



Apolipoprotein B100 quality control and the regulation of hepatic very low density lipoprotein secretion

Roger McLeod , Eric Fisher, Elizabeth Lake

Biochemistry & Molecular Biology, Faculty of Medicine, Dalhousie University, Halifax, NS B3H 4R2, Canada.

Received 15 January 2014, Accepted 15 February 2014, Epub 28 March 2014

Supplementary References

References

- [36] Boren J, Rustaeus S, Olofsson SO. Studies on the assembly of apolipoprotein B-100- and B-48-containing very low density lipoproteins in McA-RH7777 cells. *The Journal of biological chemistry* 1994; 269: 25879–88.
- [37] Rustaeus S, Lindberg K, Boren J, Olofsson SO. Brefeldin A reversibly inhibits the assembly of apoB containing lipoproteins in McA-RH7777 cells. *J Biol Chem* 1995; 270: 28879–86.
- [38] Innerarity TL, Boren J, Yamanaka S, Olofsson SO. Biosynthesis of apolipoprotein B48-containing lipoproteins. regulation by novel post-transcriptional mechanisms. *J Biol Chem* 1996; 271: 2353–6.
- [39] Alexander CA, Hamilton RL, Havel RJ. Subcellular localization of B apoprotein of plasma lipoproteins in rat liver. *J Cell Biol* 1976; 69: 241–63.
- [40] Hamilton RL, Wong JS, Cham CM, Nielsen LB, Young SG. Chylomicron-sized lipid particles are formed in the setting of apolipoprotein B deficiency. *J Lipid Res* 1998; 39: 1543–57.
- [41] Rusinol A, Verkade H, Vance JE. Assembly of rat hepatic very low density lipoproteins in the endoplasmic reticulum. *The Journal of biological chemistry* 1993; 268: 3555–62.
- [42] Kulinski A, Rustaeus S, Vance JE. Microsomal triacylglycerol transfer protein is required for luminal accretion of triacylglycerol not associated with ApoB, as well as for ApoB lipidation. *J Biol Chem* 2002; 277: 31516–25.
- [43] Leiper JM, Bayliss JD, Pease RJ, Brett DJ, Scott J, Shoulders CC. Microsomal triglyceride transfer protein, the abetalipoproteinemia gene product, mediates the secretion of apolipoprotein B-containing lipoproteins from heterologous cells. *J Biol Chem* 1994; 269: 21951–4.
- [44] Gordon DA, Jamil H, Sharp D, Mullaney D, Yao Z, Gregg RE, et al. Secretion of apolipoprotein B-containing lipoproteins from HeLa cells is dependent on expression of the microsomal triglyceride transfer protein and is regulated by lipid availability. *Proc Natl Acad Sci U S A* 1994; 91: 7628–32.
- [45] Patel SB, Grundy SM. Interactions between microsomal triglyceride transfer protein and apolipoprotein B within the endoplasmic reticulum in a heterologous expression system. *J Biol Chem* 1996; 271: 18686–94.
- [46] Wang S, McLeod RS, Gordon DA, Yao Z. The microsomal triglyceride transfer protein facilitates assembly and secretion of apolipoprotein B-containing lipoproteins and decreases cotranslational degradation of apolipoprotein B in transfected COS-7 cells. *J Biol Chem* 1996; 271: 14124–33.
- [47] Liu Y, Manchekar M, Sun Z, Richardson PE, Dashti N. Apolipoprotein B-containing lipoprotein assembly in microsomal triglyceride transfer protein-deficient McA-RH7777 cells. *J Lipid Res* 2010; 51: 2253–64.
- [48] Rusinol AE, Jamil H, Vance JE. In vitro reconstitution of assembly of apolipoprotein B48-containing lipoproteins. *J Biol Chem* 1997; 272: 8019–25.
- [49] Herscovitz H, Kritis A, Talianidis I, Zanni E, Zannis V, Small DM. Murine mammary-derived cells secrete the N-terminal 41% of human apolipoprotein B on high density lipoprotein-sized lipoproteins containing a triacylglycerol-rich core. *Proc Natl Acad Sci U S A* 1995; 92: 659–63.
- [50] Sellers JA, Shelness GS. Lipoprotein assembly capacity of the mammary tumor-derived cell line C127 is due to the expression of functional microsomal triglyceride transfer protein. *J Lipid Res* 2001; 42: 1897–904.
- [51] Larsson SL, Skogsberg J, Bjorkegren J. The low density lipoprotein receptor prevents secretion of dense apoB100-containing lipoproteins from the liver. *J Biol Chem* 2004; 279: 831–6.
- [52] Pan M, Js JSL, Fisher EA, Ginsberg HN. The late addition of core lipids to nascent apolipoprotein B100, resulting in

- the assembly and secretion of triglyceride-rich lipoproteins, is independent of both microsomal triglyceride transfer protein activity and new triglyceride synthesis. *The Journal of biological chemistry* 2002; 277: 4413–21.
- [53] Swift LL, Zhu MY, Kakkad B, Jovanovska A, Neely MD, Valyi-Nagy K, et al. Subcellular localization of microsomal triglyceride transfer protein. *J Lipid Res* 2003; 44: 1841–9.
- [54] Gusarova V, Seo J, Sullivan ML, Watkins SC, Brodsky JL, Fisher EA. Golgi-associated maturation of very low density lipoproteins involves conformational changes in apolipoprotein B, but is not dependent on apolipoprotein E. *J Biol Chem* 2007; 282: 19453–62.
- [55] Pan X, Zhang Y, Wang L, Hussain MM. Diurnal regulation of MTP and plasma triglyceride by CLOCK is mediated by SHP. *Cell Metab*. 2010; 12: 174–86.
- [56] Chen Z, Newberry EP, Norris JY, Xie Y, Luo J, Kennedy SM, et al. ApoB100 is required for increased VLDL-triglyceride secretion by microsomal triglyceride transfer protein in ob/ob mice. *J Lipid Res* 2008; 49: 2013–22.
- [57] Iqbal J, Rudel LL, Hussain MM. Microsomal triglyceride transfer protein enhances cellular cholesteryl esterification by relieving product inhibition. *J Biol Chem* 2008; 283: 19967–80.
- [58] Minehira K, Young SG, Villanueva CJ, Yetukuri L, Oresic M, Hellerstein MK, et al. Blocking VLDL secretion causes hepatic steatosis but does not affect peripheral lipid stores or insulin sensitivity in mice. *J Lipid Res* 2008; 49: 2038–44.
- [59] Khatun I, Zeissig S, Iqbal J, Wang M, Curiel D, Shelness GS, et al. Phospholipid transfer activity of microsomal triglyceride transfer protein produces apolipoprotein B and reduces hepatosteatosis while maintaining low plasma lipids in mice. *Hepatology* 2012; 55: 1356–68.
- [60] Tep S, Mihaila R, Freeman A, Pickering V, Huyhn F, Tadin-Strapps M, et al. Rescue of mtp siRNA-induced hepatic steatosis by DGAT2 siRNA silencing. *J Lipid Res* 2012; 53: 859–67.
- [61] Sundaram M, Yao Z. Intrahepatic role of exchangeable apolipoproteins in lipoprotein assembly and secretion. *Arterioscler Thromb Vasc Biol* 2012; 32: 1073–8.
- [62] Lehner R, Lian J, Quiroga AD. Luminal lipid metabolism: Implications for lipoprotein assembly. *Arterioscler Thromb Vasc Biol* 2012; 32: 1087–93.
- [63] Sparks JD, Sparks CE, Adeli K. Selective hepatic insulin resistance, VLDL overproduction, and hypertriglyceridemia. *Arterioscler Thromb Vasc Biol* 2012; 32: 2104–12.
- [64] Xiao C, Hsieh J, Adeli K, Lewis GF. Gut-liver interaction in triglyceride-rich lipoprotein metabolism. *Am J Physiol Endocrinol Metab* 2011; 301: E429–46.
- [65] Sturley SL, Hussain MM. Lipid droplet formation on opposing sides of the endoplasmic reticulum. *J Lipid Res* 2012; 53: 1800–10.
- [66] Caviglia JM, Sparks JD, Toraskar N, Brinker AM, Yin TC, Dixon JL, et al. ABHD5/CGI-58 facilitates the assembly and secretion of apolipoprotein B lipoproteins by McA RH7777 rat hepatoma cells. *Biochim Biophys Acta* 2009; 1791: 198–205.
- [67] Quiroga AD, Li L, Trotschmuller M, Nelson R, Proctor SD, Kofeler H, et al. Deficiency of carboxylesterase 1/esterase-x results in obesity, hepatic steatosis, and hyperlipidemia. *Hepatology* 2012; 56: 2188–98.
- [68] Ko KW, Erickson B, Lehner R. Es-x/Ces1 prevents triacylglycerol accumulation in McArdle-RH7777 hepatocytes. *Biochim Biophys Acta* 2009; 1791: 1133–43.
- [69] Erickson B, Selvan SP, Ko KW, Kelly K, Quiroga AD, Li L, et al. Endoplasmic reticulum-localized hepatic lipase decreases triacylglycerol storage and VLDL secretion. *Biochim Biophys Acta* 2013; 1831: 1113–23.
- [70] Fuchs CD, Claudel T, Kumari P, Haemmerle G, Pollheimer MJ, Stojakovic T, et al. Absence of adipose triglyceride lipase protects from hepatic endoplasmic reticulum stress in mice. *Hepatology* 2012; 56: 270–80.
- [71] Morris EM, Meers GM, Booth FW, Fritsche KL, Hardin CD, Thyfault JP, et al. PGC-1alpha overexpression results in increased hepatic fatty acid oxidation with reduced triacylglycerol accumulation and secretion. *Am J Physiol Gastrointest Liver Physiol* 2012; 303: G979–92.
- [72] Ye J, Li JZ, Liu Y, Li X, Yang T, Ma X, et al. Cideb, an ER- and lipid droplet-associated protein, mediates VLDL lipidation and maturation by interacting with apolipoprotein B. *Cell metabolism* 2009; 9: 177–90.
- [73] Li X, Ye J, Zhou L, Gu W, Fisher EA, Li P. Opposing roles of cell death-inducing DFF45-like effector B and perilipin 2 in controlling hepatic VLDL lipidation. *J Lipid Res* 2012; 53: 1877–89.
- [74] Chen Z, Gropler MC, Norris J, Jr JCL, Harris TE, Finck BN. Alterations in hepatic metabolism in fld mice reveal a role for lipin 1 in regulating VLDL-triacylglyceride secretion. *Arterioscler Thromb Vasc Biol* 2008; 28: 1738–44.
- [75] Zheng C, Khoo C, Furtado J, Sacks FM. Apolipoprotein C-III and the metabolic basis for hypertriglyceridemia and the dense low-density lipoprotein phenotype. *Circulation* 2010; 121: 1722–34.
- [76] Lee HY, Birkenfeld AL, Jornayvaz FR, Jurczak MJ, Kanda S, Popov V, et al. Apolipoprotein CIII overexpressing mice are predisposed to diet-induced hepatic steatosis and hepatic insulin resistance. *Hepatology* 2011; 54: 1650–60.
- [77] Sundaram M, Zhong S, Khalil MB, Links PH, Zhao Y, Iqbal J, et al. Expression of apolipoprotein C-III in McA-RH7777 cells enhances VLDL assembly and secretion under lipid-rich conditions. *J Lipid Res* 2010; 51: 150–61.
- [78] Weinberg RB, Gallagher JW, Fabritius MA, Shelness GS. ApoA-IV modulates the secretory trafficking of apoB and the size of triglyceride-rich lipoproteins. *J Lipid Res* 2012; 53: 736–43.
- [79] Chan DC, Watts GF, Ooi EM, Chan DT, Wong AT, Barrett PH. Apolipoprotein A-II and adiponectin as determinants of very low-density lipoprotein apolipoprotein B-100 metabolism in nonobese men. *Metabolism* 2011; 60: 1482–7.
- [80] Triglyceride Coronary Disease Genetics Consortium and Emerging Risk Factors Collaboration, Sarwar N, Sandhu MS, Ricketts SL, Butterworth AS, Di Angelantonio E, et al. Triglyceride-mediated pathways and coronary disease: Collaborative analysis of 101 studies. *Lancet* 2010; 375: 1634–9.
- [81] Chung S, Gebre AK, Seo J, Shelness GS, Parks JS. A novel role for ABCA1-generated large pre-beta migrating

- nascent HDL in the regulation of hepatic VLDL triglyceride secretion. *J Lipid Res* 2010; 51: 729–42.
- [82] Wiersma H, Nijstad N, Gautier T, Iqbal J, Kuipers F, Hussain MM, et al. Scavenger receptor BI facilitates hepatic very low density lipoprotein production in mice. *J Lipid Res* 2010; 51: 544–53.
- [83] Willnow TE, Kjolby M, Nykjaer A. Sortilins: New players in lipoprotein metabolism. *Curr Opin Lipidol* 2011; 22: 79–85.
- [84] Kjolby M, Andersen OM, Breiderhoff T, Fjorback AW, Pedersen KM, Madsen P, et al. Sort1, encoded by the cardiovascular risk locus 1p13.3, is a regulator of hepatic lipoprotein export. *Cell Metab* 2010; 12: 213–23.
- [85] Ai D, Baez JM, Jiang H, Conlon DM, Hernandez-Ono A, Frank-Kamenetsky M, et al. Activation of ER stress and mTORC1 suppresses hepatic sortilin-1 levels in obese mice. *J Clin Invest* 2012; 122: 1677–87.
- [86] Strong A, Ding Q, Edmondson AC, Millar JS, Sachs KV, Li X, et al. Hepatic sortilin regulates both apolipoprotein B secretion and LDL catabolism. *J Clin Invest* 2012; 122: 2807–16.
- [87] Chamberlain JM, O'Dell C, Sparks CE, Sparks JD. Insulin suppression of apolipoprotein B in McArdle RH7777 cells involves increased sortilin 1 interaction and lysosomal targeting. *Biochem Biophys Res Commun* 2013; 430: 66–71.
- [88] Sun H, Samarghandi A, Zhang N, Yao Z, Xiong M, Teng BB. Proprotein convertase subtilisin/kexin type 9 interacts with apolipoprotein B and prevents its intracellular degradation, irrespective of the low-density lipoprotein receptor. *Arterioscler Thromb Vasc Biol* 2012; 32: 1585–95.
- [89] Levy E, Harmel E, Laville M, Sanchez R, Emonnot L, Sinnott D, et al. Expression of Sar1b enhances chylomicron assembly and key components of the coat protein complex II system driving vesicle budding. *Arterioscler Thromb Vasc Biol* 2011; 31: 2692–9.
- [90] Sparks JD, Collins HL, Chirieac DV, Cianci J, Jokinen J, Sowden MP, et al. Hepatic very-low-density lipoprotein and apolipoprotein B production are increased following in vivo induction of betaine-homocysteine S-methyltransferase. *Biochem J* 2006; 395: 363–71.
- [91] Sidiropoulos KG, Pontrelli L, Adeli K. Insulin-mediated suppression of apolipoprotein B mRNA translation requires the 5' UTR and is characterized by decreased binding of an insulin-sensitive 110-kDa 5' UTR RNA-binding protein. *Biochemistry (N Y)* 2005; 44: 12572–81.
- [92] Sidiropoulos KG, Zastepa A, Adeli K. Translational control of apolipoprotein B mRNA via insulin and the protein kinase C signaling cascades: Evidence for modulation of RNA-protein interactions at the 5'UTR. *Arch Biochem Biophys* 2007; 459: 10–9.
- [93] Pontrelli L, Sidiropoulos KG, Adeli K. Translational control of apolipoprotein B mRNA: Regulation via cis elements in the 5' and 3' untranslated regions. *Biochemistry (N Y)* 2004; 43: 6734–44.
- [94] Olofsson SO, Boren J. Apolipoprotein B secretory regulation by degradation. *Arterioscler Thromb Vasc Biol* 2012; 32: 1334–8.
- [95] Fisher EA, Ginsberg HN. Complexity in the secretory pathway: The assembly and secretion of apolipoprotein B-containing lipoproteins. *The Journal of biological chemistry* 2002; 277: 17377–80.
- [96] Ellgaard L, Molinari M, Helenius A. Setting the standards: Quality control in the secretory pathway. *Science* 1999; 286: 1882–8.
- [97] Schubert U, Anton LC, Gibbs J, Norbury CC, Yewdell JW, Bennink JR. Rapid degradation of a large fraction of newly synthesized proteins by proteasomes. *Nature* 2000; 404: 770–4.
- [98] Oyadomari S, Yun C, Fisher EA, Kreglinger N, Kreibich G, Oyadomari M, et al. Cotranslocational degradation protects the stressed endoplasmic reticulum from protein overload. *Cell* 2006; 126: 727–39.
- [99] Schroder M, Kaufman RJ. The mammalian unfolded protein response. *Annu Rev Biochem* 2005; 74: 739–89.
- [100] Brodsky JL. The protective and destructive roles played by molecular chaperones during ERAD (endoplasmic-reticulum-associated degradation). *Biochem J* 2007; 404: 353–63.
- [101] Brodsky JL, Gusarova V, Fisher EA. Vesicular trafficking of hepatic apolipoprotein B100 and its maturation to very low-density lipoprotein particles; studies from cells and cell-free systems. *Trends Cardiovasc Med* 2004; 14: 127–32.
- [102] Maattanen P, Gehring K, Bergeron JJ, Thomas DY. Protein quality control in the ER: The recognition of misfolded proteins. *Semin Cell Dev Biol* 2010; 21: 500–11.
- [103] 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: 1277–87.
- [104] Christian P, Sacco J, Adeli K. Autophagy: Emerging roles in lipid homeostasis and metabolic control. *Biochim Biophys Acta* 2013; 1831: 819–24.
- [105] Fourn VL, Park S, Jang I, Gaplovska-Kysela K, Guhl B, Lee Y, et al. Large protein complexes retained in the ER are dislocated by non-COPII vesicles and degraded by selective autophagy. *Cellular and molecular life sciences : CMLS* 2013; .
- [106] Bernasconi R, Galli C, Noack J, Bianchi S, Haan CA, Reggiori F, et al. Role of the SEL1L:LC3-I complex as an ERAD tuning receptor in the mammalian ER. *Mol Cell* 2012; 46: 809–19.
- [107] Borchardt RA, Davis RA. Intrahepatic assembly of very low density lipoproteins. rate of transport out of the endoplasmic reticulum determines rate of secretion. *J Biol Chem* 1987; 262: 16394–402.
- [108] Yeung SJ, Chen SH, Chan L. Ubiquitin-proteasome pathway mediates intracellular degradation of apolipoprotein B. *Biochemistry (N Y)* 1996; 35: 13843–8.
- [109] Samanez CH, Caron S, Briand O, Dehondt H, Duplan I, Kuipers F, et al. The human hepatocyte cell lines IHH and HepaRG: Models to study glucose, lipid and lipoprotein metabolism. *Arch Physiol Biochem* 2012; 118: 102–11.
- [110] 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: 152–8.
- [111] Cardozo C, Wu X, Pan M, Wang H, Fisher EA. The inhibition of microsomal triglyceride transfer protein activity in rat hepatoma cells promotes proteasomal and

- nonproteasomal degradation of apoprotein b100. *Biochemistry (N Y)* 2002; 41: 10105–14.
- [112] Dixon JL, Furukawa S, Ginsberg HN. Oleate stimulates secretion of apolipoprotein B-containing lipoproteins from hep G2 cells by inhibiting early intracellular degradation of apolipoprotein B. *J Biol Chem* 1991; 266: 5080–6.
- [113] 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: 20435–42.
- [114] Lapiere LR, Currie DL, Yao Z, Wang J, McLeod RS. Amino acid sequences within the beta1 domain of human apolipoprotein B can mediate rapid intracellular degradation. *J Lipid Res* 2004; 45: 366–77.
- [115] Fisher EA, Zhou M, Mitchell DM, Wu X, Omura S, Wang H, et al. The degradation of apolipoprotein B100 is mediated by the ubiquitin-proteasome pathway and involves heat shock protein 70. *The Journal of biological chemistry* 1997; 272: 20427–34.
- [116] Liang J, Wu X, Jiang H, Zhou M, Yang H, Angkeow P, et al. Translocation efficiency, susceptibility to proteasomal degradation, and lipid responsiveness of apolipoprotein B are determined by the presence of beta sheet domains. *The Journal of biological chemistry* 1998; 273: 35216–21.
- [117] Mitchell DM, Zhou M, Pariyarath R, Wang H, Aitchison JD, Ginsberg HN, et al. Apoprotein B100 has a prolonged interaction with the translocon during which its lipidation and translocation change from dependence on the microsomal triglyceride transfer protein to independence. *Proc Natl Acad Sci U S A* 1998; 95: 14733–8.
- [118] Zhou M, Wu X, Huang LS, Ginsberg HN. Apoprotein B100, an inefficiently translocated secretory protein, is bound to the cytosolic chaperone, heat shock protein 70. *J Biol Chem* 1995; 270: 25220–4.
- [119] Jiang ZG, Liu Y, Hussain MM, Atkinson D, McKnight CJ. Reconstituting initial events during the assembly of apolipoprotein B-containing lipoproteins in a cell-free system. *J Mol Biol* 2008; 383: 1181–94.
- [120] Baker BM, Tortorella D. Dislocation of an endoplasmic reticulum membrane glycoprotein involves the formation of partially dislocated ubiquitinated polypeptides. *The Journal of biological chemistry* 2007; 282: 26845–56.
- [121] Sato BK, Schulz D, Do PH, Hampton RY. Misfolded membrane proteins are specifically recognized by the transmembrane domain of the Hrd1p ubiquitin ligase. *Mol Cell* 2009; 34: 212–22.
- [122] Carvalho P, Goder V, Rapoport TA. Distinct ubiquitin-ligase complexes define convergent pathways for the degradation of ER proteins. *Cell* 2006; 126: 361–73.
- [123] Linnik KM, Herscovitz H. Multiple molecular chaperones interact with apolipoprotein B during its maturation. the network of endoplasmic reticulum-resident chaperones (ERp72, GRP94, calreticulin, and BiP) interacts with apolipoprotein b regardless of its lipidation state. *The Journal of biological chemistry* 1998; 273: 21368–73.
- [124] 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: 579–85.
- [125] 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: 316–32.
- [126] Grubb S, Guo L, Fisher EA, Brodsky JL. Protein disulfide isomerases contribute differentially to the endoplasmic reticulum-associated degradation of apolipoprotein B and other substrates. *Mol Biol Cell* 2012; 23: 520–32.
- [127] Adeli K, Macri J, Mohammadi A, Kito M, Urade R, Cavallo D. Apolipoprotein B is intracellularly associated with an ER-60 protease homologue in HepG2 cells. *The Journal of biological chemistry* 1997; 272: 22489–94.
- [128] Qiu W, Kohen-Avramoglu R, Rashid-Kolvear F, Au CS, Chong TM, Lewis GF, et al. Overexpression of the endoplasmic reticulum 60 protein ER-60 downregulates apoB100 secretion by inducing its intracellular degradation via a nonproteasomal pathway: Evidence for an ER-60-mediated and pCMB-sensitive intracellular degradative pathway. *Biochemistry (N Y)* 2004; 43: 4819–31.
- [129] Rutledge AC, Qiu W, Zhang R, Urade R, Adeli K. Role of cysteine-protease CGHC motifs of ER-60, a protein disulfide isomerase, in hepatic apolipoprotein B100 degradation. *Arch Biochem Biophys* 2013; 537: 104–12.
- [130] Liang S, Wu X, Fisher EA, Ginsberg HN. The amino-terminal domain of apolipoprotein B does not undergo retrograde translocation from the endoplasmic reticulum to the cytosol. proteasomal degradation of nascent apolipoprotein B begins at the carboxyl terminus of the protein, while apolipoprotein B is still in its original translocon. *The Journal of biological chemistry* 2000; 275: 32003–10.
- [131] Du EZ, Kurth J, Wang SL, Humiston P, Davis RA. Proteolysis-coupled secretion of the N terminus of apolipoprotein B. characterization of a transient, translocation arrested intermediate. *The Journal of biological chemistry* 1994; 269: 24169–76.
- [132] 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: 24891–900.
- [133] Liao W, Yeung SC, Chan L. Proteasome-mediated degradation of apolipoprotein B targets both nascent peptides cotranslationally before translocation and full-length apolipoprotein B after translocation into the endoplasmic reticulum. *J Biol Chem* 1998; 273: 27225–30.
- [134] Tsai J, Qiu W, Kohen-Avramoglu R, Adeli K. MEK-ERK inhibition corrects the defect in VLDL assembly in HepG2 cells: Potential role of ERK in VLDL-ApoB100 particle assembly. *Arterioscler Thromb Vasc Biol* 2007; 27: 211–8.
- [135] Fisher EA, Khanna NK, McLeod RS. Ubiquitination regulates the assembly of very low density lipoprotein in HepG2 cells and is the committing step of the apoB100 ERAD pathway. 2011; .
- [136] Cavallo D, McLeod RS, Rudy D, Aiton A, Yao Z, Adeli K. Intracellular translocation and stability of apolipoprotein B are inversely proportional to the length of the nascent polypeptide. *J Biol Chem* 1998; 273: 33397–405.

- [137] Yamaguchi J, Conlon DM, Liang JJ, Fisher EA, Ginsberg HN. Translocation efficiency of apolipoprotein B is determined by the presence of beta-sheet domains, not pause transfer sequences. *J Biol Chem* 2006; 281: 27063–71.
- [138] Fleig L, Bergbold N, Sahasrabudhe P, Geiger B, Kaltak L, Lemberg M. Ubiquitin-dependent intramembrane rhomboid protease promotes ERAD of membrane proteins. *Mol Cell* 2012; 47: 558–69.
- [139] Liang JS, Kim T, Fang S, Yamaguchi J, Weissman AM, Fisher EA, et al. Overexpression of the tumor autocrine motility factor receptor Gp78, a ubiquitin protein ligase, results in increased ubiquitinylation and decreased secretion of apolipoprotein B100 in HepG2 cells. *J Biol Chem* 2003; 278: 23984–8.
- [140] Hampton RY, Sommer T. Finding the will and the way of ERAD substrate retrotranslocation. *Curr Opin Cell Biol* 2012; .
- [141] Petris G, Casini A, Sasset L, Cesaratto F, Bestagno M, Cereseto A, et al. CD4 and BST-2/Tetherin proteins retro-translocate from endoplasmic reticulum to cytosol as partially folded and multimeric molecules. *J Biol Chem* 2014; 289: 1–12.
- [142] Pariyarath R, Wang H, Aitchison JD, Ginsberg HN, Welch WJ, Johnson AE, et al. Co-translational interactions of apoprotein B with the ribosome and translocon during lipoprotein assembly or targeting to the proteasome. *The Journal of biological chemistry* 2001; 276: 541–50.
- [143] Chen Y, Caherec FL, Chuck SL. Calnexin and other factors that alter translocation affect the rapid binding of ubiquitin to apoB in the Sec61 complex. *The Journal of biological chemistry* 1998; 273: 11887–94.
- [144] Junne T, Kocik L, Spiess M. The hydrophobic core of the Sec61 translocon defines the hydrophobicity threshold for membrane integration. *Mol Biol Cell* 2010; 21: 1662–70.
- [145] Lilley BN, Ploegh HL. A membrane protein required for dislocation of misfolded proteins from the ER. *Nature* 2004; 429: 834–40.
- [146] Ye Y, Shibata Y, Yun C, Ron D, Rapoport TA. A membrane protein complex mediates retro-translocation from the ER lumen into the cytosol. *Nature* 2004; 429: 841–7.
- [147] Dougan SK, Hu CC, Paquet ME, Greenblatt MB, Kim J, Lilley BN, et al. Derlin-2-deficient mice reveal an essential role for protein dislocation in chondrocytes. *Mol Cell Biol* 2011; 31: 1145–59.
- [148] Moore P, Bernardi KM, Tsai B. The Ero1alpha-PDI redox cycle regulates retro-translocation of cholera toxin. *Mol Biol Cell* 2010; 21: 1305–13.
- [149] Greenblatt EJ, Olzmann JA, Kopito RR. Derlin-1 is a rhomboid pseudoprotease required for the dislocation of mutant alpha-1 antitrypsin from the endoplasmic reticulum. *Nature structural & molecular biology* 2011; 18: 1147–52.
- [150] Carvalho P, Stanley AM, Rapoport TA. Retrotranslocation of a misfolded luminal ER protein by the ubiquitin-ligase Hrd1p. *Cell* 2010; 143: 579–91.
- [151] Stanley AM, Carvalho P, Rapoport T. Recognition of an ERAD-L substrate analyzed by site-specific *in vivo* photocrosslinking. *FEBS Lett* 2011; 585: 1281–6.
- [152] Horn SC, Hanna J, Hirsch C, Volkwein C, SchA 1/4tz A, Heinemann U, et al. Usa1 functions as a scaffold of the HRD-ubiquitin ligase. *Mol Cell* 2009; 36: 782–93.
- [153] Mehnert M, Sommer T, Jarosch E. Der1 promotes movement of misfolded proteins through the endoplasmic reticulum membrane. *Nat Cell Biol* 2014; 16: 77–86.
- [154] Fisher EA, Lapierre LR, Junkins RD, McLeod RS. The AAA-ATPase p97 facilitates degradation of apolipoprotein B by the ubiquitin-proteasome pathway. *J Lipid Res* 2008; 49: 2149–60.
- [155] Suzuki M, Otsuka T, Ohsaki Y, Cheng J, Taniguchi T, Hashimoto H, et al. Derlin-1 and UBXD8 are engaged in dislocation and degradation of lipidated ApoB-100 at lipid droplets. *Mol Biol Cell* 2012; 23: 800–10.
- [156] Wang CW, Lee SC. The ubiquitin-like (UBX)-domain-containing protein Ubx2/Ubxd8 regulates lipid droplet homeostasis. *J Cell Sci* 2012; 125: 2930–9.
- [157] Ye J. Cellular responses to unsaturated fatty acids mediated by their sensor Ubxd8. *Frontiers in Biology* 2012; 7: 397–403.
- [158] Moon YA, Liang G, Xie X, Frank-Kamenetsky M, Fitzgerald K, Koteliensky V, et al. The Scap/SREBP pathway is essential for developing diabetic fatty liver and carbohydrate-induced hypertriglyceridemia in animals. *Cell metabolism* 2012; 15: 240–6.
- [159] Martin S, Parton RG. Lipid droplets: A unified view of a dynamic organelle. *Nature reviews.Molecular cell biology* 2006; 7: 373–8.
- [160] Cermelli S, Guo Y, Gross SP, Welte MA. The lipid-droplet proteome reveals that droplets are a protein-storage depot. *Current biology : CB* 2006; 16: 1783–95.
- [161] Klemm EJ, Spooner E, Ploegh HL. Dual role of ancient ubiquitous protein 1 (AUP1) in lipid droplet accumulation and endoplasmic reticulum (ER) protein quality control. *The Journal of biological chemistry* 2011; 286: 37602–14.
- [162] Hartman IZ, Liu P, Zehmer JK, Luby-Phelps K, Jo Y, Anderson RGW, et al. Sterol-induced dislocation of 3-hydroxy-3-methylglutaryl coenzyme A reductase from endoplasmic reticulum membranes into the cytosol through a subcellular compartment resembling lipid droplets. *J Biol Chem* 2010; 285: 19288–98.
- [163] Wang L, Martin DD, Genter E, Wang J, McLeod RS, Small DM. Surface study of apoB1694-1880, a sequence that can anchor apoB to lipoproteins and make it nonexchangeable. *J Lipid Res* 2009; 50: 1340–52.
- [164] Komander D, Clague MJ, Urbe S. Breaking the chains: Structure and function of the deubiquitinases. *Nature reviews.Molecular cell biology* 2009; 10: 550–63.
- [165] Sowa ME, Bennett EJ, Gygi SP, Harper JW. Defining the human deubiquitinating enzyme interaction landscape. *Cell* 2009; 138: 389–403.
- [166] Liu Y, Ye Y. Roles of p97-associated deubiquitinases in protein quality control at the endoplasmic reticulum. *Curr Protein Pept Sci* 2012; 13: 436–46.
- [167] Meyer HH, Shorter JG, Seemann J, Pappin D, Warren G. A complex of mammalian ufd1 and npl4 links the AAA-ATPase, p97, to ubiquitin and nuclear transport pathways. *EMBO J* 2000; 19: 2181–92.
- [168] Wang Q, Liu Y, Soetandyo N, Baek K, Hegde R, Ye Y. A ubiquitin ligase-associated chaperone holdase maintains polypeptides in soluble states for proteasome degradation. *Mol Cell* 2011; 42: 758–70.
- [169] Takiyama Y, Nishizawa M, Tanaka H, Kawashima S, Sakamoto H, Karube Y, et al. The gene for machado-

- joseph disease maps to human chromosome 14q. *Nat Genet* 1993; 4: 300–4.
- [170] Zhong X, Pittman RN. Ataxin-3 binds VCP/p97 and regulates retrotranslocation of ERAD substrates. *Hum Mol Genet* 2006; 15: 2409–20.
- [171] Wang Q, Li L, Ye Y. Regulation of retrotranslocation by p97-associated deubiquitinating enzyme ataxin-3. *J Cell Biol* 2006; 174: 963–71.
- [172] Ernst R, Mueller B, Ploegh HL, Schlieker C. The otubain YOD1 is a deubiquitinating enzyme that associates with p97 to facilitate protein dislocation from the ER. *Mol Cell* 2009; 36: 28–38.
- [173] Bernardi KM, Williams JM, Inoue T, Schultz A, Tsai B. A deubiquitinase negatively regulates retro-translocation of nonubiquitinated substrates. *Mol Biol Cell* 2013; 24: 3545–56.
- [174] Liu Y, Soetandyo N, Lee JG, Liu L, Xu Y, Clemons WM Jr, et al. USP13 antagonizes gp78 to maintain functionality of a chaperone in ER-associated degradation. *Elife* 2014; 3: e01369.
- [175] Blount JR, Burr AA, Denuc A, Marfany G, Todi SV. Ubiquitin-specific protease 25 functions in endoplasmic reticulum-associated degradation. *PLoS One* 2012; 7: e36542.
- [176] Zhang ZR, Bonifacino JS, Hegde RS. Deubiquitinases sharpen substrate discrimination during membrane protein degradation from the ER. *Cell* 2013; 154: 609–22.
- [177] Kuang E, Qi J, Ronai Z. Emerging roles of E3 ubiquitin ligases in autophagy. *Trends Biochem Sci* 2013; 38: 453–60.
- [178] Seiberlich V, Borchert J, Zhukareva V, Richter-Landsberg C. Inhibition of protein deubiquitination by PR-619 activates the autophagic pathway in OLN-t40 oligodendroglial cells. *Cell Biochem Biophys* 2013; 67: 149–60.
- [179] Fisher EA. The degradation of apolipoprotein B100: Multiple opportunities to regulate VLDL triglyceride production by different proteolytic pathways. *Biochim Biophys Acta* 2012; 1821: 778–81.
- [180] Yang L, Li P, Fu S, Calay ES, Hotamisligil GS. Defective hepatic autophagy in obesity promotes ER stress and causes insulin resistance. *Cell metabolism* 2010; 11: 467–78.
- [181] Pan M, Maitin V, Parathath S, Andreo U, Lin SX, Germain CS, et al. Presecretory oxidation, aggregation, and autophagic destruction of apoprotein-B: A pathway for late-stage quality control. *Proc Natl Acad Sci U S A* 2008; 105: 5862–7.
- [182] Maitin V, Andreo U, Guo L, Fisher EA. Docosahexaenoic acid impairs the maturation of very low density lipoproteins in rat hepatic cells. *J Lipid Res* 2014; 55: 75–84.
- [183] Andreo U, Guo L, Chirieac DV, Tuyama AC, Montenont E, Brodsky JL, et al. Insulin-stimulated degradation of apolipoprotein B100: Roles of class II phosphatidylinositol-3-kinase and autophagy. *PLoS One* 2013; 8: e57590.
- [184] Sparks JD, O'Dell C, Chamberlain JM, Sparks CE. Insulin-dependent apolipoprotein B degradation is mediated by autophagy and involves class I and class III phosphatidylinositol 3-kinases. *Biochem Biophys Res Commun* 2013; 435: 616–20.
- [185] Allister EM, Mulvihill EE, Barrett PH, Edwards JY, Carter LP, Huff MW. Inhibition of apoB secretion from HepG2 cells by insulin is amplified by naringenin, independent of the insulin receptor. *J Lipid Res* 2008; 49: 2218–29.
- [186] Mulvihill EE, Allister EM, Sutherland BG, Telford DE, Sawyez CG, Edwards JY, et al. Naringenin prevents dyslipidemia, apolipoprotein B overproduction, and hyperinsulinemia in LDL receptor-null mice with diet-induced insulin resistance. *Diabetes* 2009; 58: 2198–210.
- [187] 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: 2674–83.
- [188] 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: 2415–22.
- [189] Qiu W, Avramoglu RK, Rutledge AC, Tsai J, Adeli K. Mechanisms of glucosamine-induced suppression of the hepatic assembly and secretion of apolipoprotein B-100-containing lipoproteins. *J Lipid Res* 2006; 47: 1749–61.
- [190] Qiu W, Su Q, Rutledge AC, Zhang J, Adeli K. Glucosamine-induced endoplasmic reticulum stress attenuates apolipoprotein B100 synthesis via PERK signaling. *J Lipid Res* 2009; 50: 1814–23.
- [191] Qiu W, Zhang J, Dekker MJ, Wang H, Huang J, Brumell JH, et al. Hepatic autophagy mediates endoplasmic reticulum stress-induced degradation of misfolded apolipoprotein B. *Hepatology* 2011; 53: 1515–25.
- [192] Komatsu M, Kageyama S, Ichimura Y. p62/SQSTM1/A170: Physiology and pathology. *Pharmacological research : the official journal of the Italian Pharmacological Society* 2012; 66: 457–62.
- [193] Komatsu M, Kurokawa H, Waguri S, Taguchi K, Kobayashi A, Ichimura Y, et al. The selective autophagy substrate p62 activates the stress responsive transcription factor Nrf2 through inactivation of Keap1. *Nat Cell Biol* 2010; 12: 213–23.
- [194] Digaleh H, Kiaei M, Khodaghli F. Nrf2 and Nrf1 signaling and ER stress crosstalk: Implication for proteasomal degradation and autophagy. *Cell Mol Life Sci* 2013; 70: 4681–94.
- [195] Ron D, Walter P. Signal integration in the endoplasmic reticulum unfolded protein response. *Nature reviews.Molecular cell biology* 2007; 8: 519–29.
- [196] Rutkowski DT, Hegde RS. Regulation of basal cellular physiology by the homeostatic unfolded protein response. *J Cell Biol* 2010; 189: 783–94.
- [197] Walter P, Ron D. The unfolded protein response: From stress pathway to homeostatic regulation. *Science (New York, N.Y.)* 2011; 334: 1081–6.
- [198] Rutkowski DT, Kaufman RJ. That which does not kill me makes me stronger: Adapting to chronic ER stress. *Trends Biochem Sci* 2007; 32: 469–76.
- [199] Sparks CE, Sparks JD. Hepatic postprandial transition and very low-density lipoprotein biogenesis. *Curr Opin Lipidol* 2013; 24: 450–2.
- [200] Ning J, Hong T, Ward A, Pi J, Liu Z, Liu HY, et al. Constitutive role for IRE1alpha-XBP1 signaling pathway in the insulin-mediated hepatic lipogenic program. *Endocrinology* 2011; 152: 2247–55.
- [201] Lee AH, Glimcher LH. Intersection of the unfolded protein response and hepatic lipid metabolism. *Cellular and molecular life sciences : CMLS* 2009; 66: 2835–50.

- [202] Wang S, Chen Z, Lam V, Han J, Hassler J, Finck B, et al. IRE1 \pm -XBPs induces PDI expression to increase MTP activity for hepatic VLDL assembly and lipid homeostasis. *Cell Metabolism* 2012; 16: 473–86.
- [203] Duvel K, Yecies JL, Menon S, Raman P, Lipovsky AI, Souza AL, et al. Activation of a metabolic gene regulatory network downstream of mTOR complex 1. *Mol Cell* 2010; 39: 171–83.
- [204] Cnop M, Foufelle F, Velloso LA. Endoplasmic reticulum stress, obesity and diabetes. *Trends Mol Med* 2012; 18: 59–68.
- [205] Pfaffenbach KT, Nivala AM, Reese L, Ellis F, Wang D, Wei Y, et al. Rapamycin inhibits postprandial-mediated X-box-binding protein-1 splicing in rat liver. *J Nutr* 2010; 140: 879–84.
- [206] Tremblay F, Brule S, Um SH, Li Y, Masuda K, Roden M, et al. Identification of IRS-1 ser-1101 as a target of S6K1 in nutrient- and obesity-induced insulin resistance. *Proc Natl Acad Sci U S A* 2007; 104: 14056–61.
- [207] Deng Y, Wang ZV, Tao C, Gao N, Holland WL, Ferdous A, et al. The Xbp1s/GalE axis links ER stress to postprandial hepatic metabolism. *J Clin Invest* 2013; 123: 455–68.
- [208] Haas ME, Attie AD, Biddinger SB. The regulation of ApoB metabolism by insulin. *Trends Endocrinol Metab* 2013; 24: 391–7.
- [209] Verges B. Abnormal hepatic apolipoprotein B metabolism in type 2 diabetes. *Atherosclerosis* 2010; 211: 353–60.
- [210] Li S, Brown MS, Goldstein JL. Bifurcation of insulin signaling pathway in rat liver: MTORC1 required for stimulation of lipogenesis, but not inhibition of gluconeogenesis. *Proc Natl Acad Sci U S A* 2010; 107: 3441–6.
- [211] Meshkani R, Adeli K. Hepatic insulin resistance, metabolic syndrome and cardiovascular disease. *Clin Biochem* 2009; 42: 1331–46.
- [212] Kammoun HL, Chabanon H, Hainault I, Luquet S, Magnan C, Koike T, et al. GRP78 expression inhibits insulin and ER stress-induced SREBP-1c activation and reduces hepatic steatosis in mice. *J Clin Invest* 2009; 119: 1201–15.
- [213] Kumashiro N, Erion DM, Zhang D, Kahn M, Beddow SA, Chu X, et al. Cellular mechanism of insulin resistance in nonalcoholic fatty liver disease. *Proc Natl Acad Sci U S A* 2011; 108: 16381–5.
- [214] Pour NK, Adeli K. Insulin silences apolipoprotein B mRNA translation by inducing intracellular traffic into cytoplasmic RNA granules. *Biochemistry (N Y)* 2011; 50: 6942–50.
- [215] Sparks JD, Chamberlain JM, O'Dell C, Khatun I, Hussain MM, Sparks CE. Acute suppression of apo B secretion by insulin occurs independently of MTP. *Biochem Biophys Res Commun* 2011; 406: 252–6.
- [216] Tsai J, Zhang R, Qiu W, Su Q, Naples M, Adeli K. Inflammatory NF-kappaB activation promotes hepatic apolipoprotein B100 secretion: Evidence for a link between hepatic inflammation and lipoprotein production. *American Journal of Physiology. Gastrointestinal and Liver Physiology* 2009; 296: G1287–98.
- [217] Peairs AD, Rankin JW, Lee YW. Effects of acute ingestion of different fats on oxidative stress and inflammation in overweight and obese adults. *Nutrition journal* 2011; 10: 122.
- [218] Pellis L, Erk MJv, Ommen Bv, Bakker GC, Hendriks HF, Cnubben NH, et al. Plasma metabolomics and proteomics profiling after a postprandial challenge reveal subtle diet effects on human metabolic status. *Metabolomics : Official journal of the Metabolomic Society* 2012; 8: 347–59.
- [219] Hotamisligil GS. Endoplasmic reticulum stress and the inflammatory basis of metabolic disease. *Cell* 2010; 140: 900–17.
- [220] Rath E, Haller D. Inflammation and cellular stress: A mechanistic link between immune-mediated and metabolically driven pathologies. *Eur J Nutr* 2011; 50: 219–33.
- [221] Garg AD, Kaczmarek A, Krysko O, Vandenabeele P, Krysko DV, Agostinis P. ER stress-induced inflammation: Does it aid or impede disease progression? *Trends Mol Med* 2012; .
- [222] Basciano H, Miller A, Baker C, Naples M, Adeli K. LXRalpha activation perturbs hepatic insulin signaling and stimulates production of apolipoprotein B-containing lipoproteins. *American Journal of Physiology. Gastrointestinal and Liver Physiology* 2009; 297: G323–32.
- [223] Okazaki H, Goldstein JL, Brown MS, Liang G. LXR-SREBP-1c-phospholipid transfer protein axis controls very low density lipoprotein (VLDL) particle size. *The Journal of biological chemistry* 2010; 285: 6801–10.
- [224] Li Z, Agellon LB, Allen TM, Umeda M, Jewell L, Mason A, et al. The ratio of phosphatidylcholine to phosphatidylethanolamine influences membrane integrity and steatohepatitis. *Cell metabolism* 2006; 3: 321–31.
- [225] Rong X, Albert CJ, Hong C, Duerr MA, Chamberlain BT, Tarling EJ, et al. LXRs regulate ER stress and inflammation through dynamic modulation of membrane phospholipid composition. *Cell Metab* 2013; 18: 685–97.
- [226] Fu S, Yang L, Li P, Hofmann O, Dicker L, Hide W, et al. Aberrant lipid metabolism disrupts calcium homeostasis causing liver endoplasmic reticulum stress in obesity. *Nature* 2011; 473: 528–31.
- [227] Magkos F, Fabbrini E, Mohammed BS, Patterson BW, Klein S. Increased whole-body adiposity without a concomitant increase in liver fat is not associated with augmented metabolic dysfunction. *Obesity (Silver Spring)* 2010; 18: 1510–5.
- [228] Duvillard L, Florentin E, Pont F, Petit JM, Baillot-Rudoni S, Penfornis A, et al. Endogenous chronic hyperinsulinemia does not increase the production rate of VLDL apolipoprotein B: Proof from a kinetic study in patients with insulinoma. *J Clin Endocrinol Metab* 2011; 96: 2163–70.
- [229] Qiu W, Federico L, Naples M, Avramoglu RK, Meshkani R, Zhang J, et al. Phosphatase and tensin homolog (PTEN) regulates hepatic lipogenesis, microsomal triglyceride transfer protein, and the secretion of apolipoprotein B-containing lipoproteins. *Hepatology* 2008; 48: 1799–809.
- [230] Moon BC, Hernandez-Ono A, Stiles B, Wu H, Ginsberg HN. Apolipoprotein B secretion is regulated by hepatic triglyceride, and not insulin, in a model of increased hepatic insulin signaling. *Arterioscler Thromb Vasc Biol* 2012; 32: 236–46.
- [231] Ren LP, Chan SM, Zeng XY, Laybutt DR, Iseli TJ, Sun RQ, et al. Differing endoplasmic reticulum stress response

- to excess lipogenesis versus lipid oversupply in relation to hepatic steatosis and insulin resistance. *PLoS one* 2012; 7: e30816.
- [232] Higuchi N, Kato M, Tanaka M, Miyazaki M, Takao S, Kohjima M, et al. Effects of insulin resistance and hepatic lipid accumulation on hepatic mRNA expression levels of apoB, MTP and L-FABP in non-alcoholic fatty liver disease. *Experimental and therapeutic medicine* 2011; 2: 1077–81.
- [233] Su Q, Tsai J, Xu E, Qiu W, Berezcki E, Santha M, et al. Apolipoprotein B100 acts as a molecular link between lipid-induced endoplasmic reticulum stress and hepatic insulin resistance. *Hepatology* 2009; 50: 77–84.
- [234] Yao Z, Zhou H, Figeys D, Wang Y, Sundaram M. Microsome-associated luminal lipid droplets in the regulation of lipoprotein secretion. *Curr Opin Lipidol* 2012; .
- [235] Fu S, Watkins SM, Hotamisligil GS. The role of endoplasmic reticulum in hepatic lipid homeostasis and stress signaling. *Cell metabolism* 2012; 15: 623–34.
- [236] Calderwood SK, Murshid A, Prince T. The shock of aging: Molecular chaperones and the heat shock response in longevity and aging—a mini-review. *Gerontology* 2009; 55: 550–8.
- [237] Morimoto RI. The heat shock response: Systems biology of proteotoxic stress in aging and disease. *Cold Spring Harb Symp Quant Biol* 2011; 76: 91–9.
- [238] Xiao C, Giacca A, Lewis GF. Sodium phenylbutyrate, a drug with known capacity to reduce endoplasmic reticulum stress, partially alleviates lipid-induced insulin resistance and beta-cell dysfunction in humans. *Diabetes* 2011; 60: 918–24.
- [239] Kars M, Yang L, Gregor MF, Mohammed BS, Pietka TA, Finck BN, et al. Tauroursodeoxycholic acid may improve liver and muscle but not adipose tissue insulin sensitivity in obese men and women. *Diabetes* 2010; 59: 1899–905.
- [240] Imrie D, Sadler KC. Stress management: How the unfolded protein response impacts fatty liver disease. *J Hepatol* 2012; 57: 1147–51.