TG secretion in hepatic cells [15]. It is now clear that there are other examples of PERPP, such as insulin-stimulated (e.g., [16]) and sortilin 1-mediated apoB100 degradation [17], as well the degradation of human apoB100 mutant A31P [18]. The cell biological and molecular details are not revealed sufficiently to determine whether the different examples of PERPP all represent the same fundamental degradative pathway, completely distinct pathways, or, more likely, pathways that overlap in some key features. It has been reported that for 3 of the examples of apoB100 PERPP- DHA-stimulated [19], sortilin 1-mediated [17], and apoB100 mutant A31P [18]- the degradation appears to be lysosomal, suggesting an autophagic process. As will be reviewed below, explicit evidence to support this suggestion has been reported to date for DHA-stimulated and apoB100 mutant A31P degradation [18, 19].

AUTOPHAGY- A BRIEF INTRODUCTION

This increasingly active area of investigation has been recently reviewed in a number of excellent articles (e.g., [20, 21]), and will only be briefly summarized here. It was originally recognized as a process induced by starvation such that intracellular proteins were encapsulated into structures (autophagosomes) that ultimately fused with lysosomes. In this way, the amino acids could be recovered and directed to the synthesis of the most critical proteins needed for survival. It is now recognized that there are a number of flavors of

autophagy, ranging from the disposal of microorganisms and misfolded or long-lived proteins to superfluous and damaged organelles [20].

The form that is responsible for the degradation of the majority of proteins processed by autophagy is called macroautophagy. The fundamental importance of macroautophagy is perhaps best illustrated by its conservation from yeast to man. At present, there are over 30 known products of autophagy-related genes (*Atg*) that participate in autophagy, with many involved in the autophagosome formation and lysosomal fusion processes. There is comparatively less detail known about the factors that recognize and direct substrate proteins to autophagy. Recent results, especially following the studies in mice deficient in *ATG5* or *ATG7* (e.g., [22, 23]), have shown that there is also a basal autophagic process responsible, for example, for the clearance of aggregated or damaged proteins that are always forming at a low rate in cells. Autophagy has also been shown to cooperate with the proteasome pathway when that route is overwhelmed, and to participate in crosstalk with apoptosis [24]. Perhaps most relevant to this review is that there is a growing list of examples of proteins [20] whose intracellular levels are regulated by macroautophagy, including apoB100 (see below), indicating a capacity for specificity, but as alluded to above, information on how such specificity is accomplished, for the most part, is lacking. Another aspect of autophagy relevant to hepatic lipid and lipoprotein metabolism is that this process can also turn over cellular lipid droplets, and thereby regulate the amount of TG stored, as well as secreted as part of VLDL [25].

AUTOPHAGY AND APOB100

The first link between apoB100 and autophagy came from studies in human Huh7 cells [26]. The authors found that when the proteasome was inhibited, apoB100 molecules were increasingly found associated with lipid droplets in structures they dubbed “ApoB-crescents”. These crescents were originally thought to be cytoplasmic, but subsequent electron microscopic analyses suggested that the apoB-crescent is between the two leaflets of the ER [27]. By using proteasomal or autophagy inhibitors, evidence was presented that apoB100 in the crescents was turned over by both degradative pathways. It should be noted that Huh7 cells assemble very little apoB100 into VLDL particles [28], which limited the relevance of these interesting findings to more physiological settings.

Rat hepatoma cells (McArdle RH-7777; McA), in contrast to the human hepatoma lines Huh7 and HepG2, assemble most of its apoB100 onto VLDL particles, as does normal mammalian liver. We had previously shown that DHA and EPA, the polyunsaturated fatty acids in fish oils, decreased the secretion and increased the intracellular degradation of apoB100 in both primary hepatocytes and in McA cells (e.g., [29, 30]). These effects were consistent with their ability to lower plasma VLDL apoB100 and TG levels in animals and humans consuming diets enriched in fish oil. Polyunsaturated fatty acids increase oxidative stress, which is both an inducer of autophagy as well as a potential effector of modifications of proteins that mark them for autophagic clearance. We hypothesized, then, that apoB100 PERPP in hepatic cells incubated with DHA or EPA was an autophagic process. Indeed, by using a variety of approaches and techniques, we showed that in McA cells incubated with DHA, apoB100 underwent an oxidative-dependent aggregation, with the aggregates slowly degraded by autophagy [19]. Besides demonstrating a novel pathway for late-stage quality control of a protein in the secretory pathway, this was the first example that autophagy was a regulator of apoB100 and VLDL secretion in response to a clinically relevant metabolic perturbation. Also, as speculated above, DHA increased the autophagic capacity, recently confirmed in other studies [31], most likely through its promotion of oxidant stress and lipid peroxidation in hepatic cells [32, 33].

Since this report, there have been two other well-documented examples of autophagy being a regulator of apoB100 and VLDL production. In the first, a non-synonymous mutation of human apoB100, A31P, associated with familial hypobetalipoproteinemia was studied in McA cells [18]. The authors found that secretion of this mutant was severely impaired. While much of it escaped from ERAD and reached the Golgi, the recombinant form of apoB containing the mutation was subsequently degraded by autophagy.

In the second example, ER-stress was induced by glucosamine treatment of McA cells [34]. This resulted in increased co-localization of apoB100 with autophagosomes coincident with apoB100 degradation. The degradation was blocked by 3-methyl adenine (3-MA), an inhibitor of autophagy. Furthermore, overexpression of PERK, an effector of some ER-stress related pathways (e.g., [35]), increased apoB100 autophagy. Interestingly, as we also found [19], autophagy not only mediated an induced form of apoB100 degradation, but also a component of basal turnover. It should be noted, however, that the results of Qiu et al. [34] may not apply to all inducers of ER-stress, as it has been recently shown that the apoB100 degradation that follows ER-stress induction by palmitic acid was related to ceramide production and did not increase autophagy [31].

In addition to the above examples in which autophagy was specifically examined as the degradative pathway for apoB100, there are at least two other scenarios consistent with autophagy being involved. In the first, the protein sortilin 1, associated with plasma levels of LDL in GWAS studies, was found in McA cells and in mouse models to regulate the secretion of apoB100 associated with VLDL [17]. When sortilin 1 expression was increased, the recovery of newly-synthesized apoB100 recovery in vitro and in vivo decreased. Intriguingly, in vitro, a lysosomal inhibitor blunted this effect.

In the second scenario, insulin sensitive hepatic cells and mammals pulsed with a “post-prandial” amount of insulin exhibited depressed VLDL secretion and, in mechanistic studies in hepatic cells, increased apoB100 degradation (e.g., [16, 36]). This degradation appears to be another example of PERPP, in that it is post-ER and non-proteasomal, and is inhibited by wortmannin, a pan PI 3-kinase inhibitor [37]. The autophagy inhibitor noted above, 3-MA, is also a PI 3-kinase inhibitor, suggesting that insulin-mediated apoB100 PERPP is also autophagic.

FUTURE DIRECTIONS

In the near term, efforts to extend the findings in sortilin 1-mediated and insulin-induced apoB100 PERPP are likely to tie these processes to autophagy. Then the challenge will be for all the known forms of apoB100-PERPP accomplished by autophagy, and for others as they arise, to define the factors that specifically target apoB100 to this pathway. It is becoming clear that basal and induced forms of macroautophagy, while sharing common convergence at the lysosome, are regulated in different ways, so progress in understanding of the autophagy of apoB100 will inform not only the field of lipoprotein metabolism, but also cell biology in general.

It will also be important to determine the quantitative impact of each of the known pathways of apoB100 degradation to the regulation of its net secretion in vitro. Typically, the role of each pathway is studied in isolation of the others. Furthermore, as more mouse models in which the pathways are rendered hypo or hyperactive by genetic manipulations, testing their effects on hepatic apoB100 production in vivo will be an important link between cell culture studies and human physiology.

Another interesting avenue of investigation will be the relationship between lipid autophagy (e.g., [25]) and apoB100 metabolism in terms of the integrated regulation of VLDL TG

content and VLDL particle number. Such studies will be relevant also to the pathogenesis of, and treatment strategies for, non-alcoholic steatohepatitis (NASH), which not only involves increased fat storage, but probably also a failure to export sufficient VLDL particles to relieve the liver of the excess accumulation of TG [38]. The cooperation between the proteasomal (ERAD) and autophagic pathways also needs to be further evaluated, as they have already been linked together for apoB100 [26], and are known to jointly participate in the degradation of other proteins. This cooperation may be particularly important in patients taking MTP inhibitors [39], given that MTP is responsible for the lipidation of nascent apoB100 in the ER. When it is inhibited in vitro, there is misfolding of the nascent polypeptides and their diversion to ERAD (e.g., [40]). If the proteasomal capacity is exceeded, then it is likely that autophagy will be needed to prevent misfolded apoB100 from accumulating to toxic levels.

In conclusion, the degradation of apoB100 is a major determinant of the number of VLDL particles that hepatic cells can secrete, and is therefore a regulator of net TG production by the liver. That there are multiple ways in which to accomplish apoB100 degradation indicates its importance in VLDL assembly and secretion, as well as the flexibility by which hepatic cells can respond to varied metabolic states and stresses.

Acknowledgments

The author apologizes to all of his colleagues whose work could not be cited in this mini-review because of its limited scope and page limitations. He thanks Drs. Jeffrey Brodsky (Univ. of Pittsburgh), Ana Maria Cuervo (Albert Einstein College of Medicine), Henry N. Ginsberg (Columbia Univ.), and Kevin Jon Williams (Temple Univ.) for helpful conversations, and present and past Fisher lab members for their many contributions. He also thanks the NIH for support of his research on apoB100 (R01 HL58541).

References

1. Havel, RJ.; Kane, JP. Structure and metabolism of plasma lipoproteins. In: Scriver, CR.; Beaudet, AL.; Sly, WS.; Valle, D., editors. The metabolic & molecular bases of inherited disease. Vol. II. McGraw-Hill; New York: 2001. p. 2705-2716.
2. Davis RA, Boogaerts JR. Intrahepatic assembly of very low density lipoproteins. Effect of fatty acids on triacylglycerol and apolipoprotein synthesis. J Biol Chem. 1982; 257:10908–10913. [PubMed: 7107636]
3. Borchardt RA, Davis RA. Intrahepatic assembly of very low density lipoproteins. Journal of Biological Chemistry. 1987; 262:16394–16402. [PubMed: 3680257]
4. Boström K, Wettsten M, Borén J, Bondjers G, Wiklund O, Olofsson S-O. Pulse-chase studies of the synthesis and intracellular transport of apolipoprotein B-100 in HepG2 cells. Journal of Biological Chemistry. 1986; 261:13800–13806. [PubMed: 3020051]
5. Ginsberg HN, Fisher EA. The ever-expanding role of degradation in the regulation of apolipoprotein B metabolism. J Lipid Res. 2009; 50(Suppl):S162–166. [PubMed: 19050312]
6. Brodsky JL, Fisher EA. The many intersecting pathways underlying apolipoprotein B secretion and degradation. Trends Endocrinol Metab. 2008; 19:254–259. [PubMed: 18691900]
7. Williams KJ, Brocia RW, Fisher EA. The unstirred water layer as a site of control of apolipoprotein B secretion. Journal of Biological Chemistry. 1990; 265:16741–16744. [PubMed: 2170353]
8. Yeung SJ, Chen SH, Chan L. Ubiquitin-proteasome pathway mediates intracellular degradation of apolipoprotein B. Biochemistry. 1996; 35:13843–13848. [PubMed: 8901527]
9. Fisher EA, Zhou M, Mitchell DM, Wu X, Omura S, Wang H, Goldberg AL, Ginsberg HN. The degradation of apolipoprotein B100 is mediated by the ubiquitin-proteasome pathway and involves heat shock protein 70. J Biol Chem. 1997; 272:20427–20434. [PubMed: 9252351]
10. Gusarova V, Caplan AJ, Brodsky JL, Fisher EA. Apoprotein B degradation is promoted by the molecular chaperones hsp90 and hsp70. J Biol Chem. 2001; 276:24891–24900. [PubMed: 11333259]

11. Oyadomari S, Yun C, Fisher EA, Kreglinger N, Kreibich G, Oyadomari M, Harding HP, Goodman AG, Harant H, Garrison JL, Taunton J, Katze MG, Ron D. Cotranslocational degradation protects the stressed endoplasmic reticulum from protein overload. *Cell*. 2006; 126:727–739. [PubMed: 16923392]
12. Hrizo SL, Gusarova V, Habel DM, Goeckeler JL, Fisher EA, Brodsky JL. The Hsp110 molecular chaperone stabilizes apolipoprotein B from endoplasmic reticulum-associated degradation (ERAD). *J Biol Chem*. 2007; 282:32665–32675. [PubMed: 17823116]
13. Fisher EA, Williams KJ. Autophagy of an oxidized, aggregated protein beyond the ER: a pathway for remarkably late-stage quality control. *Autophagy*. 2008; 4:721–723. [PubMed: 18560269]
14. Rutledge AC, Qiu W, Zhang R, Kohen-Avramoglu R, Nemat-Gorgani N, Adeli K. Mechanisms targeting apolipoprotein B100 to proteasomal degradation: evidence that degradation is initiated by BiP binding at the N terminus and the formation of a p97 complex at the C terminus. *Arterioscler Thromb Vasc Biol*. 2009; 29:579–585. [PubMed: 19164805]
15. Fisher EA, Pan M, Chen X, Wu X, Wang H, Jamil H, Sparks JD, Williams KJ. The triple threat to nascent apolipoprotein B. Evidence for multiple, distinct degradative pathways. *J Biol Chem*. 2001; 276:27855–27863. [PubMed: 11285257]
16. Sparks JD, Sparks CE. Insulin modulation of hepatic synthesis and secretion of apolipoprotein B by rat hepatocytes. *J Biol Chem*. 1990; 265:8854–8862. [PubMed: 2187873]
17. Musunuru K, Strong A, Frank-Kamenetsky M, Lee NE, Ahfeldt T, Sachs KV, Li X, Li H, Kuperwasser N, Ruda VM, Pirruccello JP, Muchmore B, Prokunina-Olsson L, Hall JL, Schadt EE, Morales CR, Lund-Katz S, Phillips MC, Wong J, Cantley W, Racie T, Ejebe KG, Orho-Melander M, Melander O, Kotliansky V, Fitzgerald K, Krauss RM, Cowan CA, Kathiresan S, Rader DJ. From noncoding variant to phenotype via SORT1 at the 1p13 cholesterol locus. *Nature*. 2010; 466:714–719. [PubMed: 20686566]
18. Zhong S, Magnolo AL, Sundaram M, Zhou H, Yao EF, Di Leo E, Loria P, Wang S, Bamji-Mirza M, Wang L, McKnight CJ, Figeys D, Wang Y, Tarugi P, Yao Z. Nonsynonymous mutations within APOB in human familial hypobetalipoproteinemia: evidence for feedback inhibition of lipogenesis and postendoplasmic reticulum degradation of apolipoprotein B. *J Biol Chem*. 2010; 285:6453–6464. [PubMed: 20032471]
19. Pan M, Maitin V, Parathath S, Andreo U, Lin S, St. Germain C, Yao Z, Maxfield FR, Williams KJ, Fisher EA. Pre-secretory oxidation, aggregation, and autophagosomal destruction of apolipoprotein-B: a pathway for late-stage quality control. *Proc Natl Acad Sci U S A*. 2008; 105:5862–5867. [PubMed: 18391222]
20. Yang Z, Klionsky DJ. Eaten alive: a history of macroautophagy. *Nat Cell Biol*. 2010; 12:814–822. [PubMed: 20811353]
21. Weidberg H, Shvets E, Elazar Z. Biogenesis and cargo selectivity of autophagosomes. *Annu Rev Biochem*. 2011; 80:125–156. [PubMed: 21548784]
22. Hara T, Nakamura K, Matsui M, Yamamoto A, Nakahara Y, Suzuki-Migishima R, Yokoyama M, Mishima K, Saito I, Okano H, Mizushima N. Suppression of basal autophagy in neural cells causes neurodegenerative disease in mice. *Nature*. 2006; 441:885–889. [PubMed: 16625204]
23. Komatsu M, Waguri S, Ueno T, Iwata J, Murata S, Tanida I, Ezaki J, Mizushima N, Ohsumi Y, Uchiyama Y, Kominami E, Tanaka K, Chiba T. Impairment of starvation-induced and constitutive autophagy in Atg7-deficient mice. *J Cell Biol*. 2005; 169:425–434. [PubMed: 15866887]
24. Mehrpour M, Esclatine A, Beau I, Codogno P. Autophagy in health and disease. 1. Regulation and significance of autophagy: an overview. *Am J Physiol Cell Physiol*. 2010; 298:C776–785. [PubMed: 20089931]
25. Singh R, Kaushik S, Wang Y, Xiang Y, Novak I, Komatsu M, Tanaka K, Cuervo AM, Czaja MJ. Autophagy regulates lipid metabolism. *Nature*. 2009; 458:1131–1135. [PubMed: 19339967]
26. Ohsaki Y, Cheng J, Fujita A, Tokumoto T, Fujimoto T. Cytoplasmic lipid droplets are sites of convergence of proteasomal and autophagic degradation of apolipoprotein B. *Mol Biol Cell*. 2006; 17:2674–2683. [PubMed: 16597703]
27. Ohsaki Y, Cheng J, Suzuki M, Fujita A, Fujimoto T. Lipid droplets are arrested in the ER membrane by tight binding of lipidated apolipoprotein B-100. *J Cell Sci*. 2008; 121:2415–2422. [PubMed: 18577578]

28. Meex SJ, Andreo U, Sparks JD, Fisher EA. Huh-7 or HepG2 cells: which is the better model for studying human apolipoprotein-B100 assembly and secretion? *J Lipid Res.* 2011; 52:152–158. [PubMed: 20956548]
29. Wang H, Chen X, Fisher EA. N-3 fatty acids stimulate intracellular degradation of apoprotein B in rat hepatocytes. *J Clin Invest.* 1993; 91:1380–1389. [PubMed: 8473489]
30. Wang H, Yao Z, Fisher EA. The effects of n-3 fatty acids on the secretion of carboxyl-terminally truncated forms of human apoprotein B. *J Biol Chem.* 1994; 269:18514–18520. [PubMed: 8034600]
31. Caviglia JM, Gayet C, Ota T, Hernandez-Ono A, Conlon DM, Jiang H, Fisher EA, Ginsberg HN. Different fatty acids inhibit apoB100 secretion by different pathways: unique roles for ER stress, ceramide, and autophagy. *J Lipid Res.* 2011; 52:1636–1651. [PubMed: 21719579]
32. Pan M, Cederbaum AI, Zhang YL, Ginsberg HN, Williams KJ, Fisher EA. Lipid peroxidation and oxidant stress regulate hepatic apolipoprotein B degradation and VLDL production. *J Clin Invest.* 2004; 113:1277–1287. [PubMed: 15124019]
33. Andreo U, Elkind J, Blachford C, Cederbaum AI, Fisher EA. Role of superoxide radical anion in the mechanism of apoB100 degradation induced by DHA in hepatic cells. *Faseb J.* 2011; 25:3554–3560. [PubMed: 21757500]
34. Qiu W, Zhang J, Dekker MJ, Wang H, Huang J, Brumell JH, Adeli K. Hepatic autophagy mediates endoplasmic reticulum stress-induced degradation of misfolded apolipoprotein B. *Hepatology.* 2011; 53:1515–1525. [PubMed: 21360721]
35. Ron D, Walter P. Signal integration in the endoplasmic reticulum unfolded protein response. *Nat Rev Mol Cell Biol.* 2007; 8:519–529. [PubMed: 17565364]
36. Chirieac DV, Chirieac LR, Corsetti JP, Cianci J, Sparks CE, Sparks JD. Glucose-stimulated insulin secretion suppresses hepatic triglyceride-rich lipoprotein and apoB production. *Am J Physiol Endocrinol Metab.* 2000; 279:E1003–1011. [PubMed: 11052954]
37. Sparks JD, Phung TL, Bolognino M, Sparks CE. Insulin-mediated inhibition of apolipoprotein B secretion requires an intracellular trafficking event and phosphatidylinositol 3-kinase activation: studies with brefeldin A and wortmannin in primary cultures of rat hepatocytes. *Biochem J.* 1996; 313:567–574. [PubMed: 8573094]
38. Ota T, Gayet C, Ginsberg HN. Inhibition of apolipoprotein B100 secretion by lipid-induced hepatic endoplasmic reticulum stress in rodents. *J Clin Invest.* 2008; 118:316–332. [PubMed: 18060040]
39. Samaha FF, McKenney J, Bloedon LT, Sasiela WJ, Rader DJ. Inhibition of microsomal triglyceride transfer protein alone or with ezetimibe in patients with moderate hypercholesterolemia. *Nat Clin Pract Cardiovasc Med.* 2008; 5:497–505. [PubMed: 18506154]
40. Benoist F, Grand-Perret T. Co-translational degradation of apolipoprotein B100 by the proteasome is prevented by microsomal triglyceride transfer protein. Synchronized translation studies on HepG2 cells treated with an inhibitor of microsomal triglyceride transfer protein. *J Biol Chem.* 1997; 272:20435–20442. [PubMed: 9252352]

HIGHLIGHTS

- Hepatic apolipoprotein B100 (apoB100) is subject to multiple pathways of degradation.
- Degradation of apoB100 determines the number of TG-rich VLDL particles secreted.
- Degradative pathways include ER-associated and post-ER proteolysis (PERPP).
- ApoB100 PERPP is mediated by autophagy in some cases (e.g., with fish oils).
- Autophagic PERPP may underlie sortilin-1 and insulin-mediated apoB100 degradation.