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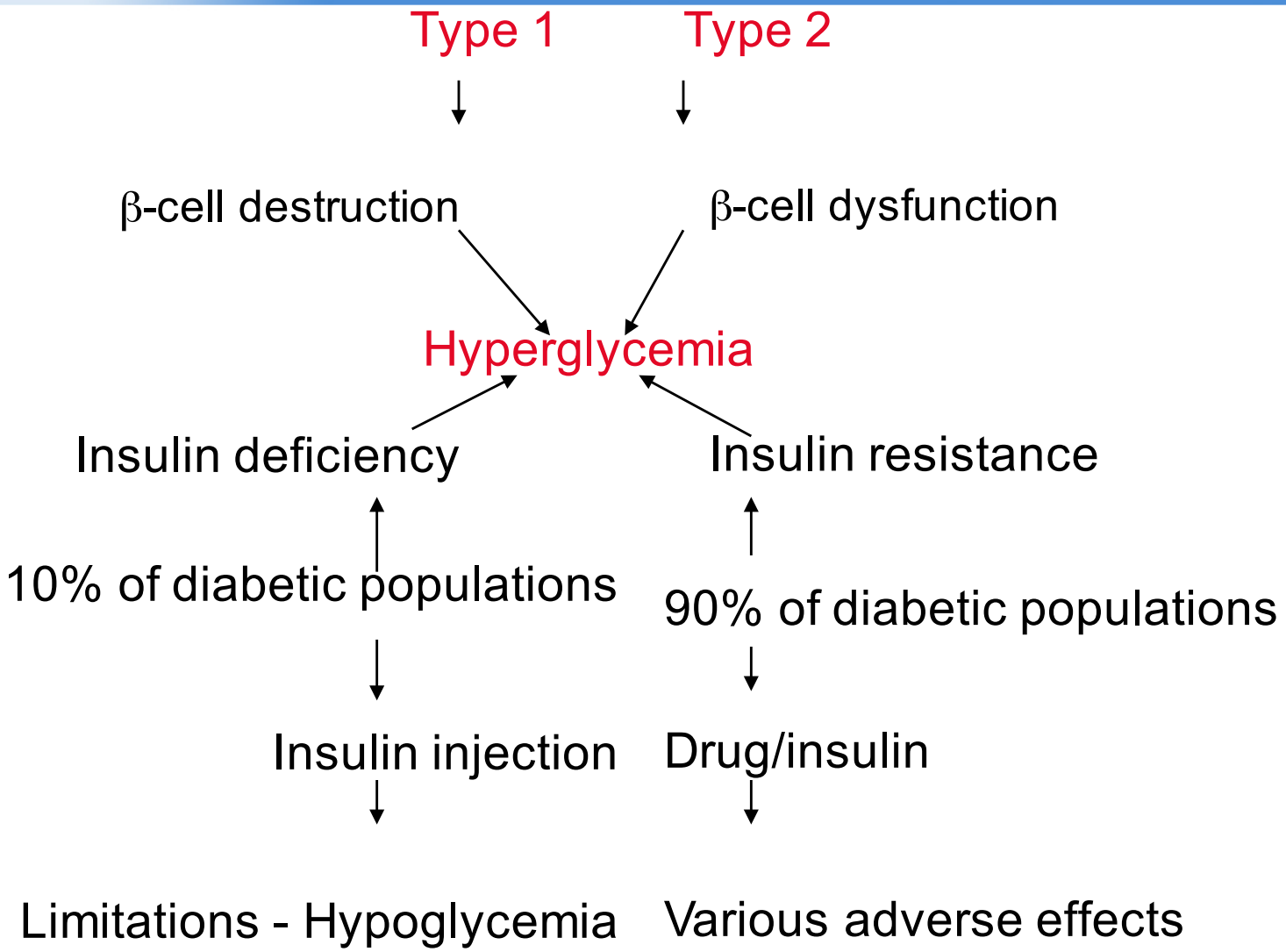
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FoxO Transcription Factors in Type 2 Diabetes

H. Henry Dong, Ph.D.
Professor of Pediatrics
Division of Endocrinology and Diabetes
Department of Pediatrics
Children's Hospital of Pittsburgh of UPMC
University of Pittsburgh School of Medicine

Type 1 vs. Type 2 Diabetes





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Causes of Type 2 Diabetes

Genetic Predisposition + **Sedentary Lifestyle**

Visceral Adiposity

↓

Insulin Resistance

↓

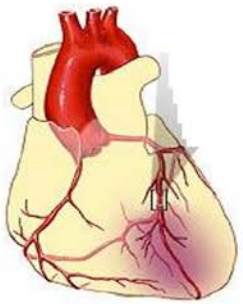
Glucose intolerance

↓

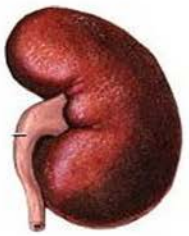
Diabesity

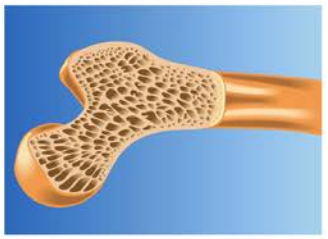
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CAD | Retinopathy | Nephropathy | Osteoporosis | Neuropathy













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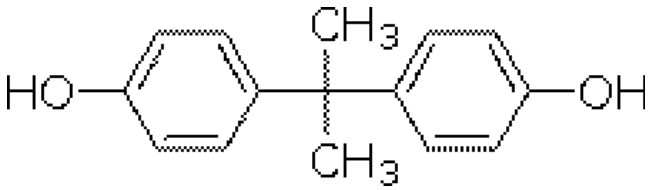
Risk Factors for Developing Obesity in Humans

JAMA, Journal of American Medical Association

September 19, 2012—Vol 308, No. 11

Association Between Urinary Bisphenol A Concentration and Obesity Prevalence in Children and Adolescents.

Bispenol:





BPA is a confounding factor for childhood obesity



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Risk Factors for Developing Obesity in Humans

N Engl J Med. 2012 Sep 21. [Epub ahead of print]
A Trial of Sugar-free or Sugar-Sweetened Beverages and Body Weight in Children.
de Ruyter JC, Olthof MR, Seidell JC, Katan MB.
VU University Amsterdam, Amsterdam, the Netherlands.

N Engl J Med. 2012 Sep 21. [Epub ahead of print]
A Randomized Trial of Sugar-Sweetened Beverages and Adolescent Body Weight.
Ebbeling CB, Feldman HA, Chomitz VR, Antonelli TA, Gortmaker SL, Osganian SK, Ludwig DS.
Harvard School of Public Health, Boston (S.L.G.) - all in Massachusetts.

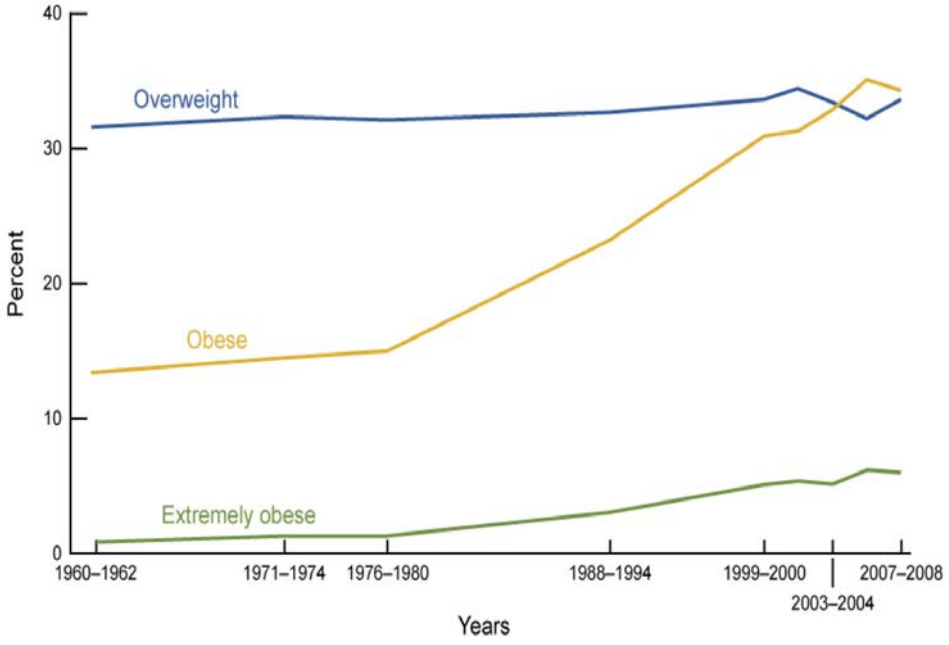
High fructose consumption is alleged as a confounding factor for childhood obesity



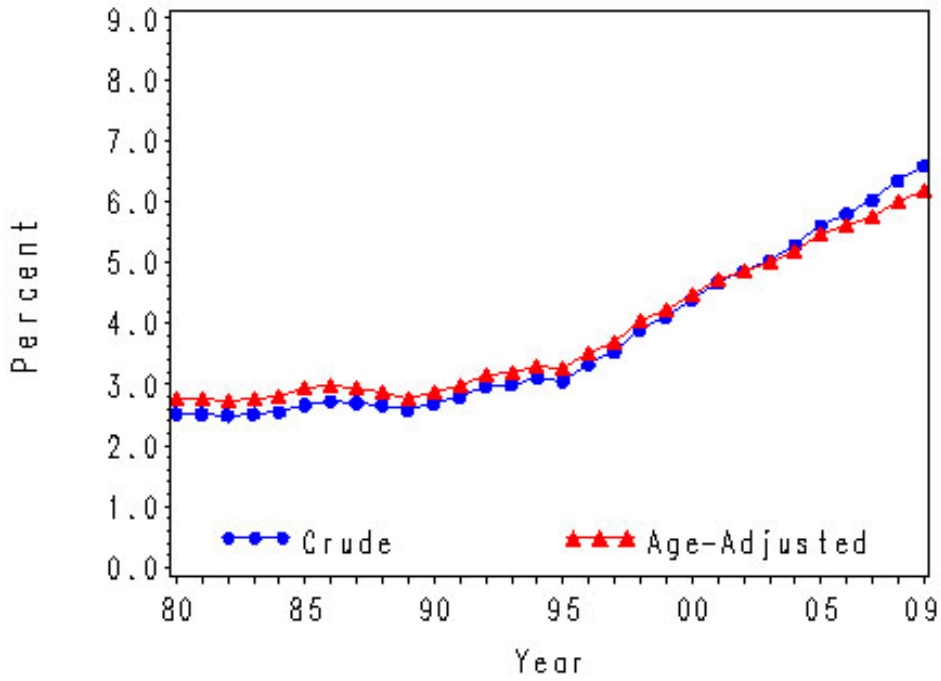
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A Majority of Obese Individuals Live with Obesity, but without Diabetes

Trend of Obesity



Trend of Type 2 Diabetes



$$\frac{\text{Prevalence of type 2 diabetes}}{\text{Prevalence of national obesity}} = 20\text{-}25\%$$



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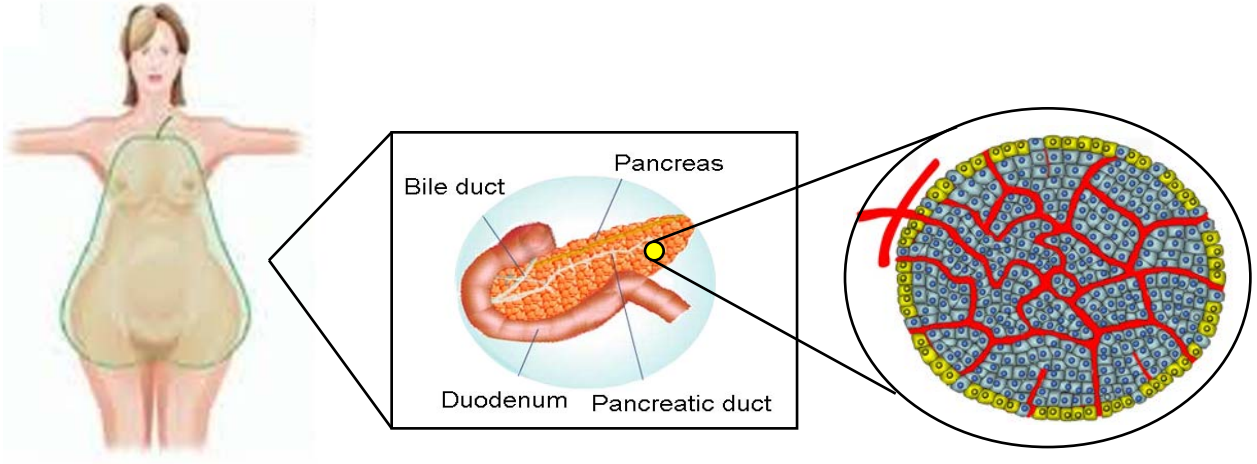
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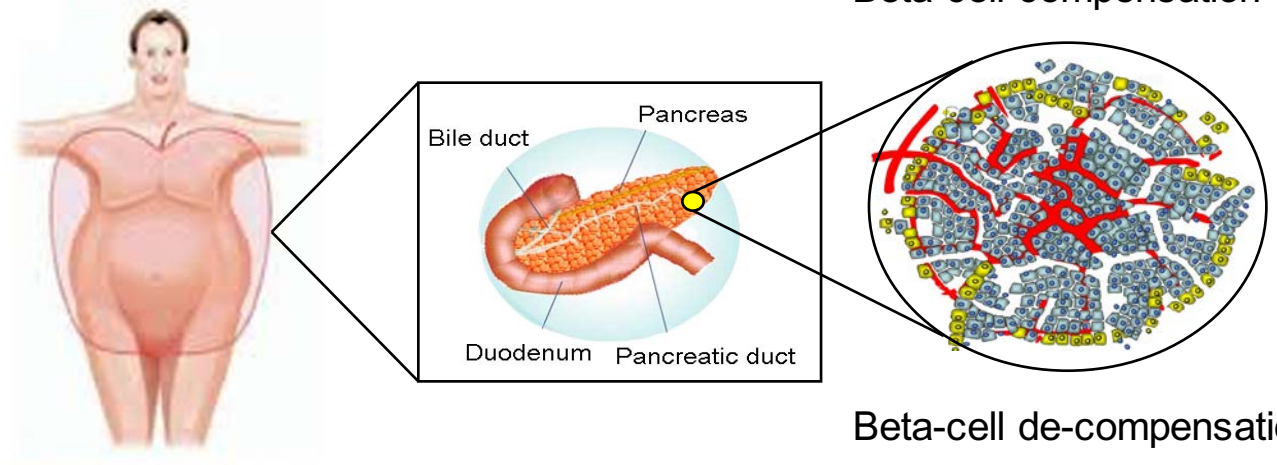
Obesity Drives Beta-Cell Compensation and Decompensation

A



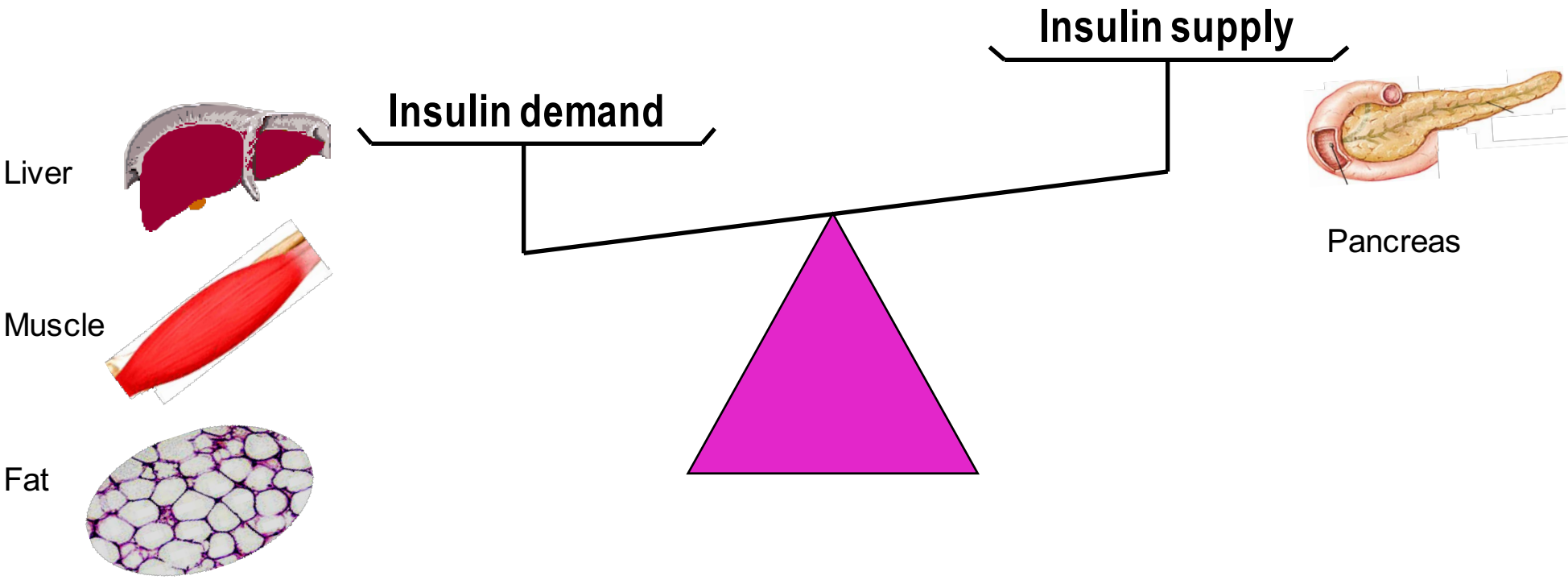
Beta-cell compensation

B



Beta-cell de-compensation

Type 2 Diabetes Onsets as A Result of Beta-Cell Failure



Prediabetic → Glucose intolerance → Insulin insufficiency → Insulin deficiency



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Beta-Cell Compensation and Gestational Diabetes



Incidence (annual) of Gestational diabetes in US:

135,000 pregnant women get the condition every year; 3-5% of pregnant women.



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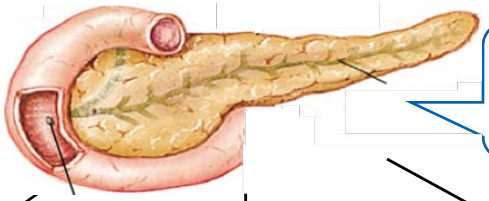
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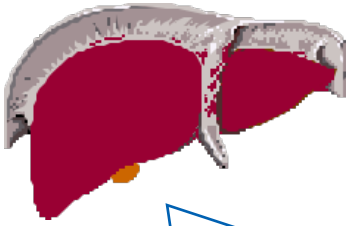
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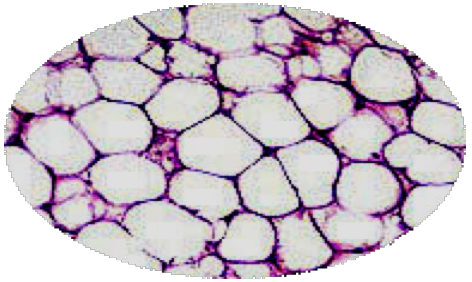
Impaired Insulin Action & Type 2 Diabetes



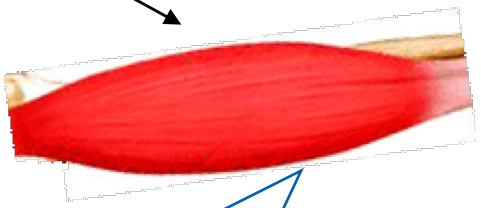
Dysregulated insulin secretion



Augmented glycogenolysis and gluconeogenesis



Unrestrained fat mobilization and impaired glucose uptake



Impaired glucose uptake/utilization



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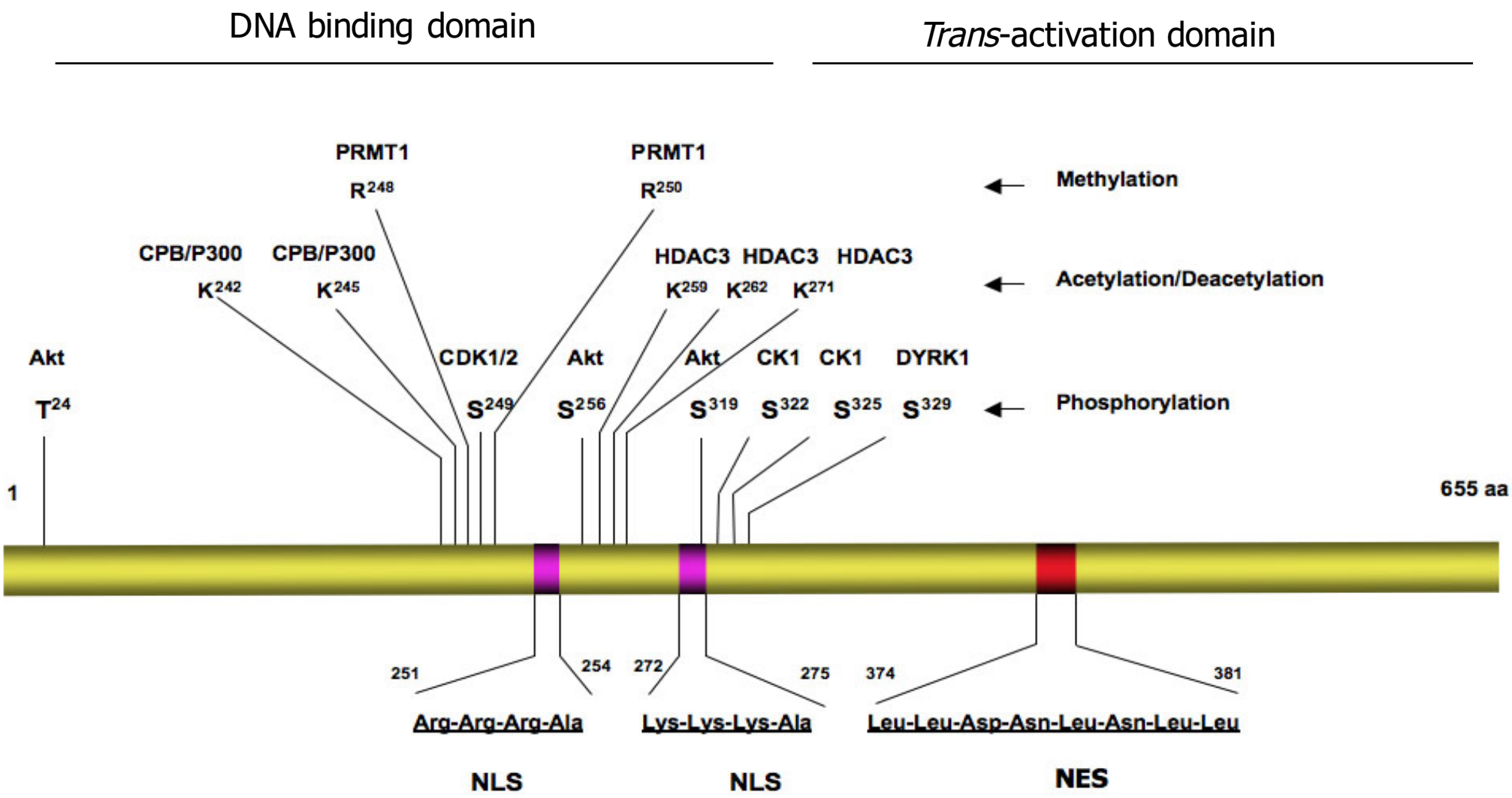
Objective

To characterize factors that link insulin resistance to glucose/lipid disorders





FoxO Transcription Factor

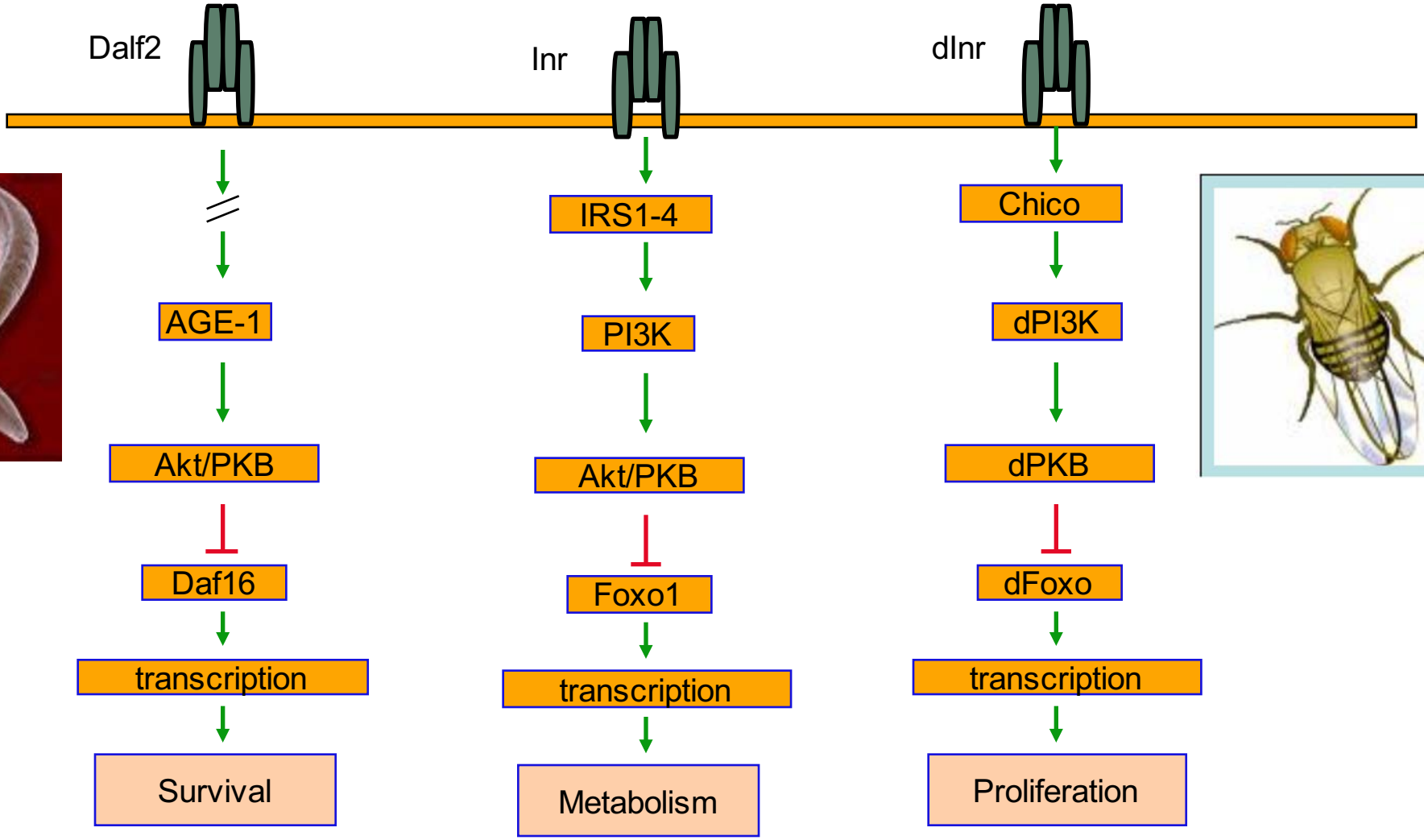




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Foxo1 acts Downstream of Insulin Signaling







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FoxO1 Gene Mutations in Humans

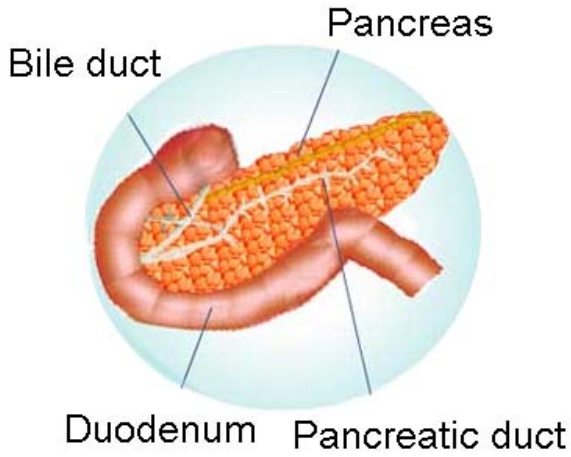
The Journal of Clinical Endocrinology & Metabolism
Vol. 94, No. 4 1353-1360, 2009

Association of Common Genetic Variation in the FOXO1 Gene with β-Cell Dysfunction, Impaired Glucose Tolerance, and Type 2 Diabetes

Karsten Müssig, ---- Hans-Ulrich Häring

Study 1, N=941 German

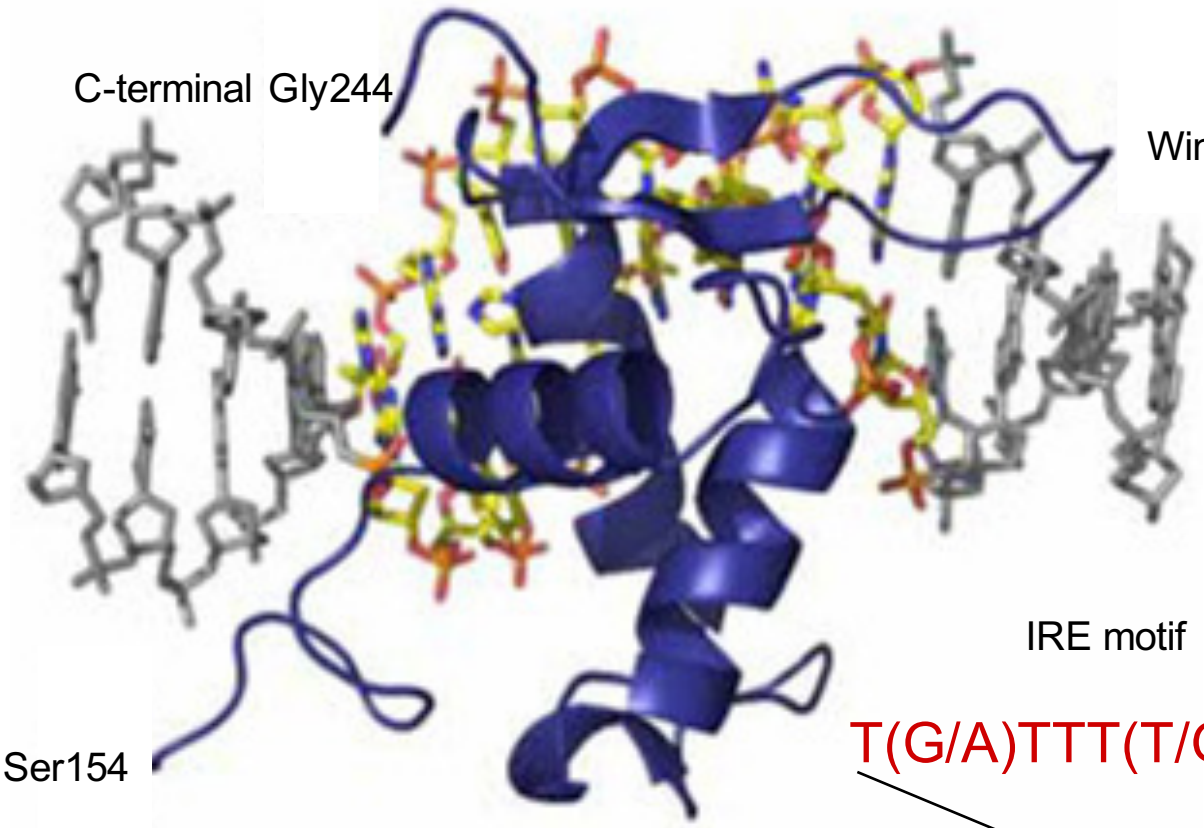
Study 2, N=5957 Finish





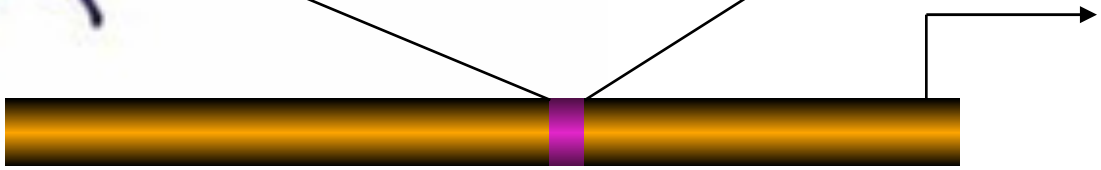
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FoxO1 binds as monomer to promoter DNA Acting as Trans-activator



IRE motif

T(G/A)TTT(T/G)(G/T)





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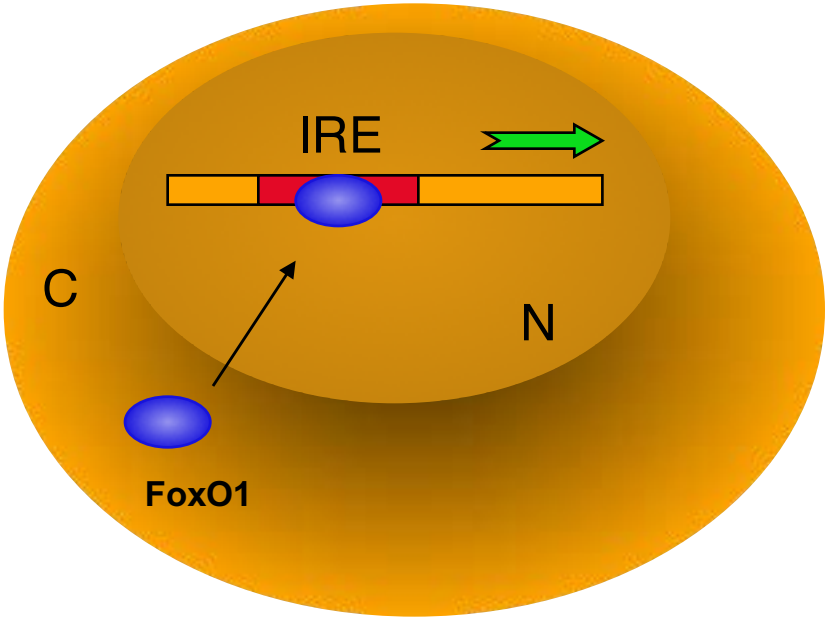
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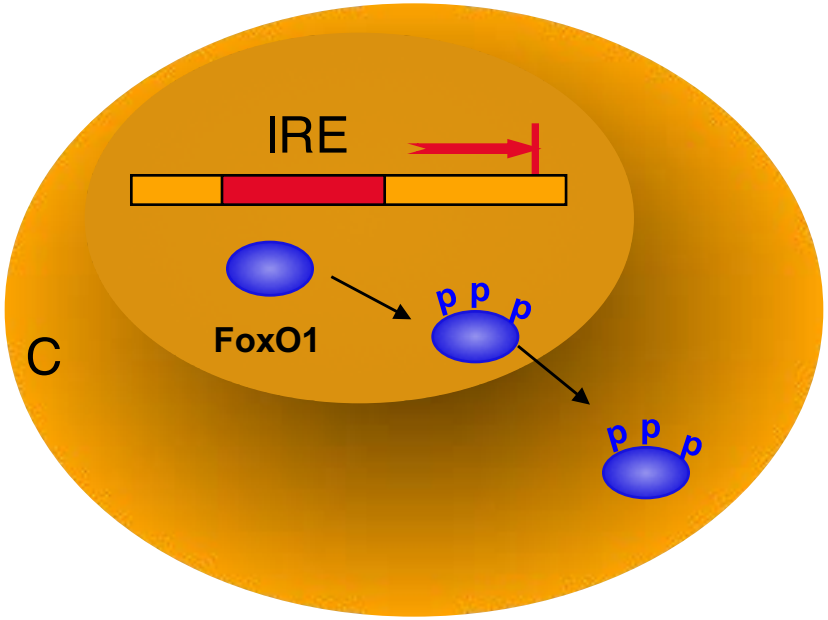
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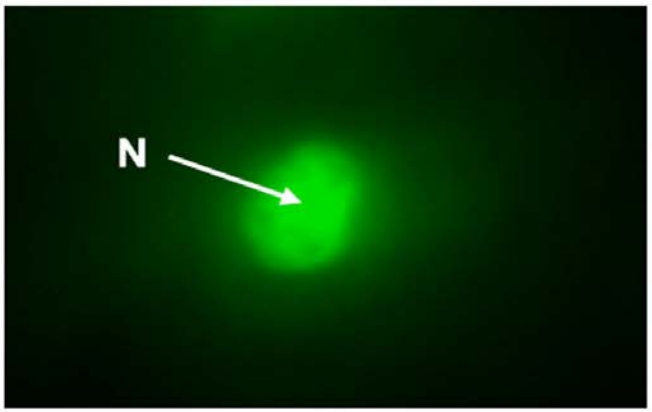
Insulin Inactivates FoxO1 Activity



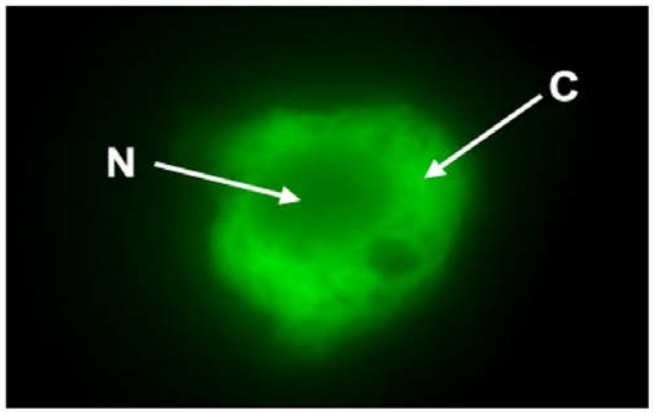
On-state



Off-state



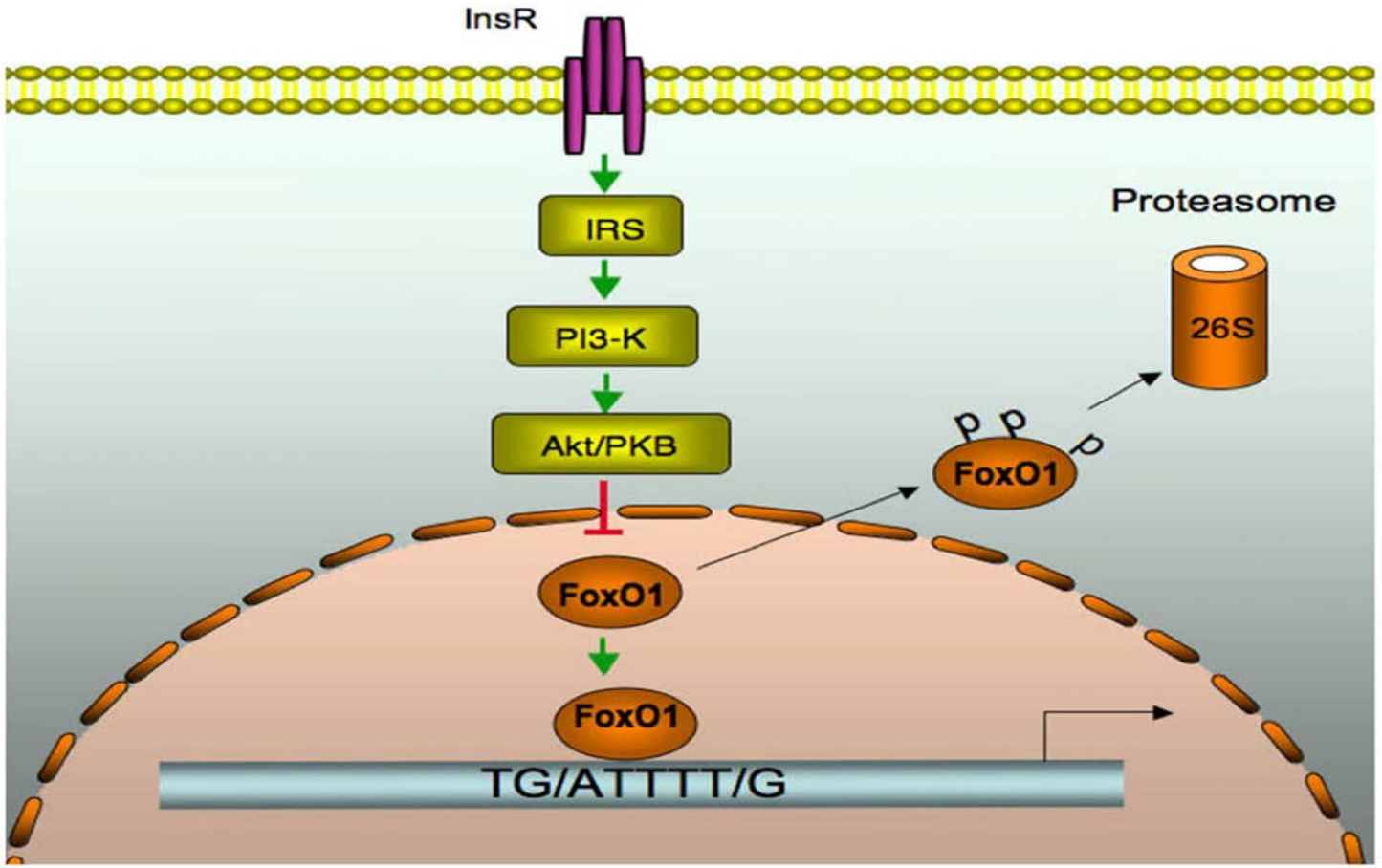
-Insulin



+Insulin

FoxO1 mediates the inhibitory effect of insulin on target gene expression

Fig. 3





Insulin exerts both positive & negative effects in the liver

Postprandial insulin release

Glucose-responsive element (GRE, E-box)

ChREBP

FoxO1

Insulin-responsive element (IRE)

Glycogen
Lipogenesis

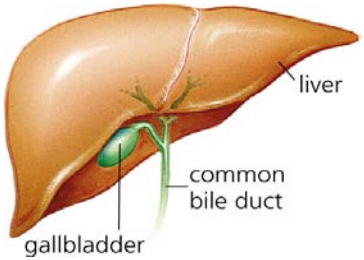
Gluconeogenesis
Glycogenolysis

The combined effects of insulin serve to limit glucose production and promote glycogen storage in the liver after meals



FoxO1 Mediates Insulin on Gluconeogenesis in Liver

Under fasting conditions



Glucose production

Insulin

Foxo1

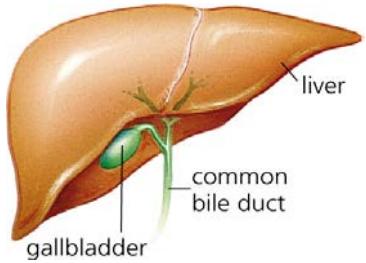
PEPCK

G6Pase

Gluconeogenesis
Glycogenolysis

Hyperglycemia

Under fed conditions



No glucose output



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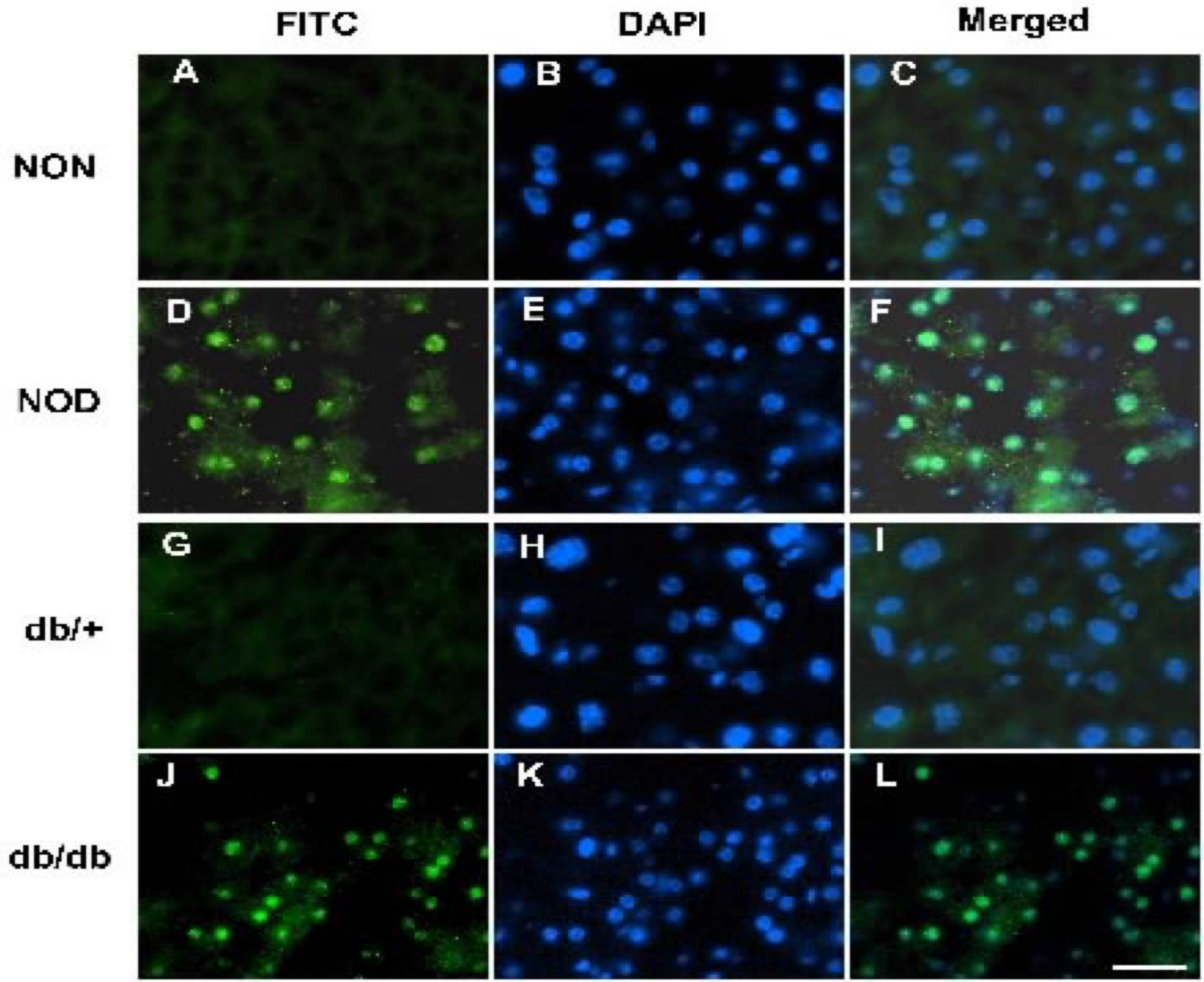
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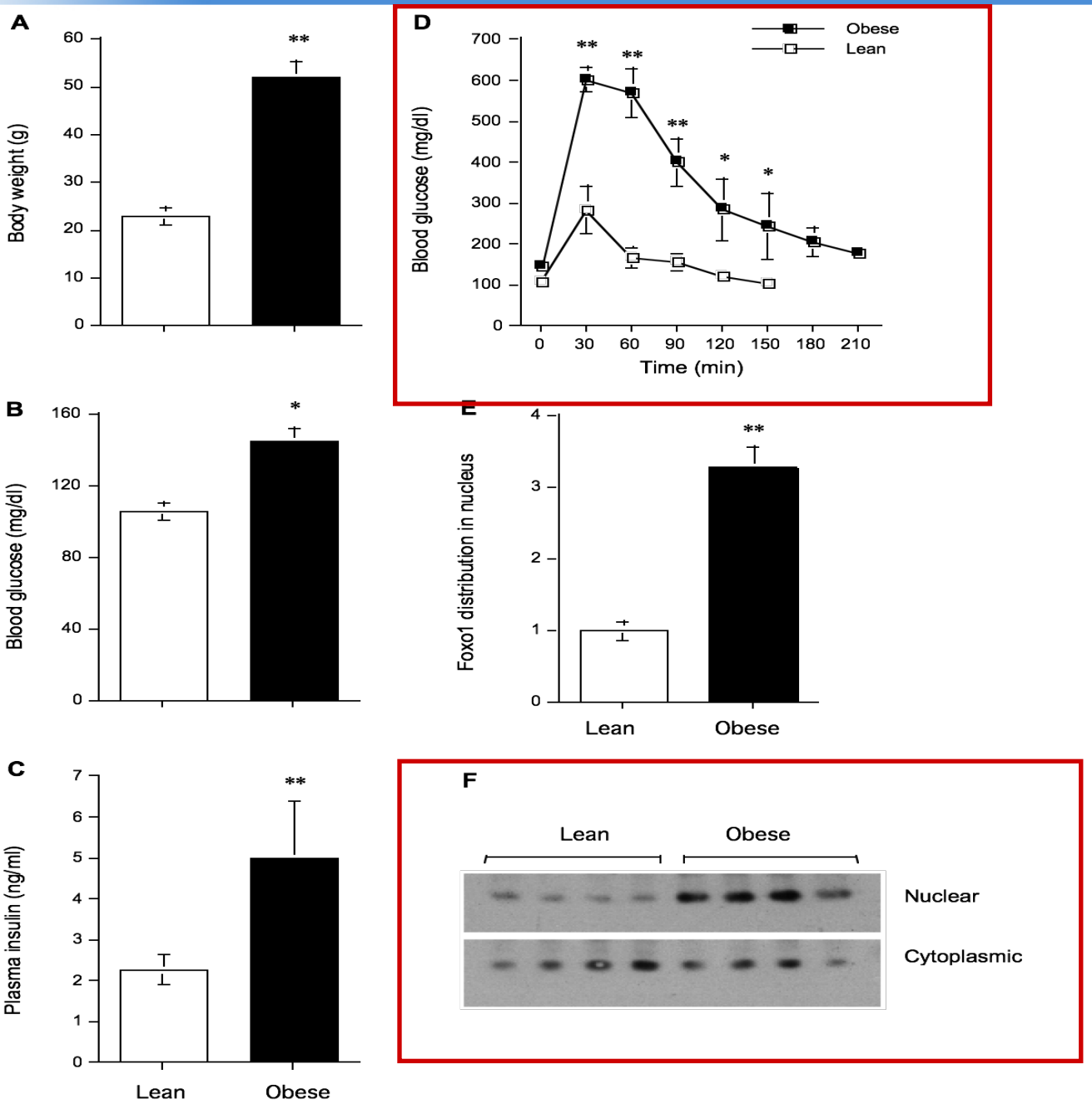
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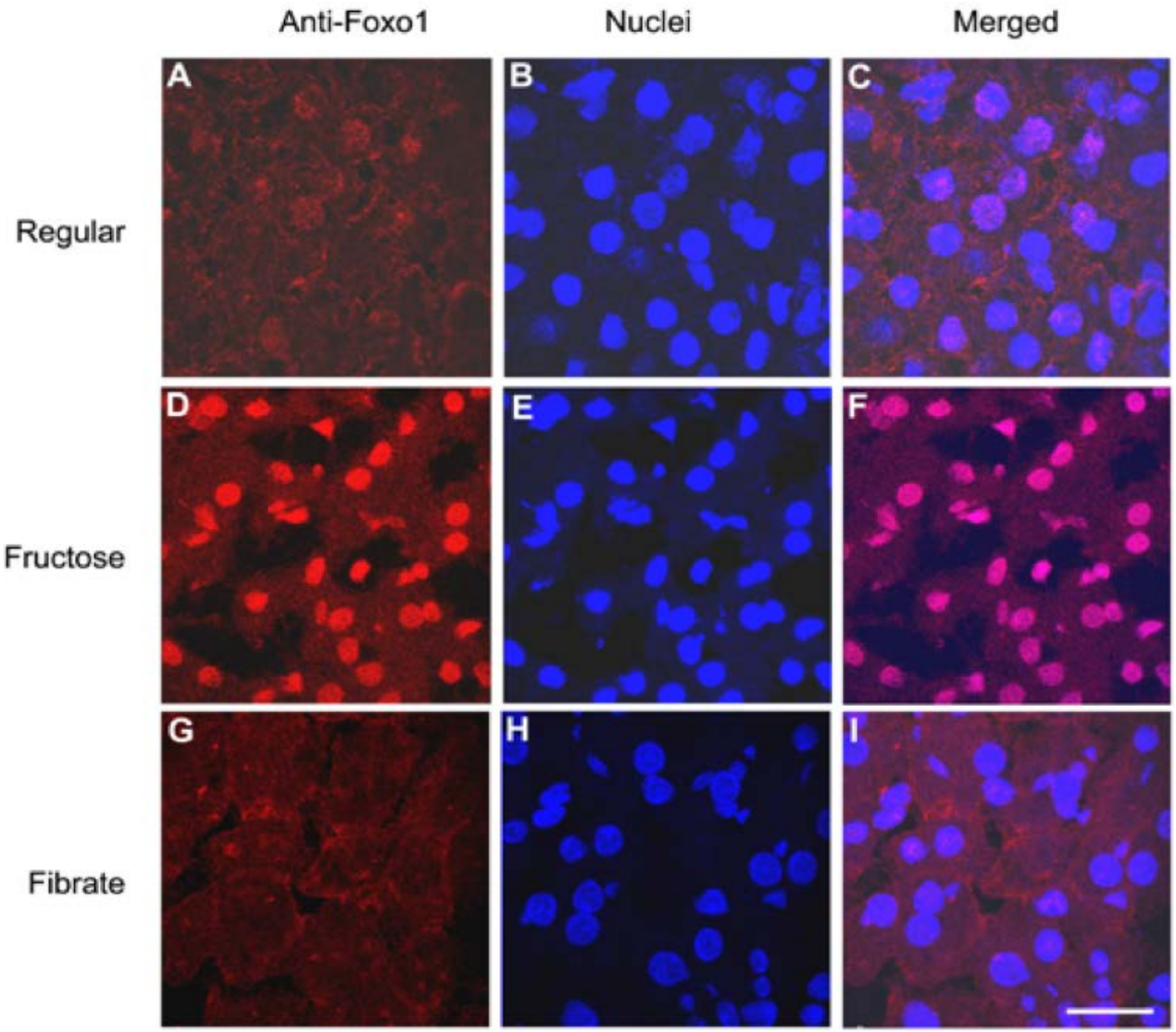
Foxo1 Subcellular Distribution in Response to Impaired Insulin Signaling in the liver



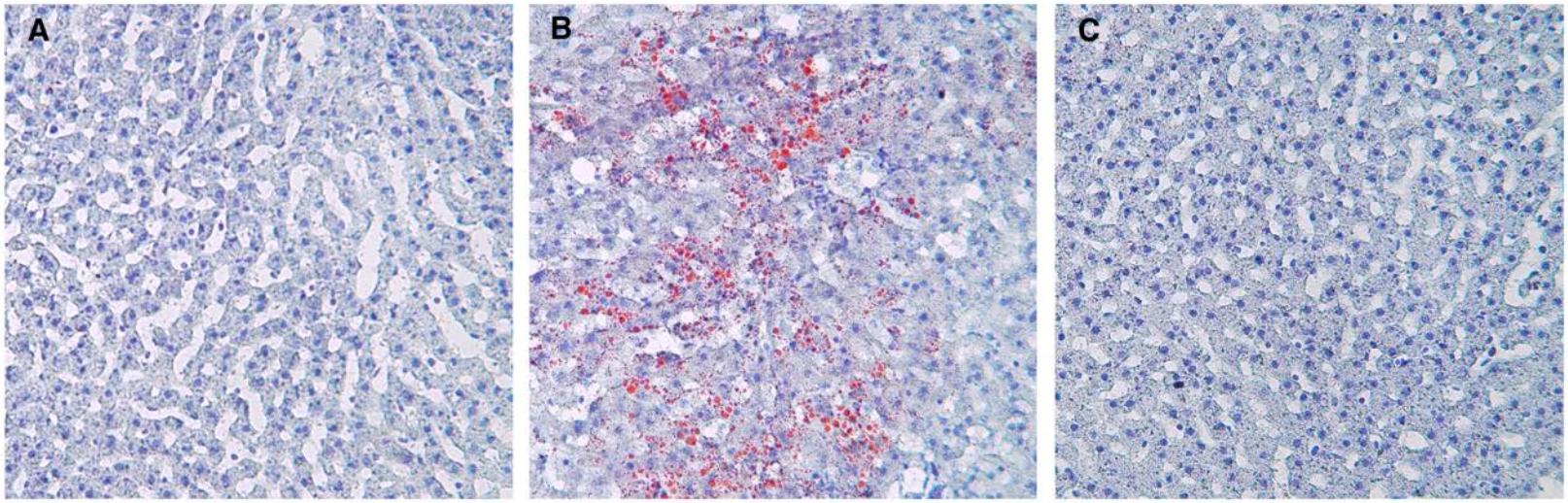
Foxo1 Expression in High Fat Diet-Induced Obese Mice



FoxO1 Becomes Deregulated in the Liver of High Fructose Diet-Induced Hyperlipidemic Hamsters

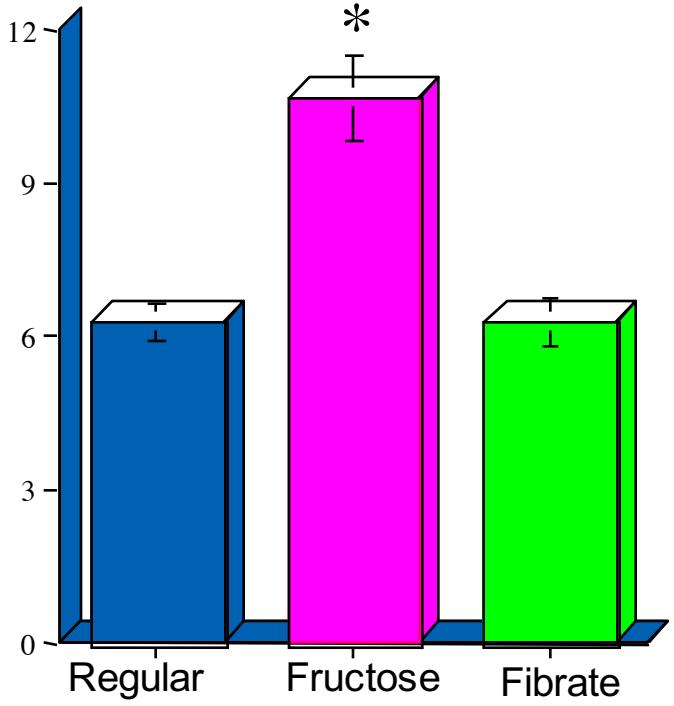


High Fructose Feeding Is Associated with Increased Fat Deposition in Liver



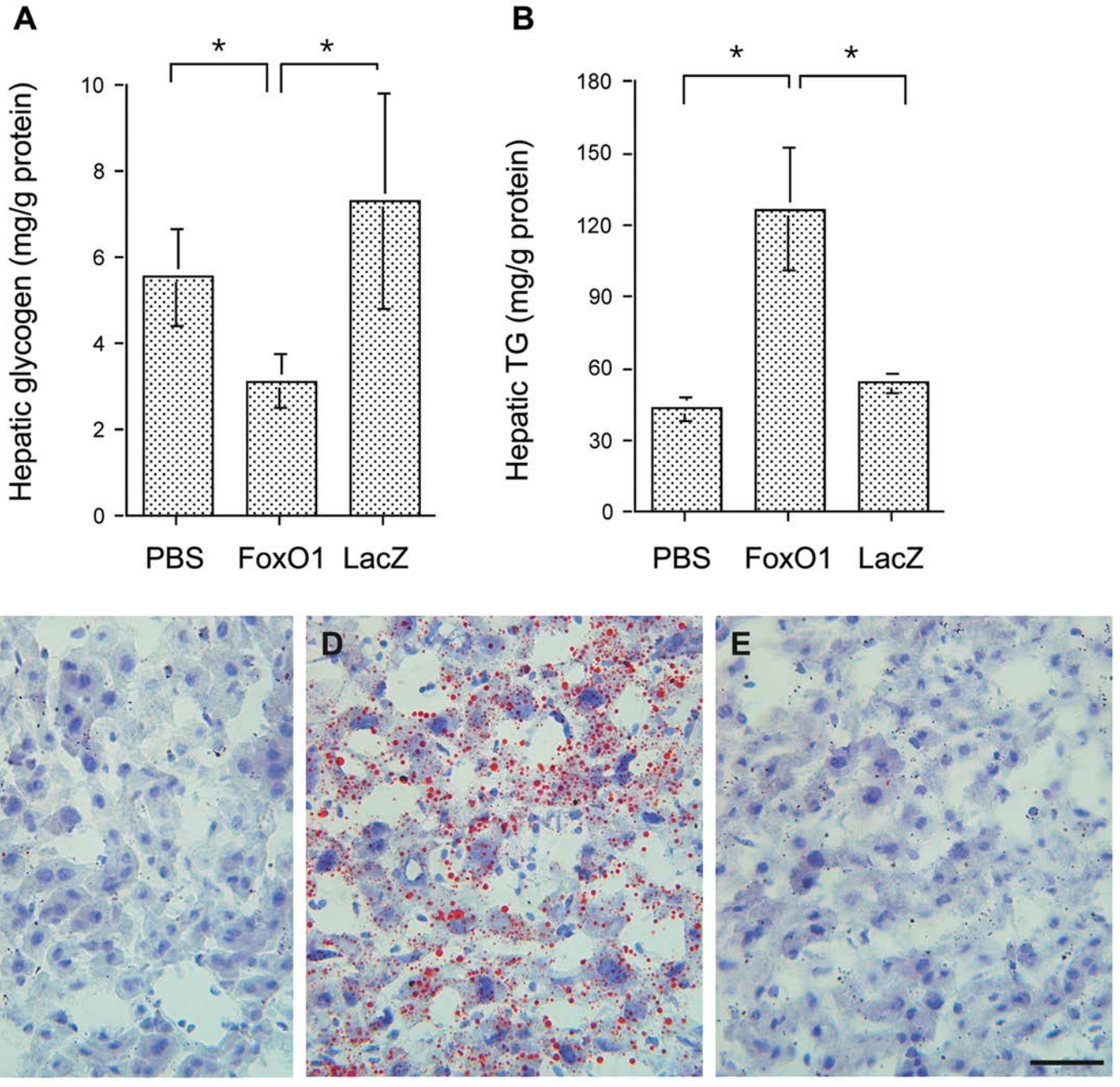
Regular Chow | High Fructose | High Fructose+Fibrate

Hepatic TG content (mg/g liver)

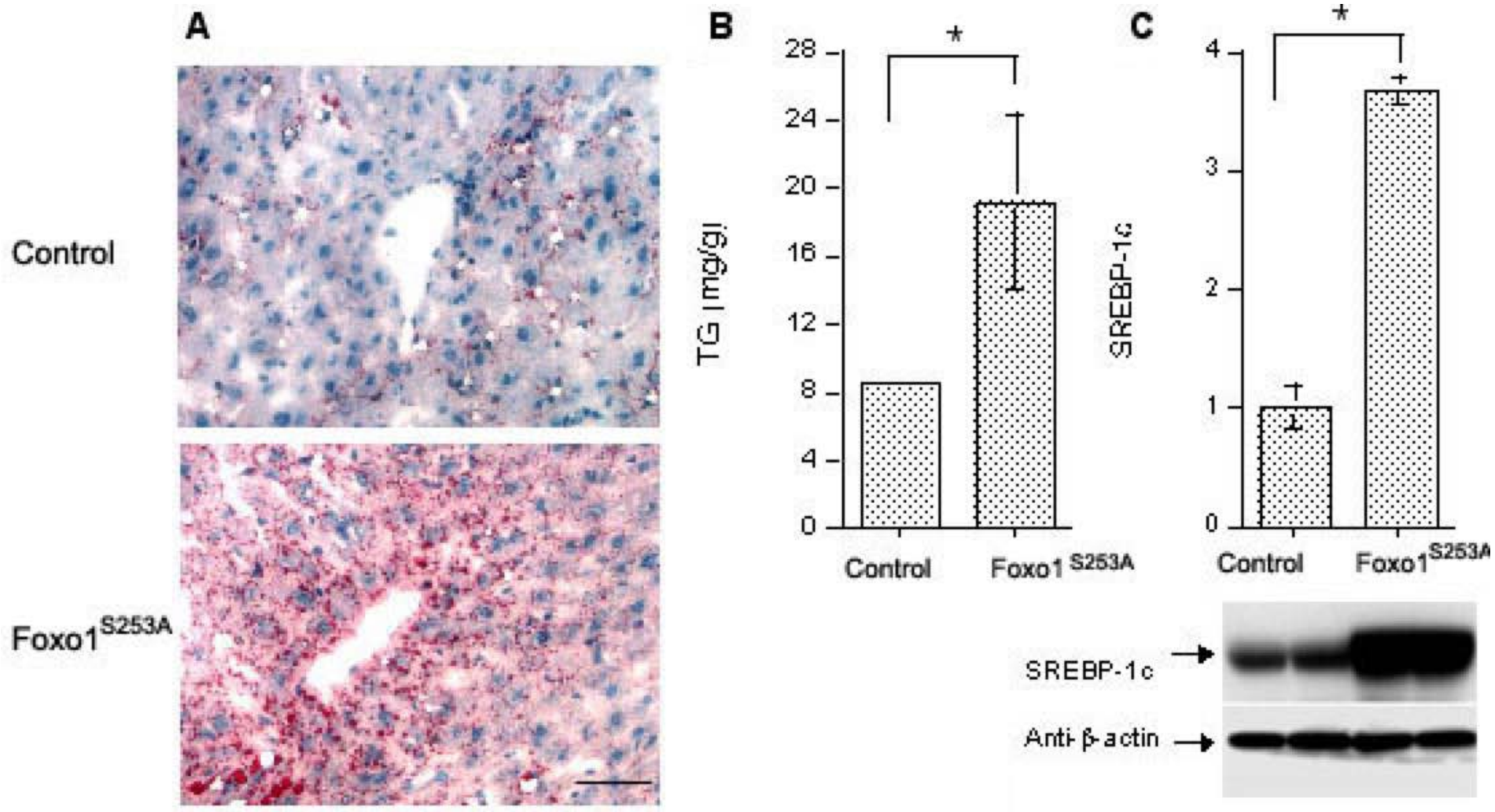


Qu…Dong, Endocrinology 2006. 147:5641-5652

Increased Fat Accumulation in the Liver of FoxO1 vector-treated mice



Increased Hepatic Lipid Content in FoxO1 Transgenic Mice



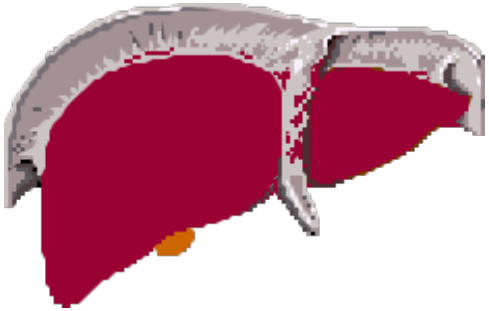
Qu…Dong, Am J Physiology, 2007. 292:E421-E434

FoxO1 is linked to hepatic steatosis in humans

Diabetes. 2008 Mar 3.
INCREASED EXPRESSION AND ACTIVITY OF THE TRANSCRIPTION FACTOR FOXO1 IN NONALCOHOLIC STEATOHEPATITIS.

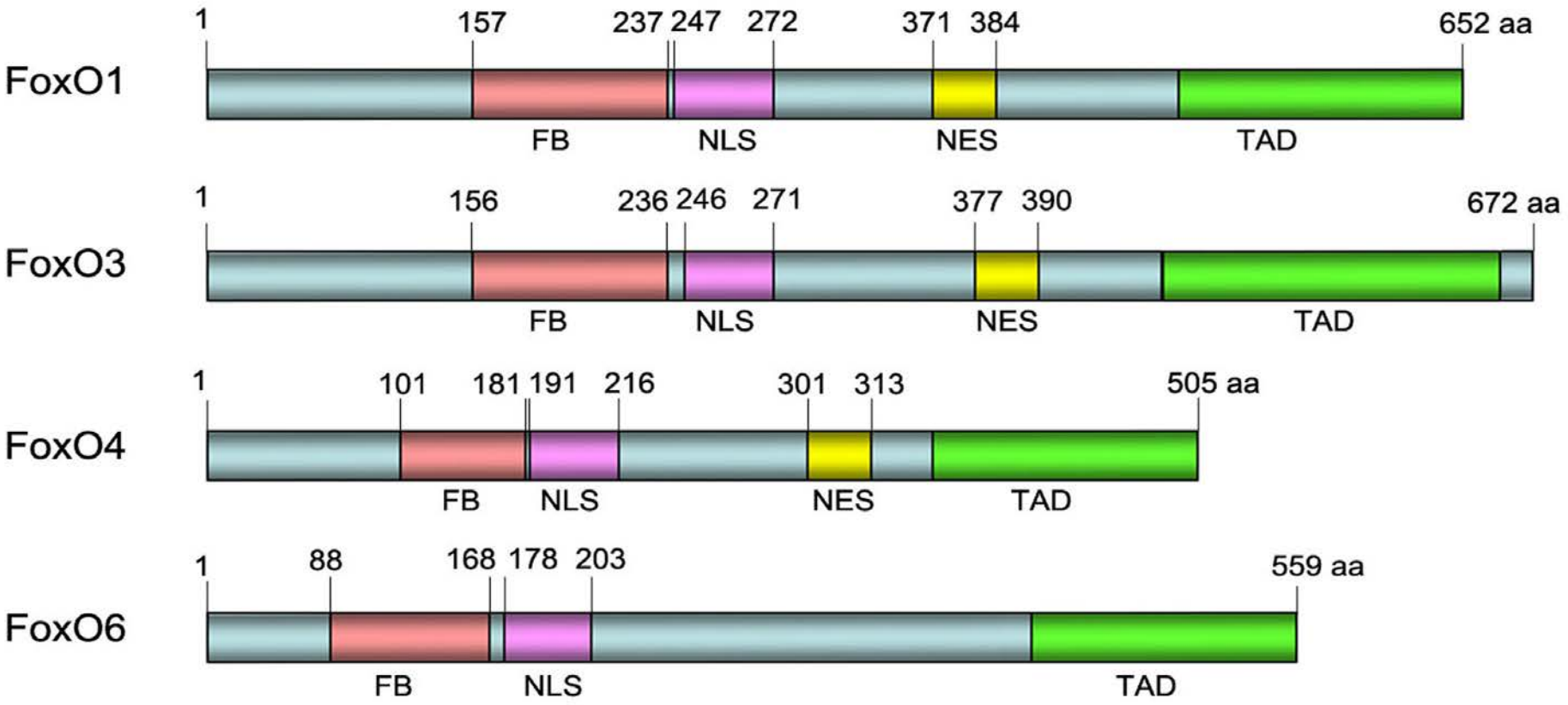
Valenti L, Rametta R, Dongiovanni P, Maggioni M, Ludovica Fracanzani A, Zappa M, Lattuada E, Roviaro G, Fargion S.r

Department of Internal Medicine, Ospedale Maggiore Policlinico Mangiagalli Regina Elena IRCCS, University of Milano



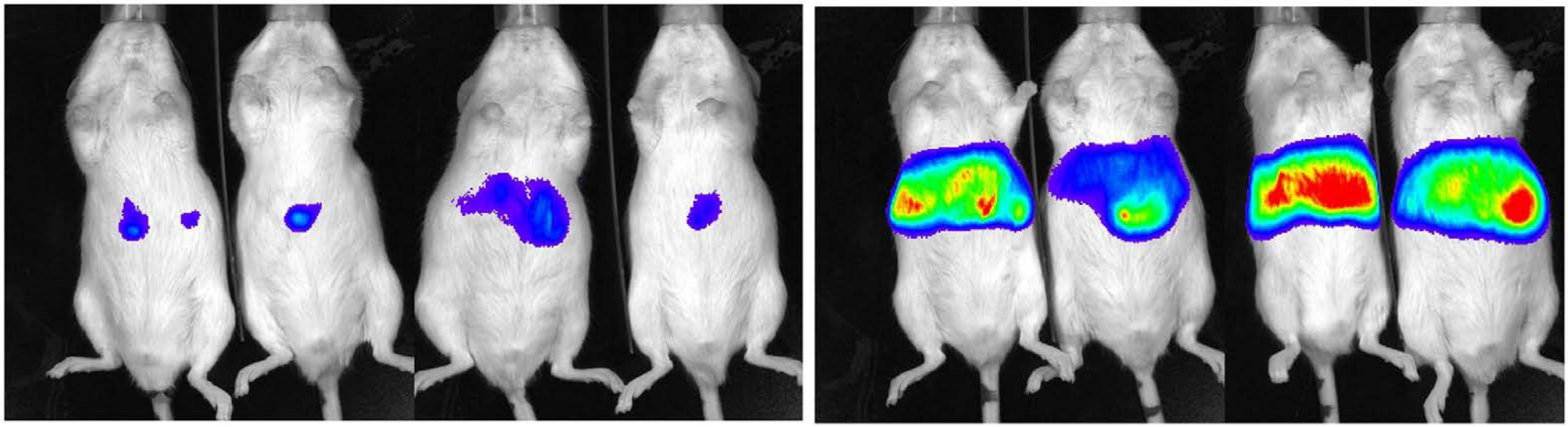


The FoxO Family Consists of 4 Members





FoxO6 Is A Key Regulator of Glucose Production in the Liver



FoxO6-transgenic mice develop pre-diabetes, due to excessive glucose production in the liver



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FoxO6 in Glucose Metabolism

Diabetes 60 (11) 2011

ORIGINAL ARTICLE

Proof Only

Forkhead Box O6 Integrates Insulin Signaling With Gluconeogenesis in the Liver

Dae Hyun Kim,[1] German Perdomo,[1] Ting Zhang,[1] Sandra Slusher,[1] Sojin Lee,[1] Brett E. Phillips,[1] Yong Fan,[1] Nick Giannoukakis,[1] Roberto Gramignoli,[2] Stephen Strom,[2] Steven Ringquist,[1] and H. Henry Dong[1]

FoxO6 transgenic mice develop pre-diabetes, characterized by fasting hyperglycemia and hyperinsulinemia, and glucose intolerance.

These effects are attributable to FoxO6-mediated induction of gluconeogenesis in the liver

Inhibition of FoxO6 activity in insulin resistant liver improves fasting and fed glycemia and enhance insulin sensitivity in diabetic db/db mice



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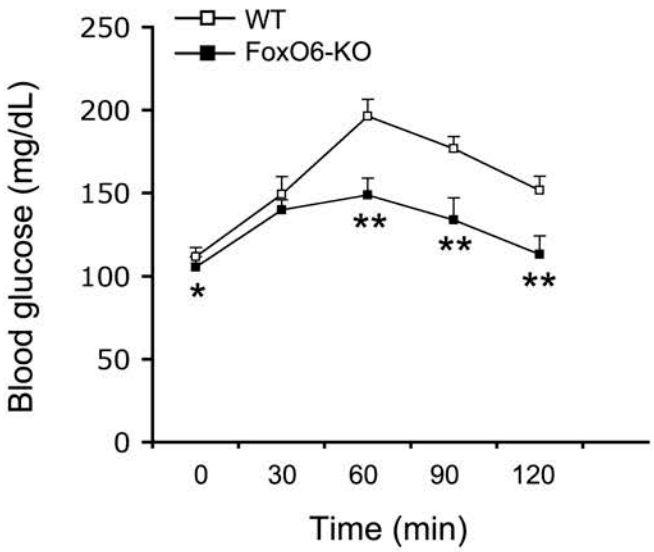
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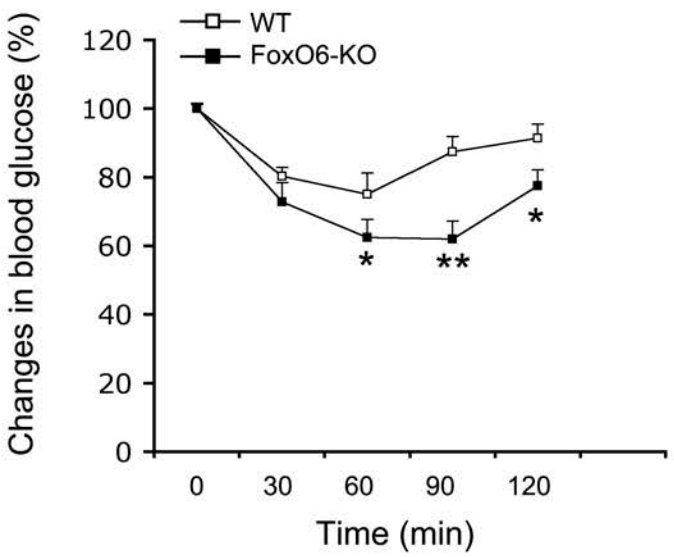
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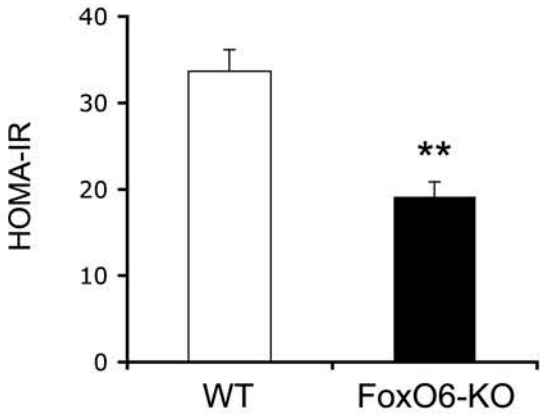
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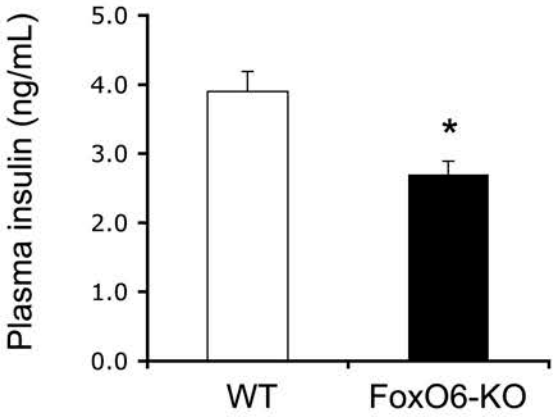
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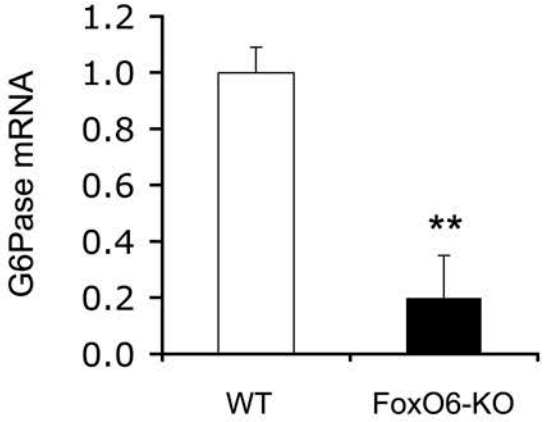
FoxO6 Knockout Mice Are Protected from Fat-Induced Diabetes

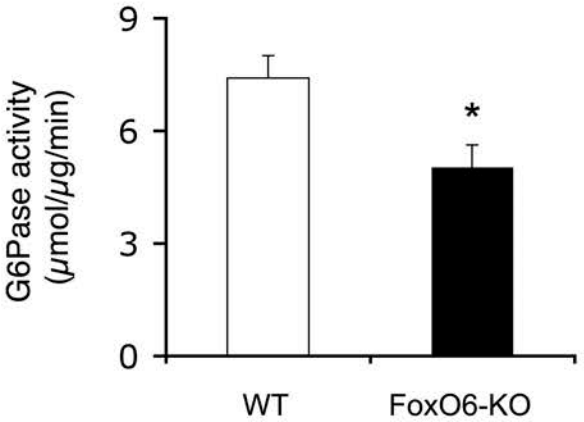














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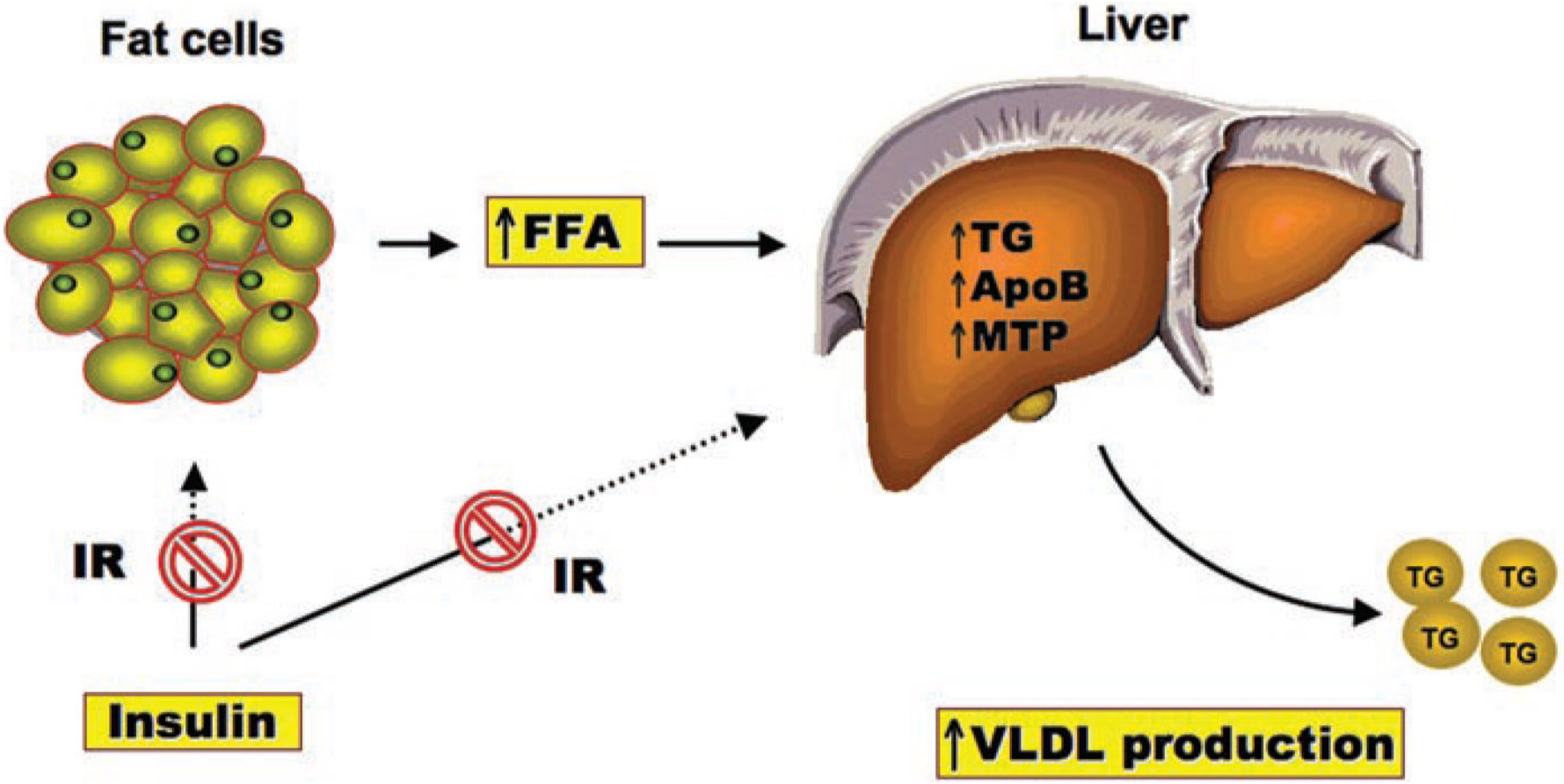
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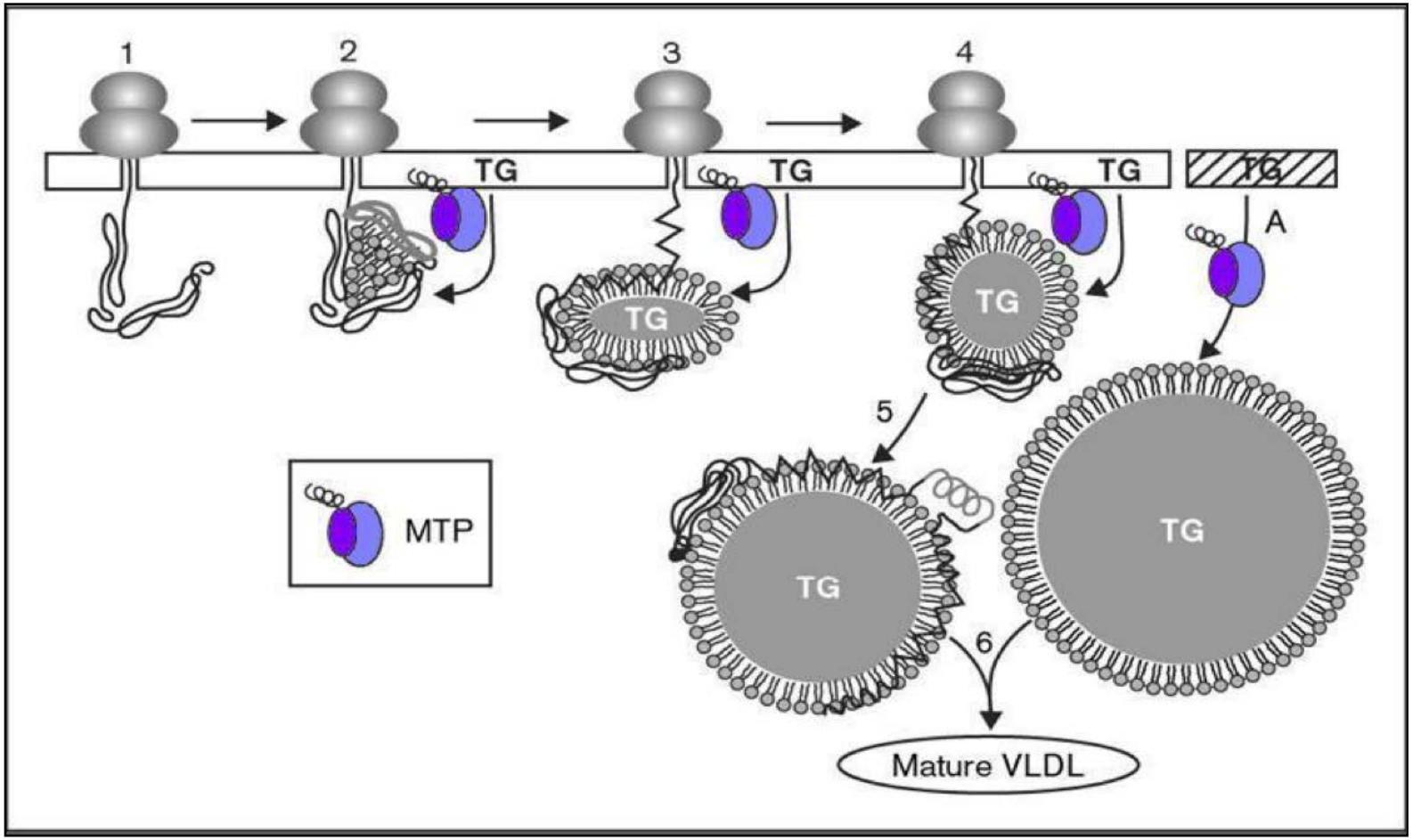
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TG-rich VLDL overproduction is a major factor for hypertriglyceridemia in Type 2 Diabetes





MTP Plays A Rate-Limiting Role in VLDL Assembly and Secretion from Liver

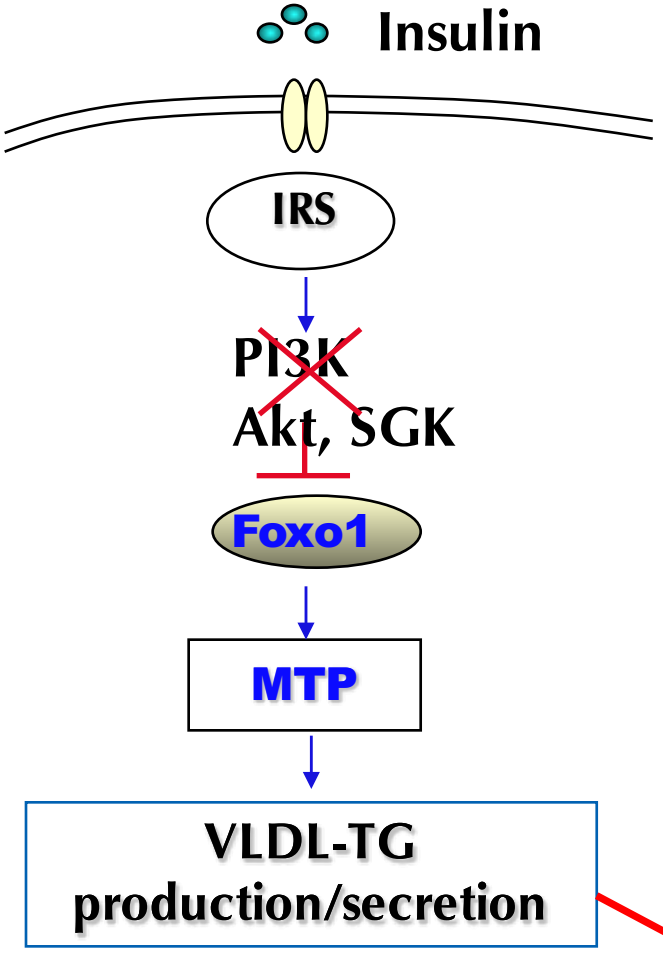


MTP transfers triglyceride to the growing polypeptide chain of apoB



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FoxO1 Mediates Insulin Action on VLDL-TG Production



Insulin resistance

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Hypertriglyceridemia



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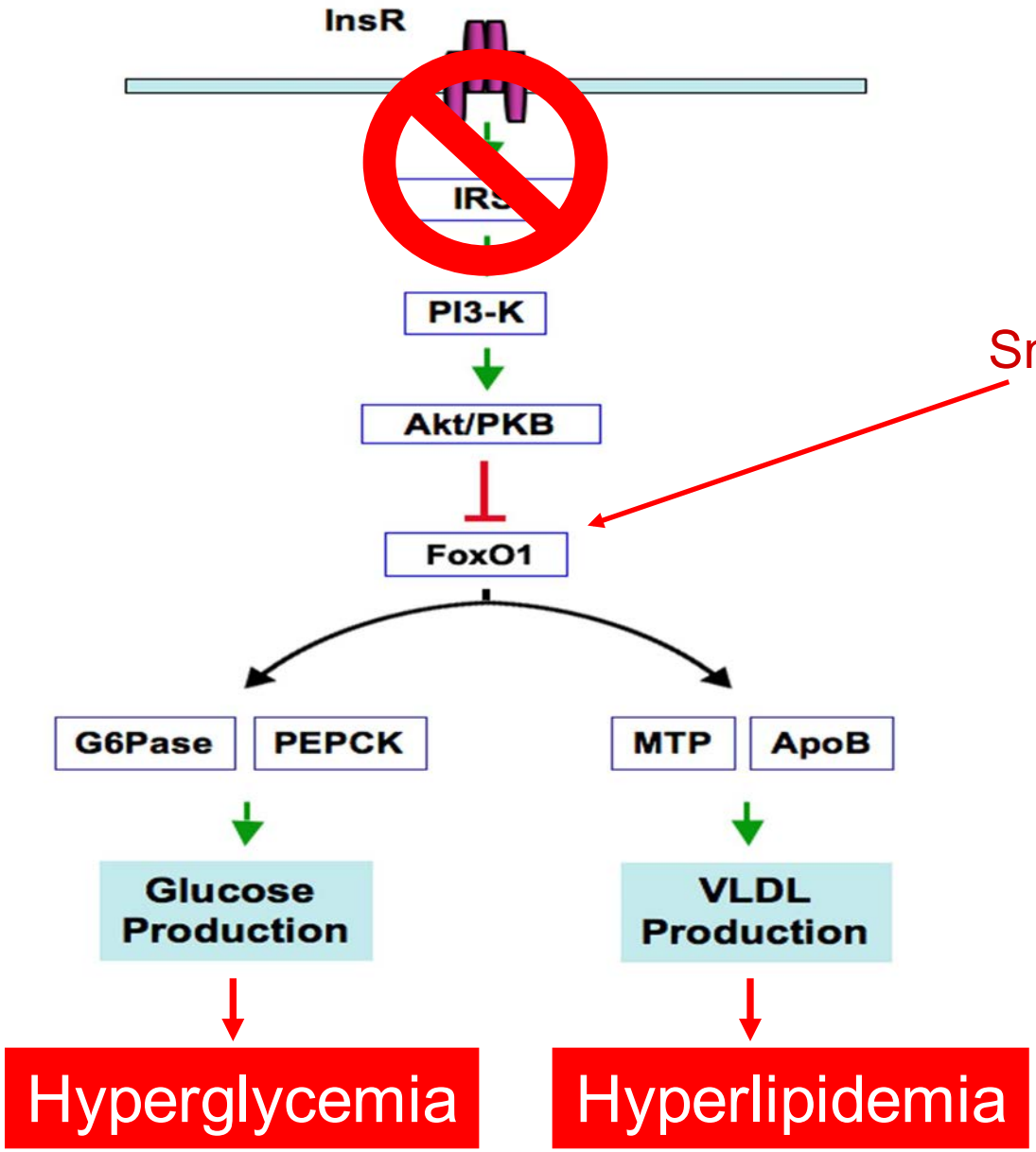
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FoxO1 Regulates Hepatic Production of Glucose and VLDL

Dong et al. JCI 2004 114:1493-1503
Dong et al. JCI 2008 118:2347-2364



Small molecule drugs

Summary

•FoxO1 is a key factor for integrating insulin signaling to glucose and lipid metabolism in liver. This effect is pivotal for maintaining glucose and lipid homeostasis in normal individuals.

•In response to insulin resistance, FoxO1 becomes deregulated in insulin resistant liver, contributing to the dual pathogenesis of hyperglycemia and hyperlipidemia in obesity and diabetes.

•FoxO1 may be a therapeutic target. Targeted inhibition of FoxO1 activity in insulin resistant states is predicted to improve both glucose and lipid metabolism. This concept awaits further investigation.

