BIOGRAPHICAL SKETCH

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NAME: Lu, Yongke

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POSITION TITLE: Assistant Professor

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE (if applicable)	END DATE MM/YYYY	FIELD OF STUDY
Shanxi Medical University, Taiyuan, China	MD	07/1991	Preventive medicine
Dalian Medical University, Dalian, China	PHD	06/2008	Biochemical and molecular toxicology
Mount Sinai School of Medicine, New York, NY	Postdoc	12/2008	Alcoholic liver disease

A. Personal Statement

I have been studying alcohol-associated fatty liver disease (ALD) since 2005. A few years ago, we found that mouse cytochrome P450 2A5 (CYP2A5), the ortholog of human CYP2A6, was induced by ethanol feeding. Ethanol induction of CYP2A5 is regulated by Nrf2, a redox-sensitive transcription factor, implicating that CYP2A5 is an antioxidant enzyme. Experiments with *cyp2a5*$^{-/-}$ mice demonstrated that CYP2A5 is protective against ALD. Nicotine is mainly metabolized by CYP2A5 and CYP2A6. We found that nicotine enhanced alcoholic fatty liver, which is due to oxidative stress in the process of CYP2A metabolizing nicotine. Interestingly, nicotine and its metabolite cotinine upregulate expression of *cdkn1a* gene, which encode P21 protein, an inhibitor of cell proliferation. We are applying *cdkn1a*$^{-/-}$ mice and liver stem cells to examine the role of suppressed hepatocyte proliferation on nicotine-enhanced ALD.

Recently, my research interests have been extended to obesity and nonalcoholic fatty liver disease (NAFLD). We found that HFD-induced NAFLD was more pronounced in *cyp2a5*$^{-/-}$ mice than in WT mice, suggesting that CYP2A5 also protects against NAFLD. Interestingly, PPARα was up-regulated in *cyp2a5*$^{-/-}$ mice, and PPARα-deficient *cyp2a5*$^{-/-}$ mice (i.e. *pparα*$^{-/-}$/*cyp2a5*$^{-/-}$ mice) enhanced HFD-induced NAFLD ranging from steatosis, to steatohepatitis and fibrosis. We are studying on the molecular mechanisms by which steatotic hepatocytes activate hepatic stellate cells (HSC) to promote liver fibrosis. In addition, we also investigate the effect of nicotine on high fat diet-induced obesity and NAFLD.

1. Wang K, Chen X, Ward SC, Liu Y, Ouedraogo Y, Xu C, Cederbaum AI, Lu Y. CYP2A6 is associated with obesity: studies in human samples and a high fat diet mouse model. Int J Obes (Lond). 2018 Feb 20;PubMed PMID: 29568101; PubMed Central PMCID: PMC6102101.
2. Chen X, Owoseni E, Salamat J, Cederbaum AI, Lu Y. Nicotine enhances alcoholic fatty liver in mice: Role of CYP2A5. Arch Biochem Biophys. 2018 Sep 15;657:65-73. PubMed PMID: 30222954.
3. Chen X, Ward SC, Cederbaum AI, Xiong H, Lu Y. Alcoholic fatty liver is enhanced in CYP2A5 knockout mice: The role of the PPARα-FGF21 axis. Toxicology. 2017 Mar 15;379:12-21. PubMed PMID: 28131861; PubMed Central PMCID: PMC5319905.
4. Lu Y, Zhang XH, Cederbaum AI. Ethanol induction of CYP2A5: role of CYP2E1-ROS-Nrf2 pathway. Toxicol Sci. 2012 Aug;128(2):427-38. PubMed PMID: 22552773; PubMed Central PMCID: PMC3493190.

B. Positions and Honors

Positions and Employment

2019-	Assistant Professor, Marshall University, Huntington, WV
2016 -2019	Assistant Professor, East Tennessee State University, Johnson City, TN
2009 - 2016	Research Assistant Professor, Icahn School of Medicine at Mount Sinai, New York, NY

Other Experience and Professional Memberships

2006 - Full member, Society of Toxicology

Honors

2000 Excellence in Teaching, Dalian Medical University, China

C. Contribution to Science

For a complete publication list: https://www.ncbi.nlm.nih.gov/pubmed/?term=lu+yongke

1. CYP2E1 was found to be induced by alcohol consumption, but it was still controversial whether CYP2E1 contributes to alcoholic liver disease. With an intragastric infusion model and *cyp2e1*$^{-/-}$ mice, Kono et al (Am J Physiol. 1999; 277: G1259-67) did not observe any difference in ALD between *cyp2e1*$^{-/-}$ mice and WT mice. Endotoxemia was considered as a major reason for the development of ALD: alcohol consumption increases permeability of gut wall and causes a leak of gut-derived LPS into blood from gut lumens; the LPS enters liver via portal vein and activates kupffer cells to produce TNF α, which results in liver damage. We found that CYP2E1 can enhance LPS liver injury. Then we applied an oral feeding model instead of the intragastric infusion model to examine the role of CYP2E1 in ALD. We found that ALD was observed in WT mice but not in *cyp2e1*$^{-/-}$ mice, importantly, when human CYP2E1 was re-introduced to *cyp2e1*$^{-/-}$ mice, the development of ALD was restored, suggesting that CYP2E1 is essential for the development of ALD.

    a. Lu Y, Wu D, Wang X, Ward SC, Cederbaum AI. Chronic alcohol-induced liver injury and oxidant stress are decreased in cytochrome P4502E1 knockout mice and restored in humanized cytochrome P4502E1 knock-in mice. Free Radic Biol Med. 2010 Nov 15;49(9):1406-16. PubMed PMID: 20692331; PubMed Central PMCID: PMC2975513.
    b. Lu Y, Zhuge J, Wang X, Bai J, Cederbaum AI. Cytochrome P450 2E1 contributes to ethanol-induced fatty liver in mice. Hepatology. 2008 May;47(5):1483-94. PubMed PMID: 18393316.
    c. Lu Y, Cederbaum AI. Enhancement by pyrazole of lipopolysaccharide-induced liver injury in mice: role of cytochrome P450 2E1 and 2A5. Hepatology. 2006 Jul;44(1):263-74. PubMed PMID: 16799984.
    d. Lu Y, Wang X, Cederbaum AI. Lipopolysaccharide-induced liver injury in rats treated with the CYP2E1 inducer pyrazole. Am J Physiol Gastrointest Liver Physiol. 2005 Aug;289(2):G308-19. PubMed PMID: 15845871.

2. Alcoholic fatty liver disease ranges from fatty liver, inflammation, liver fibrosis and cirrhosis. Alcohol feeding does not induce evident liver fibrosis, so we applied carbon tetrachloride (CCL4), thioacetamide (TAA), and bile duct ligation (BDL) model to induce liver fibrosis. WE examine the role of osteopontin-HMGB1 axis, fibromodulin, and CYP2A5 in liver fibrogenesis.

    a. Arriazu E, Ge X, Leung TM, Magdaleno F, Lopategi A, Lu Y, Kitamura N, Urtasun R, Theise N, Antoine DJ, Nieto N. Signalling via the osteopontin and high mobility group box-1 axis drives the fibrogenic response to liver injury. Gut. 2017 Jun;66(6):1123-1137. PubMed PMID: 26818617; PubMed Central PMCID: PMC5532463.
    b. Hong F, Si C, Gao P, Cederbaum AI, Xiong H, Lu Y. The role of CYP2A5 in liver injury and fibrosis: chemical-specific difference. Naunyn Schmiedebergs Arch Pharmacol. 2016 Jan;389(1):33-43. PubMed PMID: 26363552; PubMed Central PMCID: PMC4703559.
    c. Wang X, Lopategi A, Ge X, Lu Y, Kitamura N, Urtasun R, Leung TM, Fiel MI, Nieto N. Osteopontin induces ductular reaction contributing to liver fibrosis. Gut. 2014 Nov;63(11):1805-18. PubMed PMID: 24496779.
    d. Mormone E, Lu Y, Ge X, Fiel MI, Nieto N. Fibromodulin, an oxidative stress-sensitive proteoglycan, regulates the fibrogenic response to liver injury in mice. Gastroenterology. 2012 Mar;142(3):612-621.e5. PubMed PMID: 22138190; PubMed Central PMCID: PMC3800000.

3. Levels of CYP2A6 were found to be increased in livers of patients with alcoholic or non-alcoholic liver disease. We examined liver samples from the mice subjected to oral alcohol feeding in a Lieber-DeCarli

liquid diet and found that CYP2A5 was strikingly up-regulated. more severe ALD was induced in *cyp2a5*$^{-/-}$ mice than in WT mice, suggesting that CYP2A5 protects against but not promote the development of ALD. Recently, we found that CYP2A5 interact with a PPARα-FGF21 axis to protect against alcoholic fatty liver.

a. Chen X, Ward SC, Cederbaum AI, Xiong H, Lu Y. Alcoholic fatty liver is enhanced in CYP2A5 knockout mice: The role of the PPARα-FGF21 axis. Toxicology. 2017 Mar 15;379:12-21. PubMed PMID: 28131861; PubMed Central PMCID: PMC5319905.
b. Hong F, Liu X, Ward SS, Xiong H, Cederbaum AI, Lu Y. Absence of cytochrome P450 2A5 enhances alcohol-induced liver injury in mice. Dig Liver Dis. 2015 Jun;47(6):470-7. PubMed PMID: 25804444; PubMed Central PMCID: PMC4442740.
c. Lu Y, Zhang XH, Cederbaum AI. Ethanol induction of CYP2A5: role of CYP2E1-ROS-Nrf2 pathway. Toxicol Sci. 2012 Aug;128(2):427-38. PubMed PMID: 22552773; PubMed Central PMCID: PMC3493190.
d. Lu Y, Zhuge J, Wu D, Cederbaum AI. Ethanol induction of CYP2A5: permissive role for CYP2E1. Drug Metab Dispos. 2011 Feb;39(2):330-6. PubMed PMID: 21051534; PubMed Central PMCID: PMC3033694.

4. Alcohol and tobacco are frequently co-abused. Nicotine is a major addiction-forming alkaloid in tobacco smoke. In humans, the major nicotine metabolizing enzyme is CYP2A6; in mice, it is CYP2A5. About 80% of nicotine is metabolized by CYP2A5/6 in mice. Alcohol consumption induces CYP2A5/6, and the induced enzyme metabolizes nicotine very quickly and decrease blood levels of nicotine dramatically. Thus, one has to smoke more tobacco to maintain blood nicotine levels. This might be one of the major reasons why, alcohol and tobacco are frequently co-abused. Recently, we found that nicotine can enhance alcoholic fatty liver. Very interestingly, the nicotine-enhanced alcoholic fatty liver was observed in WT mice but not in *cyp2a5*$^{-/-}$ mice, suggesting that CYP2A5 is essential for the enhancing effects of nicotine.

a. Chen X, Owoseni E, Salamat J, Cederbaum AI, Lu Y. Nicotine enhances alcoholic fatty liver in mice: Role of CYP2A5. Arch Biochem Biophys. 2018 Sep 15;657:65-73. PubMed PMID: 30222954.

b. Lu Y, Ward SC, Cederbaum AI. Nicotine enhances ethanol-induced fat accumulation and collagen deposition but not inflammation in mouse liver. Alcohol. 2013 Aug;47(5):353-7. PubMed PMID: 23731694; PubMed Central PMCID: PMC3723131.

c. Chen X, Wang K, Cederbaum AI, Lu Y. Suppressed hepatocyte proliferation via a ROS-HNE-P21 pathway is associated with nicotine- and cotinine-enhanced alcoholic fatty liver in mice. Biochem Biophys Res Commun. 2019 Apr 23;512(1):119-124. PubMed PMID: 30876690.

5. CYP2A6 (CYP2A5 in mice) is mainly expressed in the liver. Hepatic CYP2A6 expression is increased in patients with non-alcoholic fatty liver disease (NAFLD). Hepatic CYP2A5 is also increased in monosodium glutamate-induced obese mice. NAFLD is associated with obesity. we found that CYP2A6 is associated with obesity in a human population, and CYP2A5 protects against HFD-induced obesity and NAFLD in mice. PPARα interacts with CYP2A5 to protect against NAFLD but promote obesogenesis.

d. Wang K, Chen X, Ward SC, Liu Y, Ouedraogo Y, Xu C, Cederbaum AI, Lu Y. CYP2A6 is associated with obesity: studies in human samples and a high fat diet mouse model. Int J Obes (Lond). 2018 Feb 20;PubMed PMID: 29568101; PubMed Central PMCID: PMC6102101.

D. Additional Information: Research Support and/or Scholastic Performance

Ongoing Research Support

Marshall University Startup Funds
Lu, Yongke (PI)
11/25/19-11/24/22

R01 AA-024723, NIAAA
Lu, Yongke (PI)
07/15/16-06/30/21
Nicotine and alcoholic liver disease

Completed Research Support

R21 AA020877, NIAAA
Lu, Yongke (PI)
09/01/13-08/31/16
CYP2A5 and alcoholic liver disease