

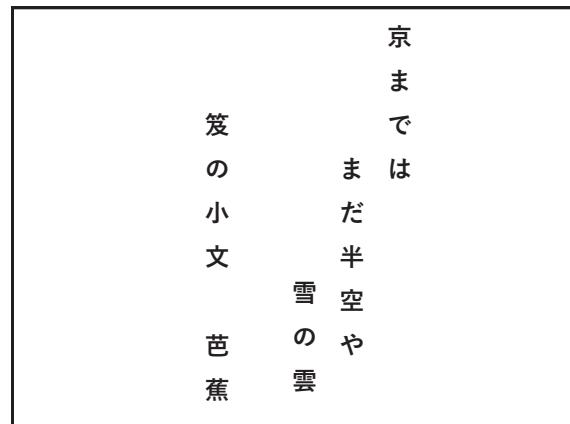
# 最 終 講 義



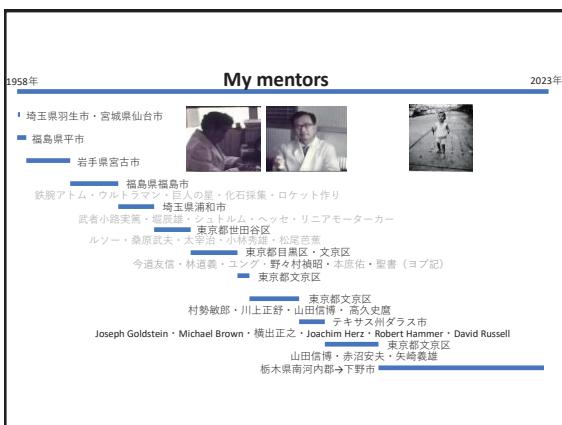
北岳（南アルプス）3192m 3回登頂



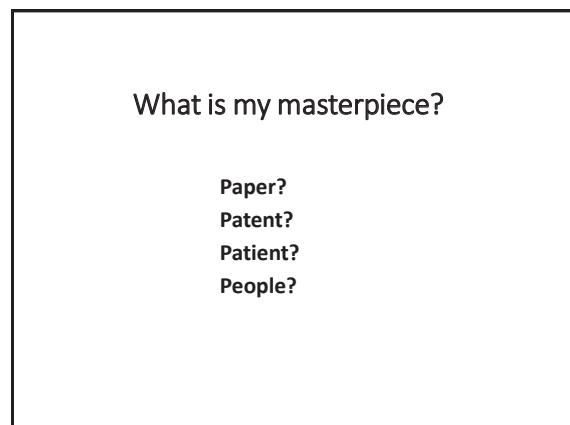
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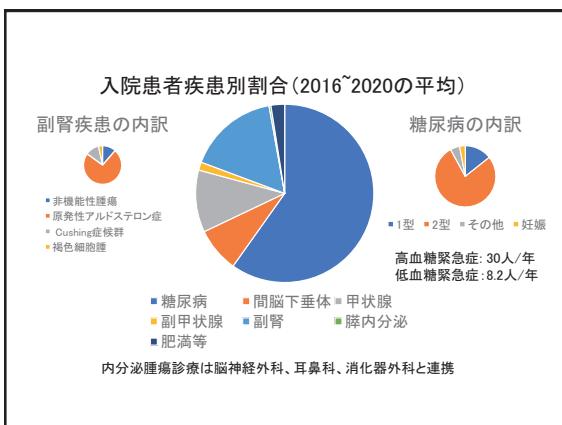
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3



4



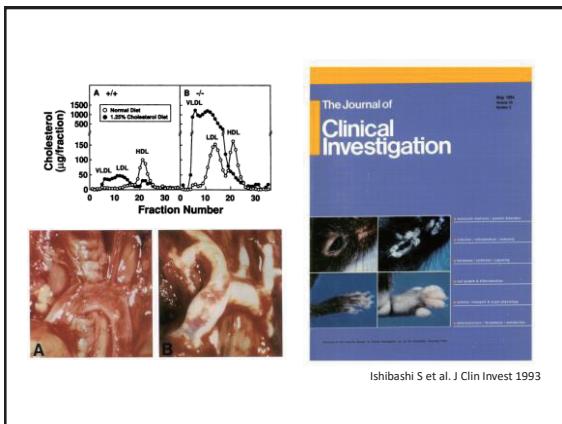
5

自治医大で出会った希少疾患

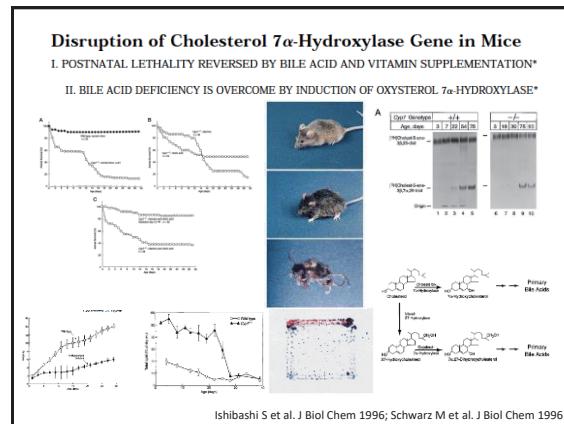
無セロロプラスミン血症	CP	Muroi R et al. Diabet Med 2006
LCAT欠損症	LCAT	Wang XL et al. J Atheroscler Thromb 2011
インスリン受容体異常症	IR	Enkhtuvshin B et al. Diabet Med 2015, 自治医大紀要2016
高カロール酸血症合併肝細胞癌	PCSK9T	Nagashima S et al. J Atheroscler Thromb 2016
無リボタバク血症	MTTP	Takahashi M et al. J Clin Lipidol 2021
Kallmann syndrome 合併 Waardenburg syndrome	SOX10	Wakabayashi T et al. Endocrinol Diabetes Metab Case Rep. 2021
VIPoma	MEN1	Sakurai M et al. Endocr J in press
高カロイロミクロン血症	LPL	未発表
高カロイロミクロン血症	GPR181	未発表
Tanger病	ABCA1	未発表

6

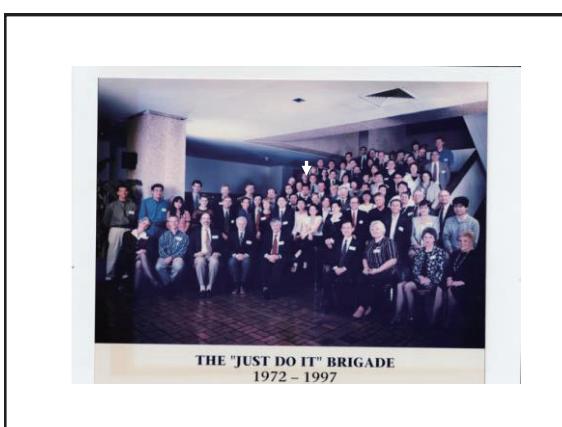




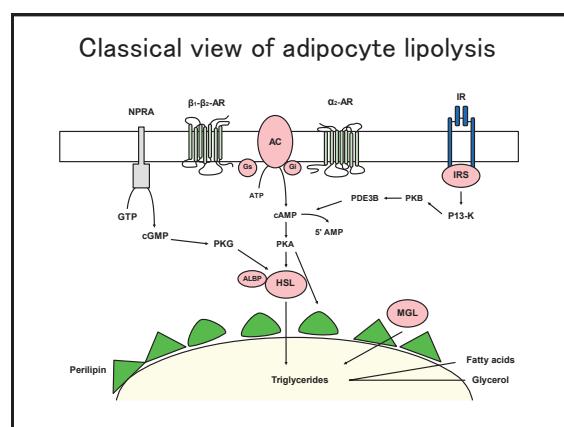
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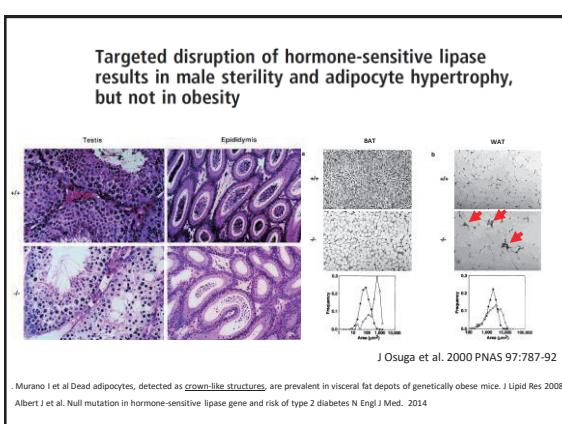
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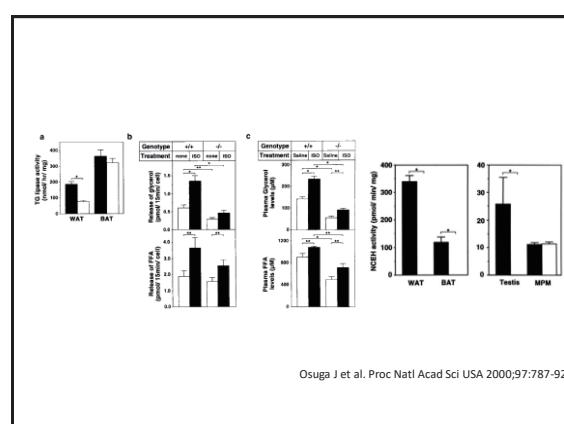
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16

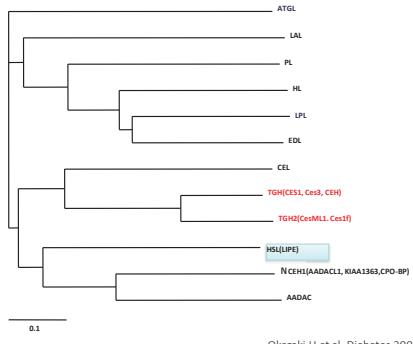


17



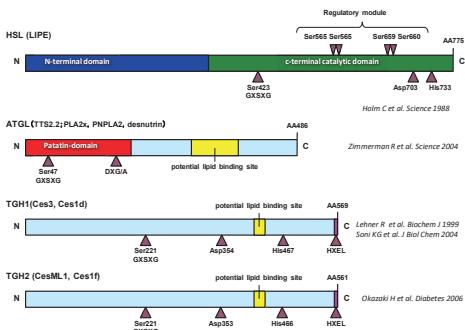
18

### Family of neutral lipid hydrolases



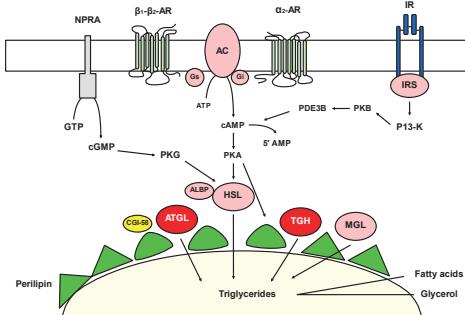
19

### Lipases responsible for adipocyte lipolysis



20

### Current view of adipocyte lipolysis



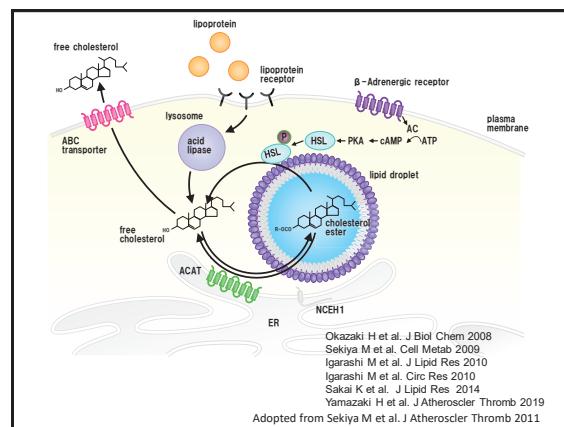
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22

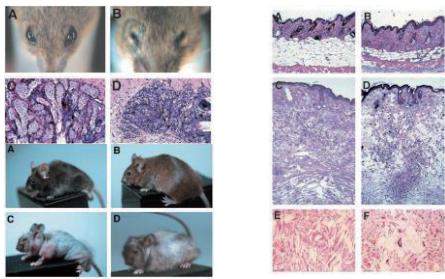


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24

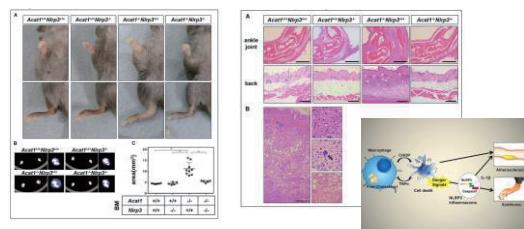
Absence of ACAT-1 Attenuates Atherosclerosis but Causes Dry Eye and Cutaneous Xanthomatosis in Mice with Congenital Hyperlipidemia\*



Yagyu H et al. J Biol Chem 2000

25

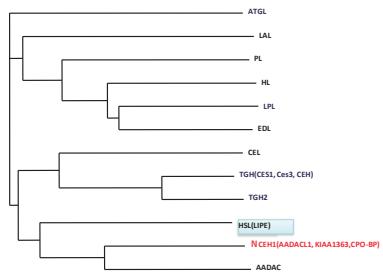
Inflammasome Activation Aggravates Cutaneous Xanthomatosis and Atherosclerosis in ACAT1 (Acyl-CoA Cholesterol Acyltransferase 1) Deficiency in Bone Marrow



Wakabayashi T et al. Arterioscler Thromb Vasc Biol 2018

26

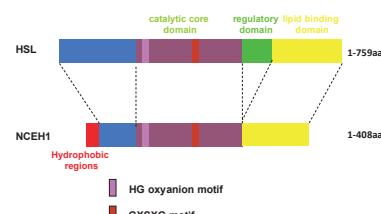
### Family of neutral lipid hydrolases



Okazaki H et al. J Biol Chem 2008;283:33357-64

27

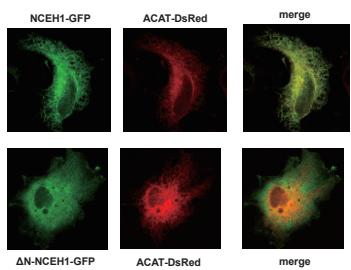
### Structure of NCEH1



Okazaki H et al. J Biol Chem 2008;283:33357-64  
Igarashi M et al. J Lipid Res 2010; 51:274-285

28

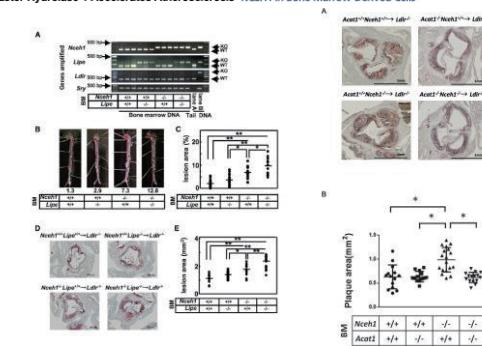
### Targeting of NCEH1 to ER requires the N-terminal sequence



Igarashi M et al. J Lipid Res 2010; 51:274-285

29

### Ablation of Neutral Cholesterol Ester Hydrolase 1 Accelerates Atherosclerosis Loss of ACAT1 Attenuates Atherosclerosis Aggravated by Loss of NCEH1 in Bone Marrow-Derived Cells



Sekiya M et al. Cell Metab 2009  
Yamazaki H et al. J Atheroscler Thromb 2019

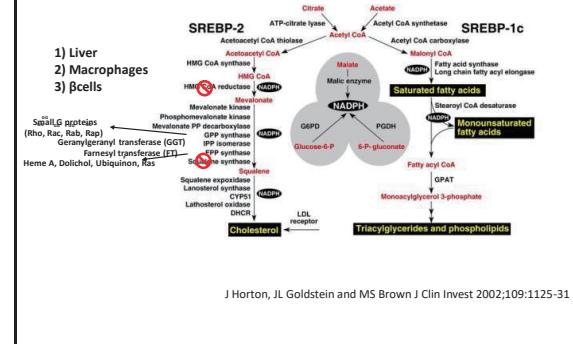
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210

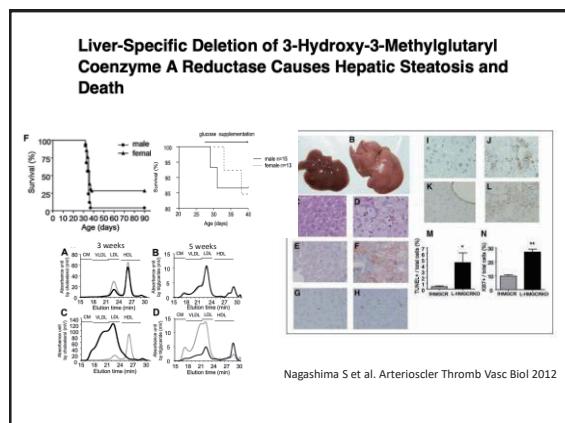
## Conditional knockout mice (2000~)

Gene	Promotor/procedure	Reference
HMG-CoA reductase	Albumin	Nagashima S et al. Arterioscler Thromb Vasc Biol. 2012
	Alfa skeletal actin	Osaki Y et al. BBRC 2015
Lysozyme	Sakai K et al. Arterioscler Thromb Vasc Biol. 2018	
Lysozyme		Takei A et al. Diabetes. 2020
Insulin		Takei S et al. Diabetes. 2020
Squalene synthase	2',3'-cyclic nucleotide phosphodiesterase (CNP)	Saher G et al. Nat Neurosci. 2005
Albumin	Nagashima S et al. J Lipid Res. 2015	
Lipoprotein lipase	Lysozyme	Takahashi M et al. J Lipid Res. 2013
	Lysozyme	Takahashi M et al. J Biol Chem. 2022

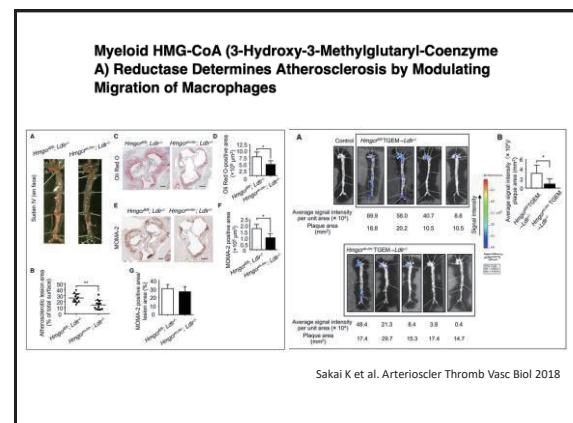
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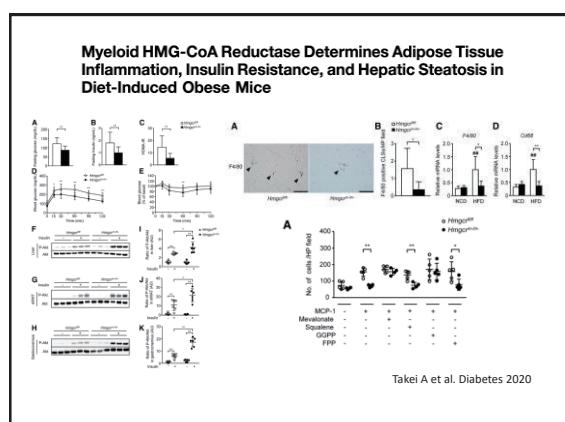
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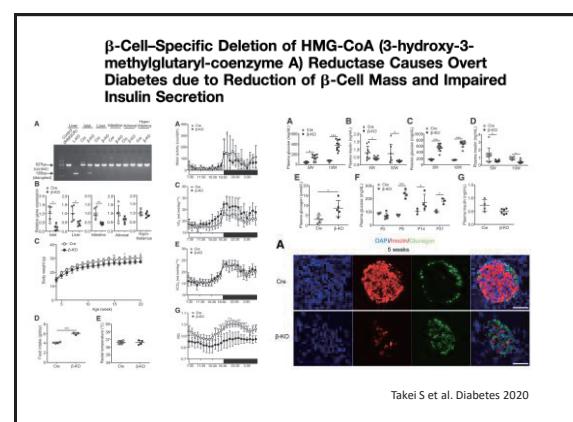
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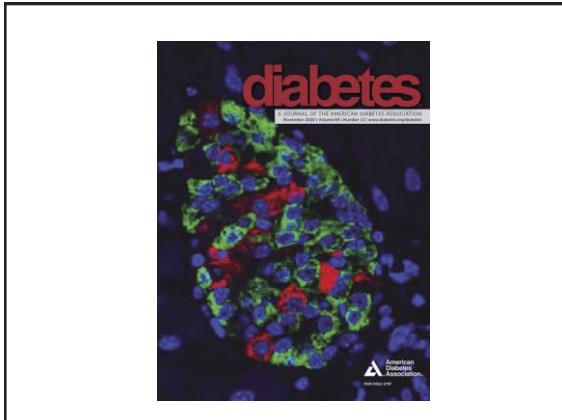
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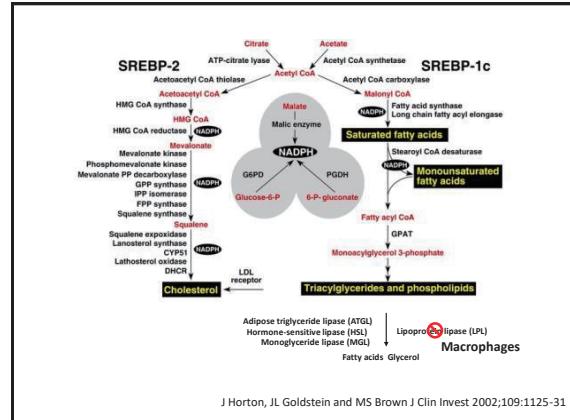
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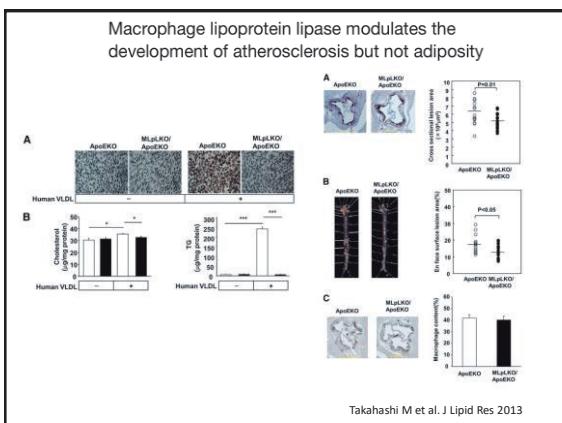
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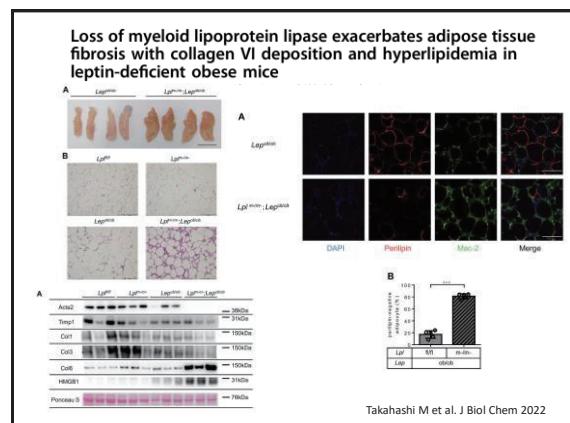
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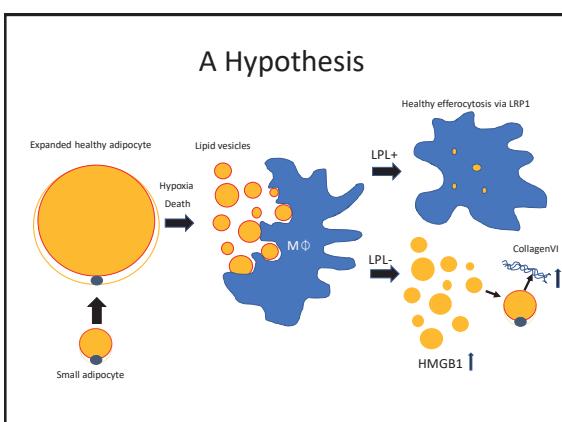
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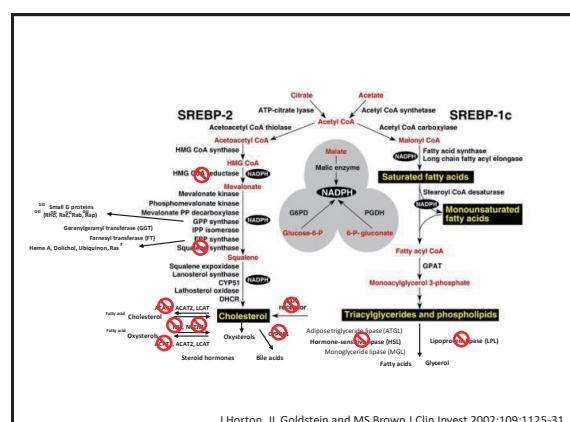
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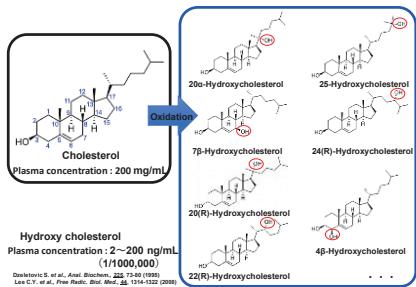
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42

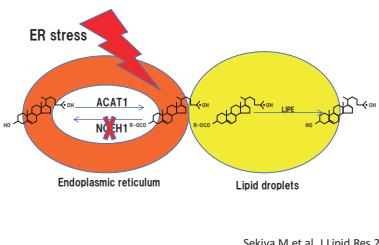
212

## Oxidative metabolites of cholesterol



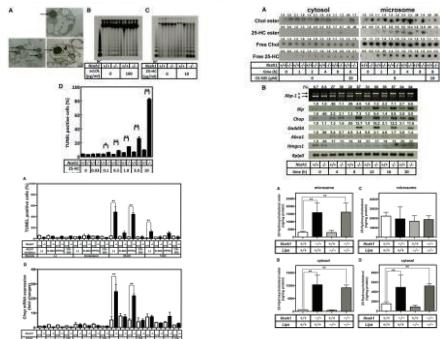
43

### **Excessive 25-HC ester may trigger ER stress**



45

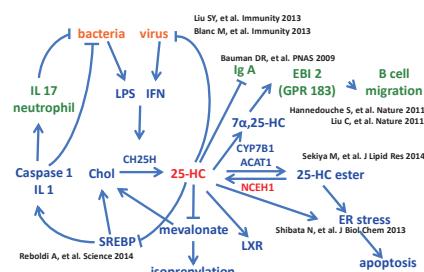
## Absence of Nceh1 augments 25-hydroxycholesterol-induced ER stress and apoptosis in macrophages<sup>†</sup>



Sekiya M et al. J Lipid Res 2014

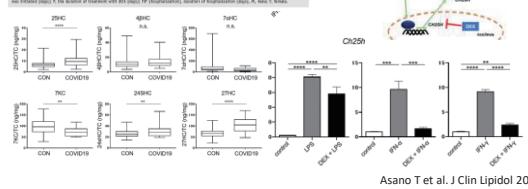
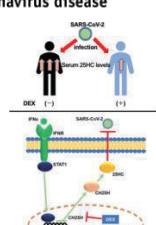
44

## Multifaceted roles of 25HC in immunity and inflammation



46

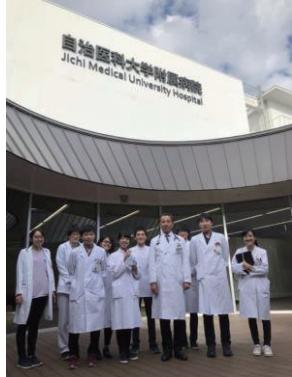
Serum 25-hydroxycholesterol levels are increased in patients with coronavirus disease 2019<sup>†</sup>



47



48



49

### 深田久弥 日本百名山

124	5	18	35	66	41	25	26	30
登頂回数	大学以前	教養	学部	卒後	ソロ	友人	山岳部	家族

2017年10月の瑞垣山が100山目



50



51

### 好きな言葉

- Honesty is the best policy.
- Stay hungry, stay foolish.
- Party is over, go back to the bench.
- 草莽の志士（医師）

52

### 4P's of POR (Patient-oriented research)

Passion  
Patients  
Patience  
Poverty

#### Collaboration

Goldstein J and Brown M. The Clinical Investigator: Bewitched, Troubled, Bewildered-But Still beloved.  
J Clin Invest 1997;99:2803-2812

53

菊を採る東籬のもと、  
悠然として南山を見る  
田園將に蕪れなんとす  
帰りなんいざ、  
酒二十首  
陶淵明

54

お世話になりました

ありがとうございました