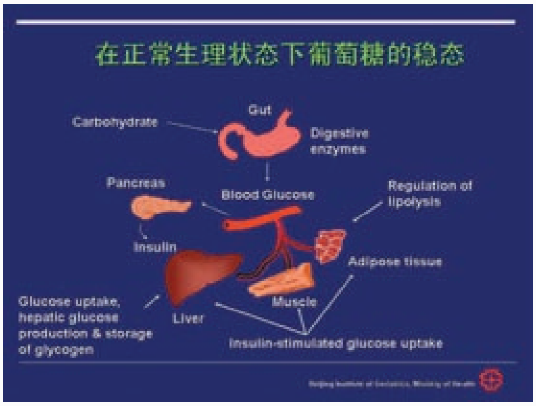
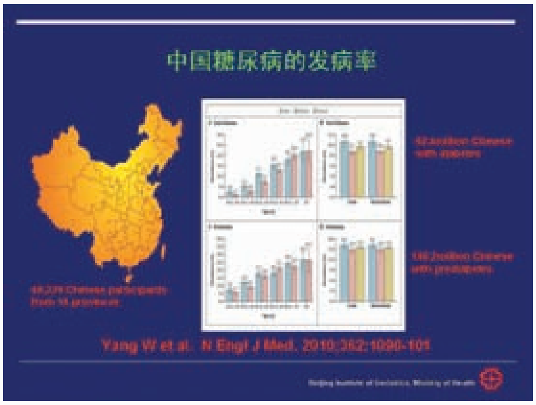
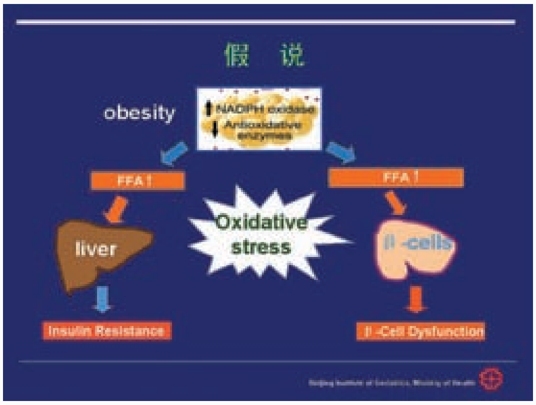
脂肪酸、氧化应激与糖尿病

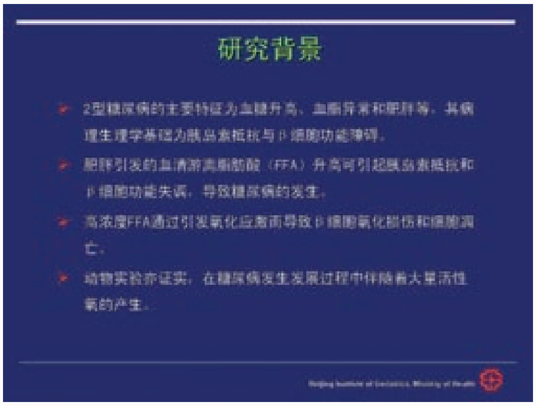
黎　健

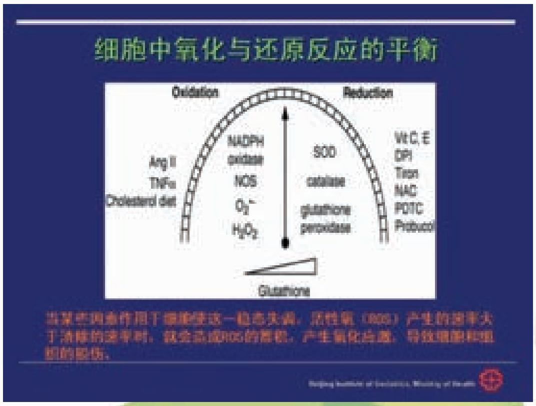
（卫生部北京老年医学研究所　研究员）











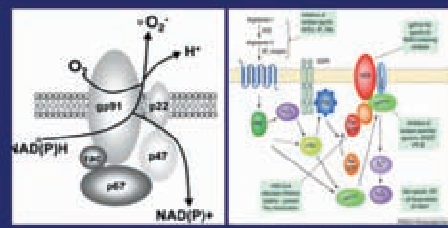
活性氧（ROS）

- 超氧阴离子
- 羟自由基
- 过氧化氢
- 一氧化氮黄嘌呤氧化酶（XO）自由基等

$O_2 \xrightarrow{\text{NADPH 氧化酶}} O_2^- \xrightarrow{\text{超氧化物歧化酶 (SOD)}} H_2O_2 \xrightarrow{\text{过氧化氢酶}} H_2O$

超氧离子　　过氧化氢

NADPH氧化酶的结构与激活



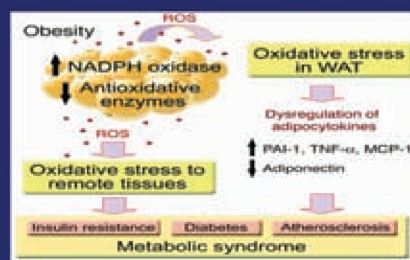
Cai H et al. Trends Pharmacol Sci. 2003; 24(9):471-478

活性氧的来源

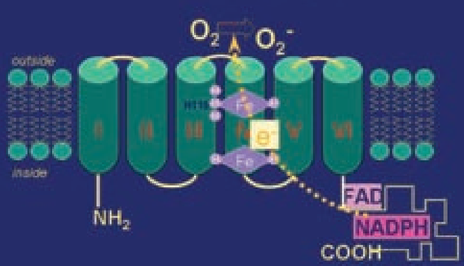
- 线粒体呼吸链酶复合体;
- 黄嘌呤氧化酶;
- 脂氧合酶;
- 内皮型一氧化氮合成酶;
- NADPH氧化酶。

★NADPH氧化酶目前被认为是血管等组织内生成活性氧的主要酶体。

脂肪蓄积引起的活性氧水平升高



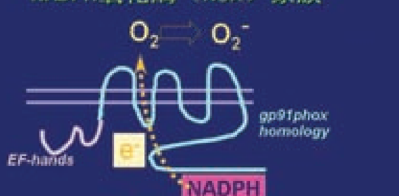
NADPH氧化酶的结构



糖尿病患者体内氧化应激状态的检测

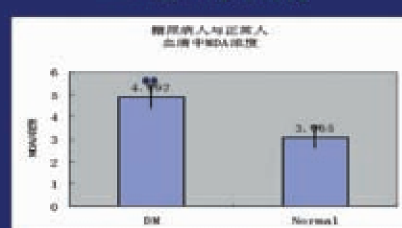
- 血清丙二醛(MDA)
- 血清蛋白羰基化
- 单核细胞ROS水平
- 单核细胞NADPH氧化酶表达
- 单核细胞NADPH氧化酶活性(P47定位)
- 血清SOD活力

NADPH氧化酶（NOX）家族

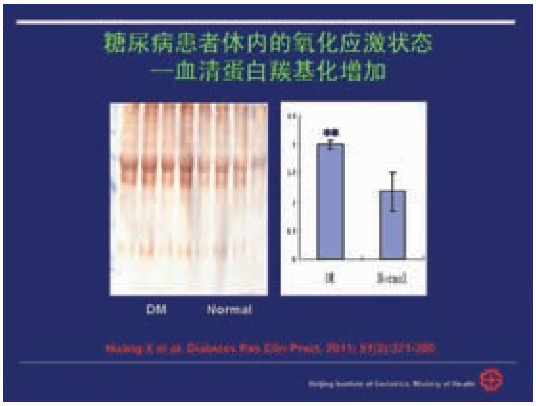


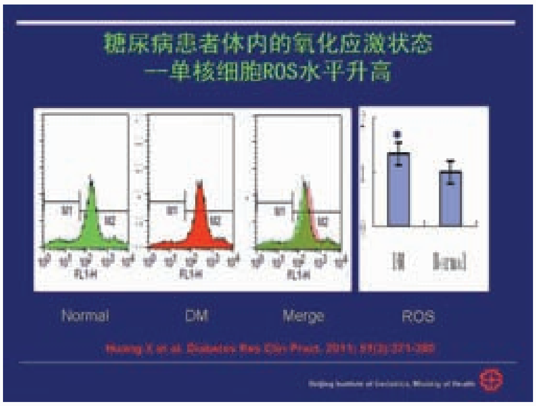
Nox1 colon
Nox2 phagocytes
Nox3 inner ear
Nox4 kidney
Nox5 testis and lymphoid tissues

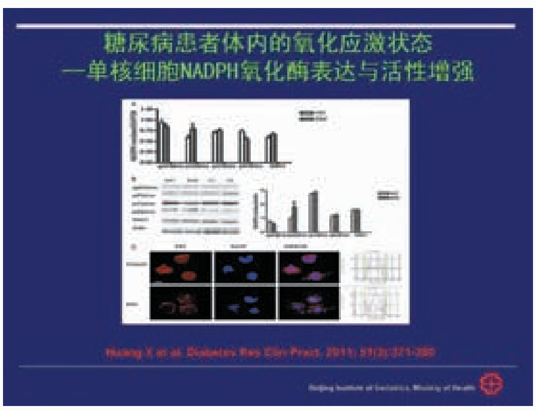
糖尿病患者体内的氧化应激状态
—血清MDA水平升高

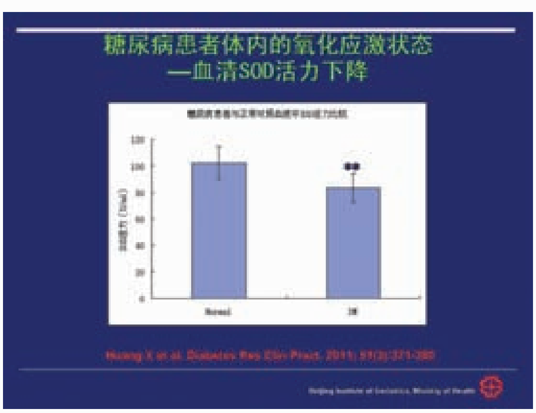


Huang X et al. Diabetes Res Clin Pract. 2011; 91(3):371-380

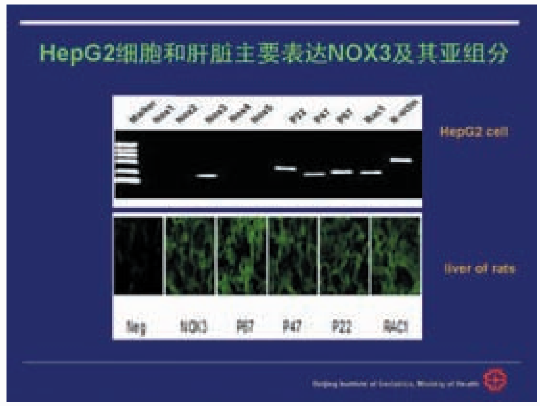

糖尿病患者体内的氧化应激状态
—血清蛋白羰基化增加
DM
Normal
Huang X et al. Diabetes Res Clin Pract. 2011; 91(3):371-380

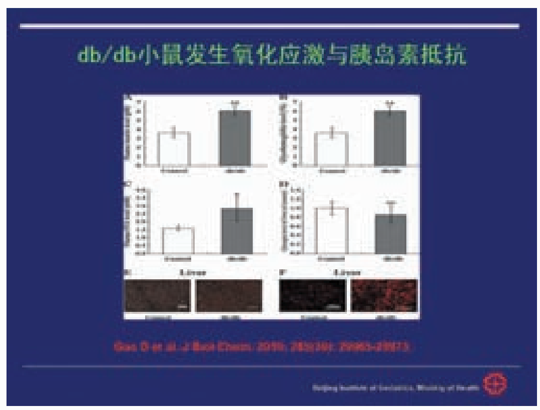

糖尿病患者体内的氧化应激状态
—单核细胞ROS水平升高
Normal
DM
Merge
ROS
Huang X et al. Diabetes Res Clin Pract. 2011; 91(3):371-380

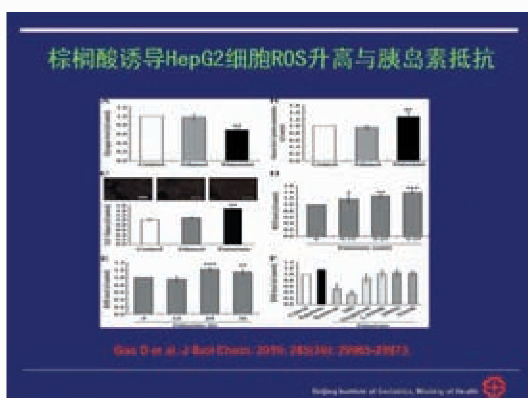

糖尿病患者体内的氧化应激状态
—单核细胞NADPH氧化酶表达与活性增强
Huang X et al. Diabetes Res Clin Pract. 2011; 91(3):371-380

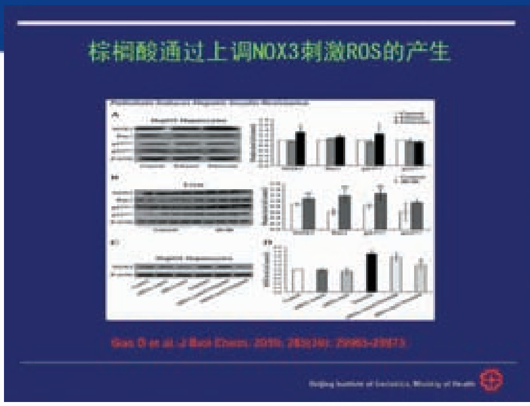

糖尿病患者体内的氧化应激状态
—血清SOD活力下降
Huang X et al. Diabetes Res Clin Pract. 2011; 91(3):371-380

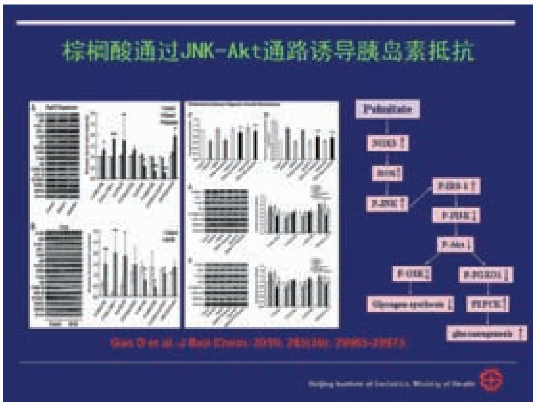

NOX在FFA诱导的肝脏胰岛素抵抗中的作用
?

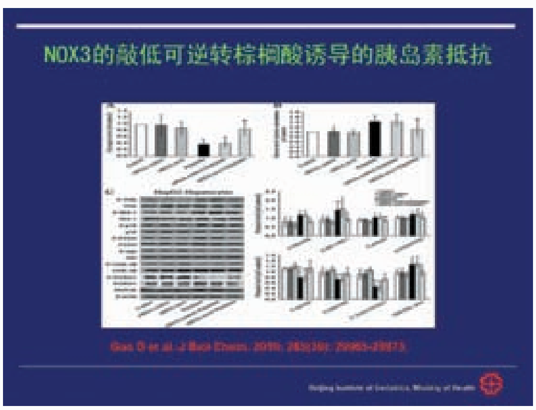

HepG2细胞和肝脏主要表达NOX3及其亚组分
HepG2 cell
liver of rats
Neg
NOX3
P67
P47
P22
RAC1

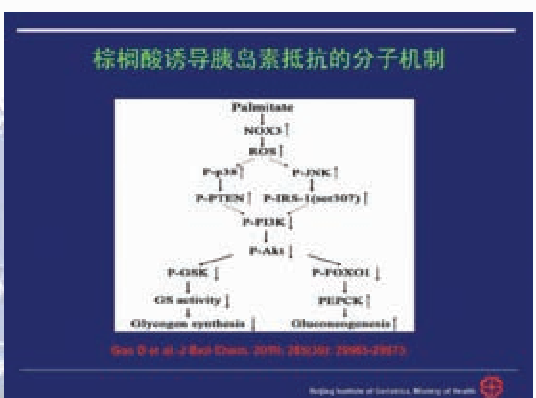

db/db小鼠发生氧化应激与胰岛素抵抗
Gao D et al. J Biol Chem. 2010; 285(39): 29965-29973

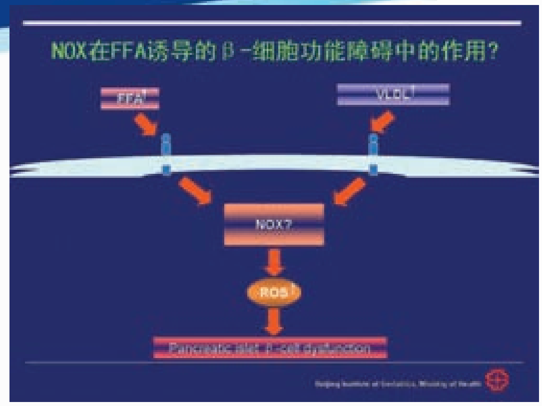

棕榈酸诱导HepG2细胞ROS升高与胰岛素抵抗
Gao D et al. J Biol Chem. 2010; 285(39): 29965-29973

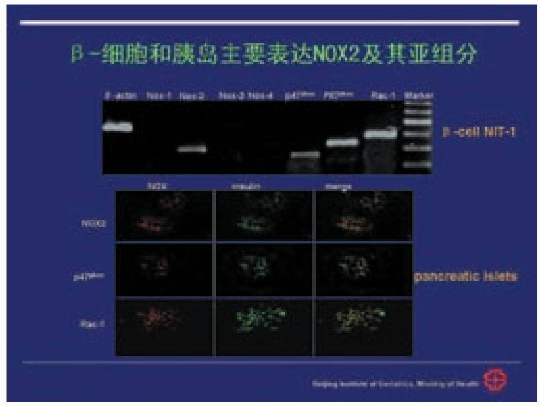

棕榈酸通过上调NOX3刺激ROS的产生
Gao D et al. J Biol Chem. 2010; 285(39): 29965-29973

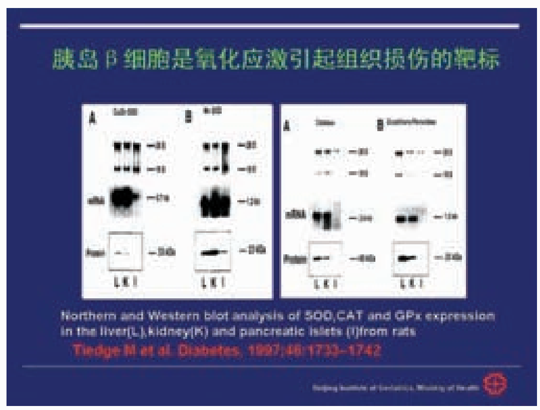

棕榈酸通过JNK-Akt通路诱导胰岛素抵抗
Palmitate
NOX3↑
ROS↑
P-JNK↑
P-IRS-1↑
P-PI3K↓
P-Akt↓
P-GSK↓
P-FOXO1↓
Glycogen synthesis↓
PEPCK↑
gluconeogenesis↑
Gao D et al. J Biol Chem. 2010; 285(39): 29965-29973

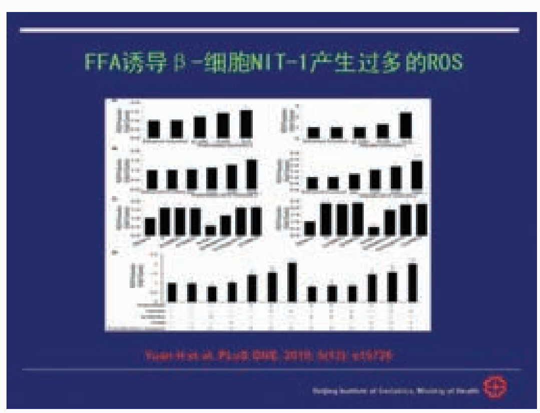

NOX3的敲低可逆转棕榈酸诱导的胰岛素抵抗
Gao D et al. J Biol Chem. 2010; 285(39): 29965-29973

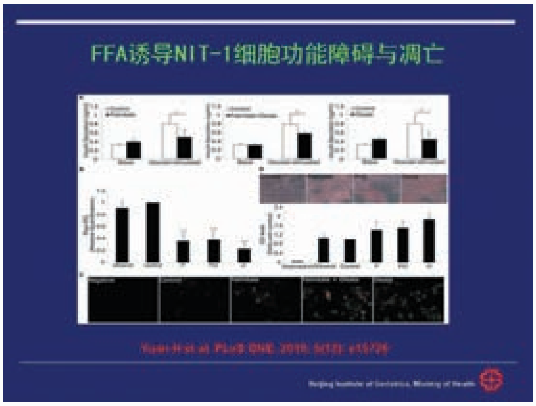

棕榈酸诱导胰岛素抵抗的分子机制
Palmitate
NOX3↑
ROS↑
P-p38↑
P-JNK↑
P-PTEN↑
P-IRS-1(ser307)↑
P-PI3K↓
P-Akt↓
P-GSK↓
P-FOXO1↓
GS activity↓
PEPCK↑
Glycogen synthesis↓
Gluconeogenesis↑
Gao D et al. J Biol Chem. 2010; 285(39): 29965-29973

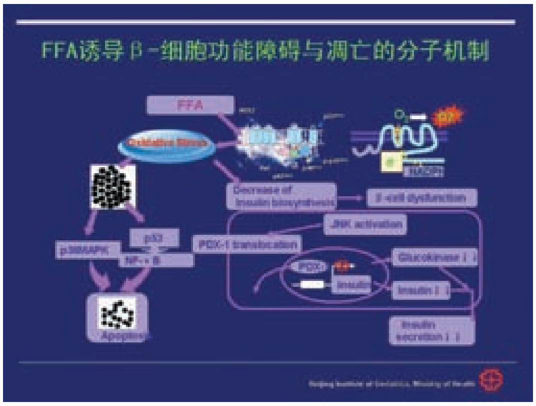

NOX在FFA诱导的β-细胞功能障碍中的作用?
FFA↑
VLDL↑
NOX?
ROS↑
Pancreatic islet β-cell dysfunction

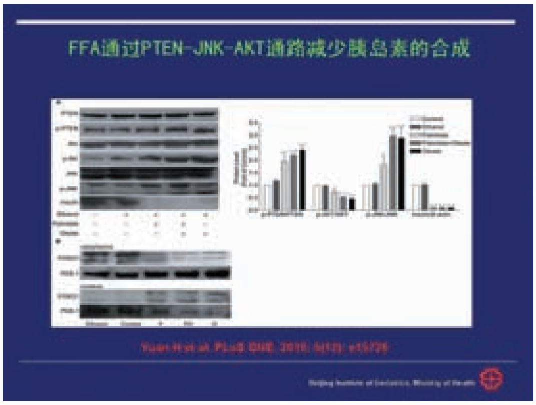

β-细胞和胰岛主要表达NOX2及其亚组分
β-actin
Nox-1
Nox-2
Nox-3
Nox-4
p47phox
P67phox
Rac-1
Marker
β-cell NIT-1
NOX
insulin
merge
NOX2
p47phox
Rac-1
pancreatic islets

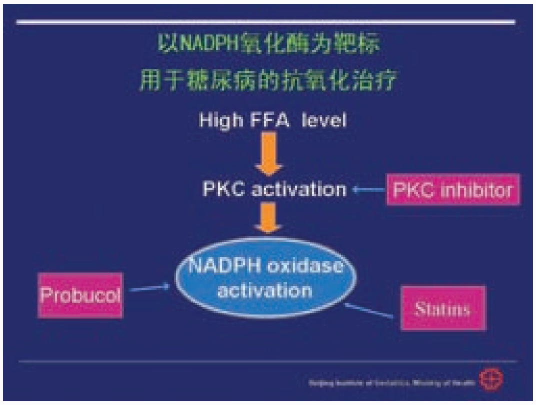

胰岛β细胞是氧化应激引起组织损伤的靶标
Northern and Western blot analysis of SOD,CAT and GPx expression
in the liver(L),kidney(K) and pancreatic islets (I)from rats
Tiedge M et al. Diabetes. 1997;46:1733-1742

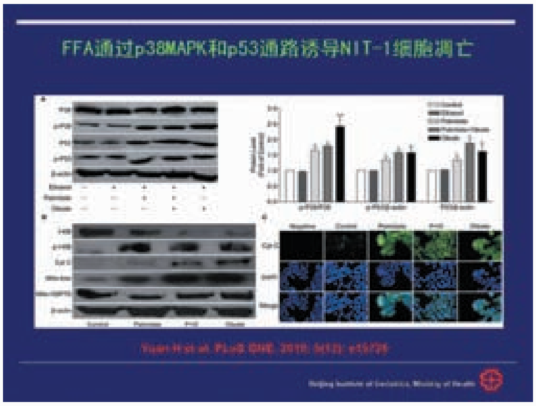

FFA诱导β-细胞NIT-1产生过多的ROS
Yuan H et al. PLoS ONE. 2010; 5(12): e15726

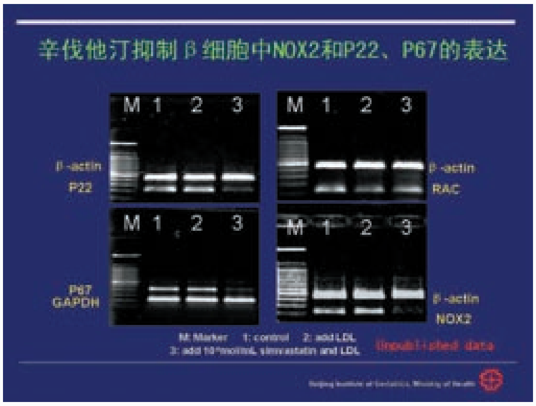

FFA诱导NIT-1细胞功能障碍与凋亡
Yuan H et al. PLoS ONE. 2010; 5(12): e15726

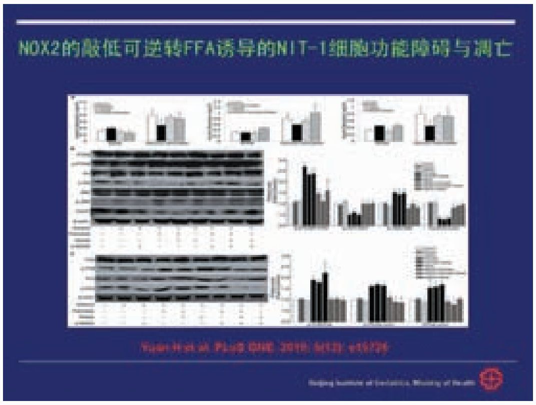

FFA诱导β-细胞功能障碍与凋亡的分子机制
FFA
Oxidative Stress
Decrease of insulin biosynthesis
β-cell dysfunction
JNK activation
p53
p38MAPK
NF-κB
PDX-1 translocation
Glucokinase↓↓
Insulin↓↓
Insulin secretion↓↓
Apoptosis

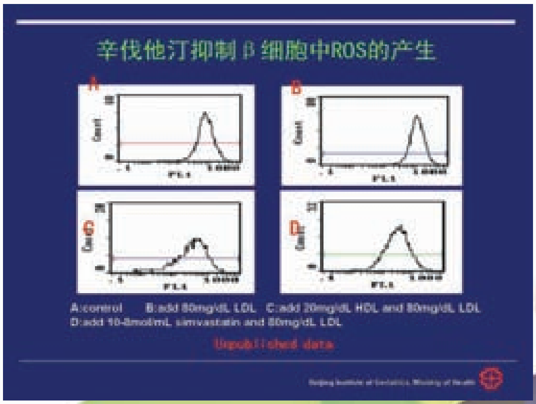

FFA通过PTEN-JNK-AKT通路减少胰岛素的合成
Yuan H et al. PLoS ONE. 2010; 5(12): e15726

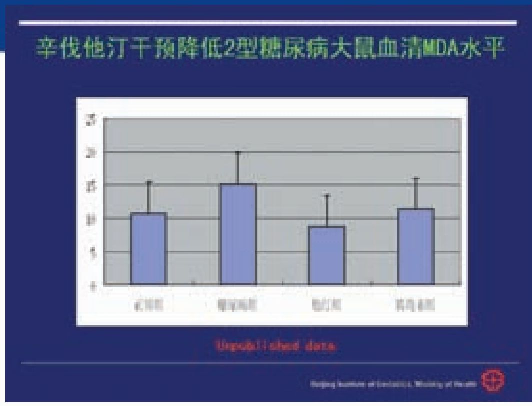

以NADPH氧化酶为靶标
用于糖尿病的抗氧化治疗
High FFA level
PKC activation
PKC inhibitor
NADPH oxidase activation
Probucol
Statins

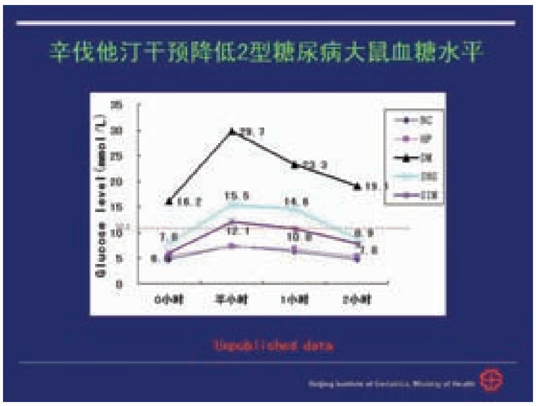

FFA通过p38MAPK和p53通路诱导NIT-1细胞凋亡
Yuan H et al. PLoS ONE. 2010; 5(12): e15726

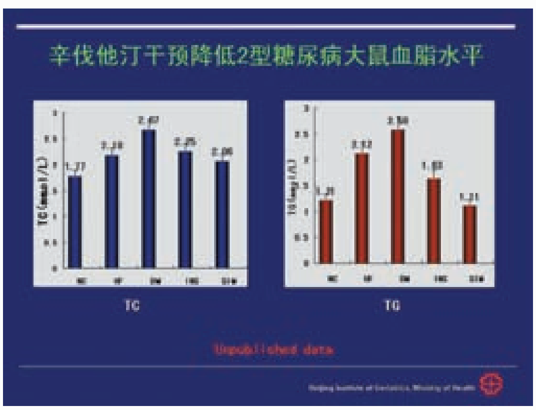

辛伐他汀抑制β细胞中NOX2和P22、P67的表达
M 1 2 3
β-actin
P22
RAC
P67
GAPDH
NOX2
M: Marker 1: control 2: add LDL
3: add 10⁻⁸mol/mL simvastatin and LDL
Unpublished data

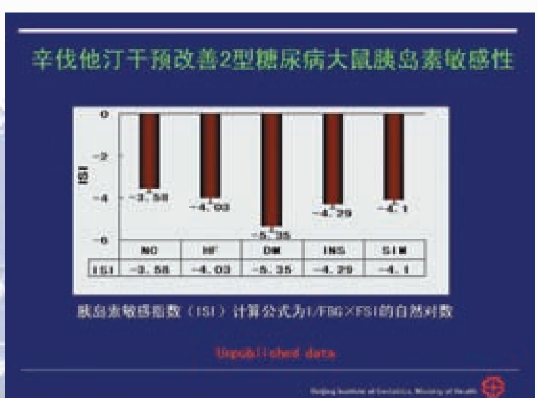

NOX2的敲低可逆转FFA诱导的NIT-1细胞功能障碍与凋亡
Yuan H et al. PLoS ONE. 2010; 5(12): e15726

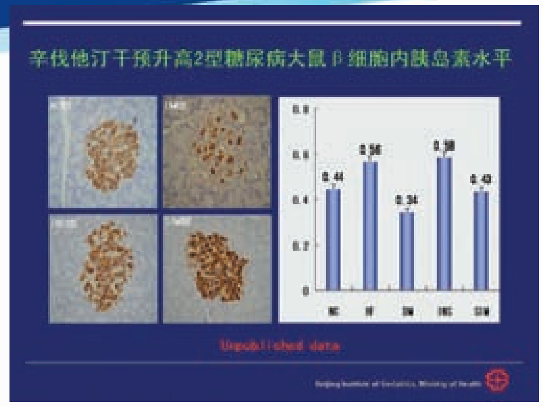

辛伐他汀抑制β细胞中ROS的产生
A
B
C
D
FL1
A:control B:add 80mg/dL LDL C:add 20mg/dL HDL and 80mg/dL LDL
D:add 10-8mol/mL simvastatin and 80mg/dL LDL
Unpublished data

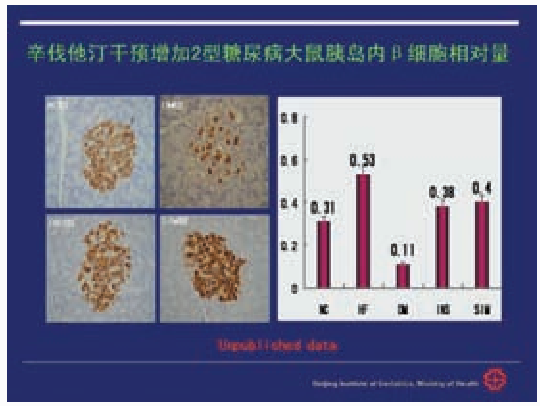

辛伐他汀干预降低2型糖尿病大鼠血清MDA水平
Unpublished data


辛伐他汀干预降低2型糖尿病大鼠血糖水平
Glucose level (mmol/L)
29.7
23.3
19.1
16.2
15.5
14.6
12.1
10.8
8.9
7.8
0小时
半小时
1小时
2小时
NC
HF
DM
INS
SIM
Unpublished data


辛伐他汀干预降低2型糖尿病大鼠血脂水平
1.77
2.18
2.67
2.25
2.06
NC
HF
DM
INS
SIM
TC
1.31
2.12
2.58
1.63
1.21
TG
Unpublished data


辛伐他汀干预改善2型糖尿病大鼠胰岛素敏感性
ISI
-3.58
-4.03
-5.35
-4.29
-4.1
NC
HF
DM
INS
SIM
ISI -3.58 -4.03 -5.35 -4.29 -4.1
胰岛素敏感指数（ISI）计算公式为1/FBG×FSI的自然对数
Unpublished data


辛伐他汀干预升高2型糖尿病大鼠β细胞内胰岛素水平
0.44
0.56
0.34
0.58
0.43
NC
HF
DM
INS
SIM
Unpublished data


辛伐他汀干预增加2型糖尿病大鼠胰岛内β细胞相对量
0.31
0.53
0.11
0.38
0.4
NC
HF
DM
INS
SIM
Unpublished data


他汀的抗氧化作用
Suppress expression of NADPH oxidase.
Decrease ROS generation.
Increase expression of eNOS and elevate NO level.


Acknowledgments


Thank you!