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Role of mitochondrial ROS induced by high calorie diet in pancreatic β-cell destruction

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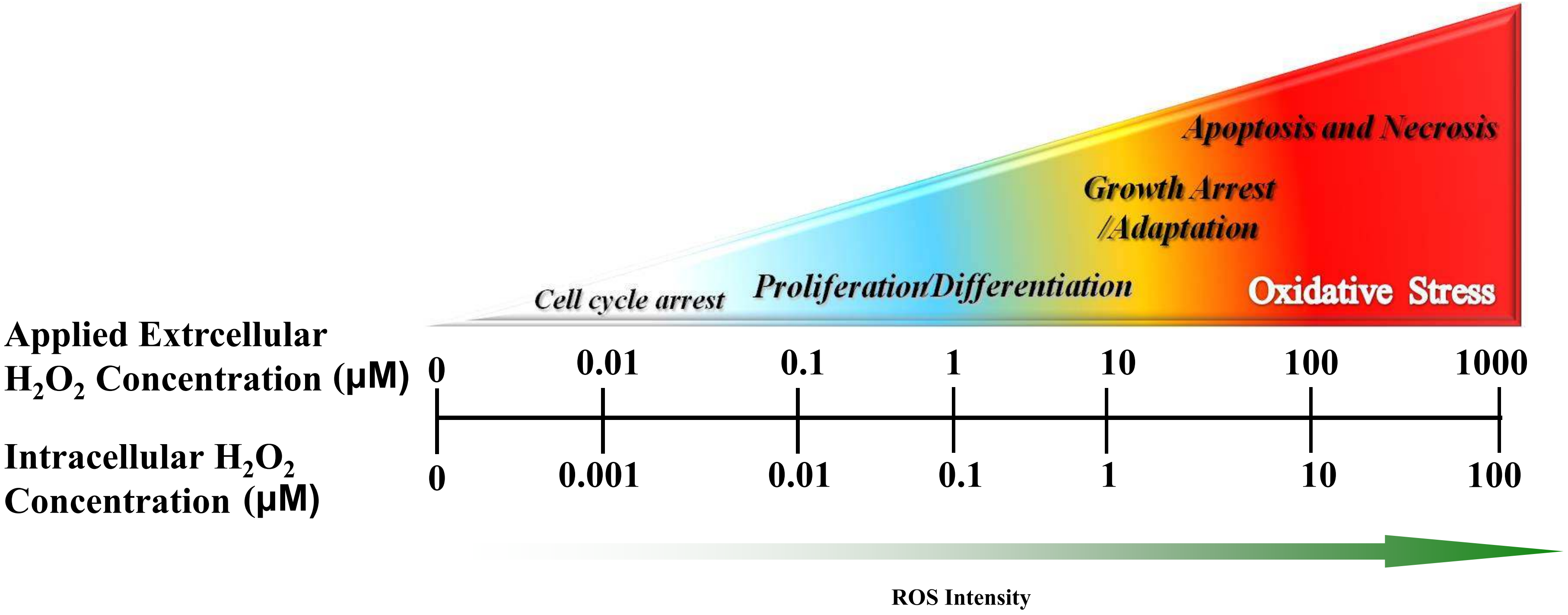
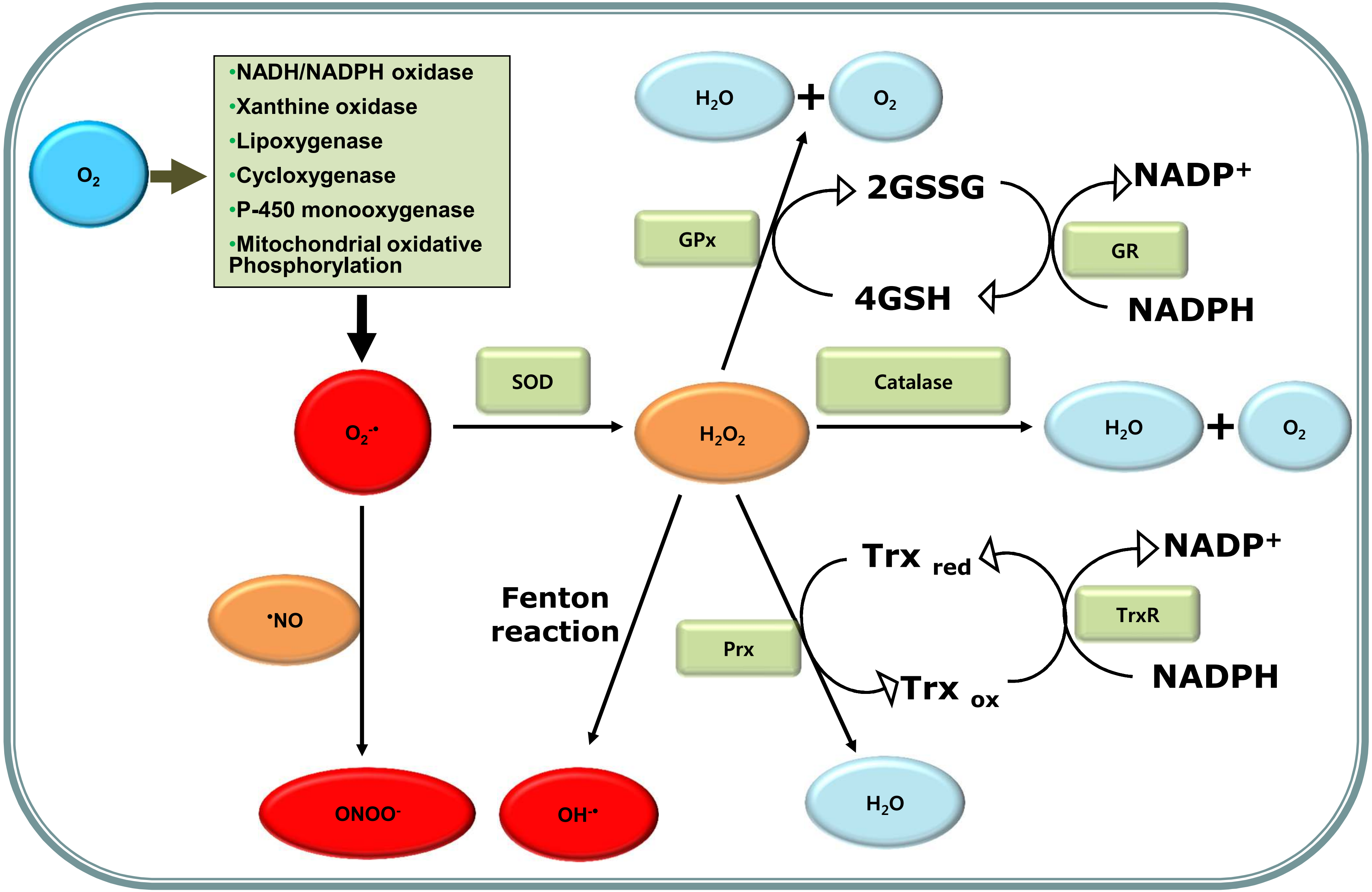
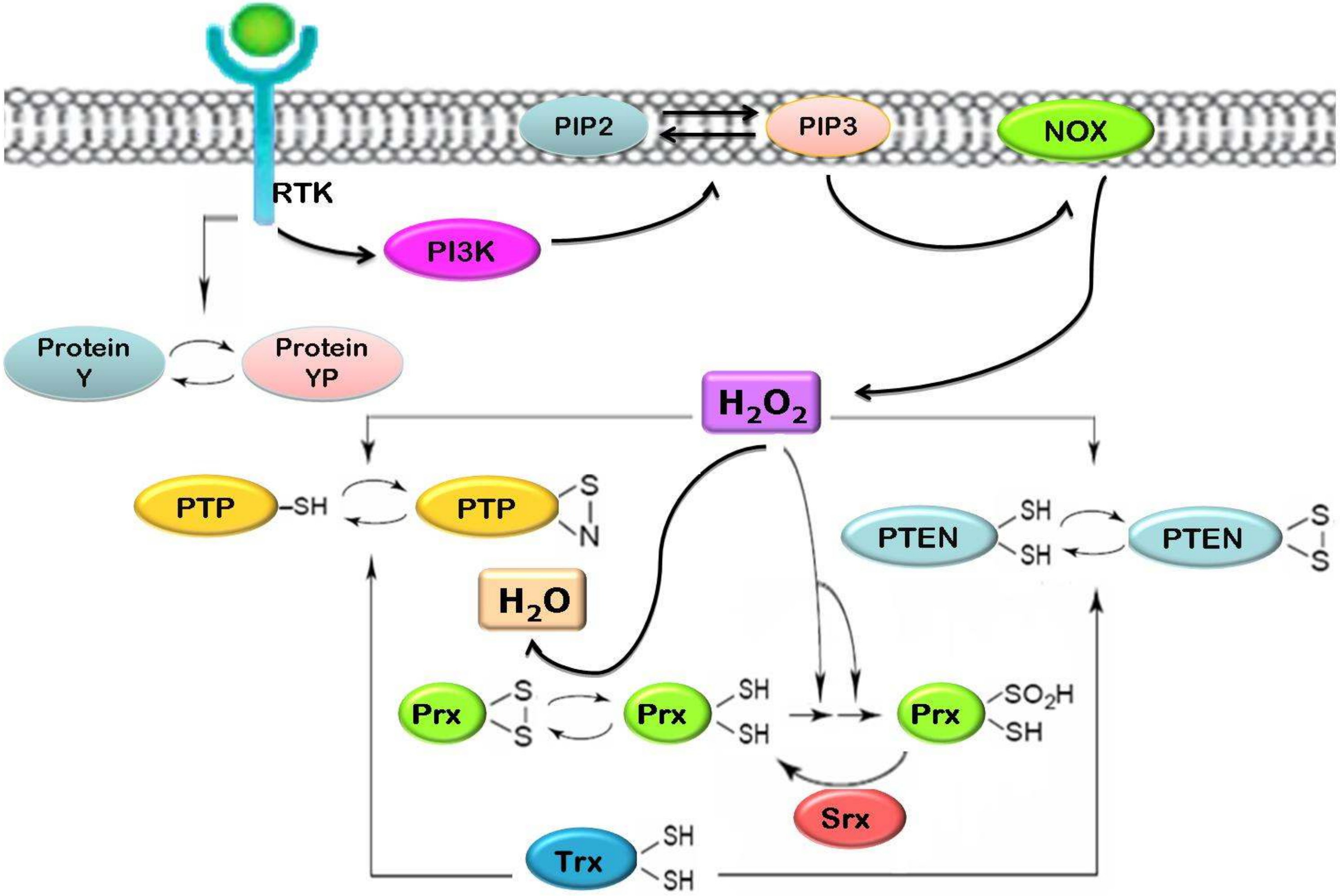
Cellular response to reactive oxygen species (ROS)



Reactive oxygen species (ROS) and key cellular antioxidant enzymatic pathways.



H_2O_2 in growth-factor-stimulated Signaling



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ROS damage in DM

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Beneficial Effects of Antioxidant Gene Transfers into Beta Cells

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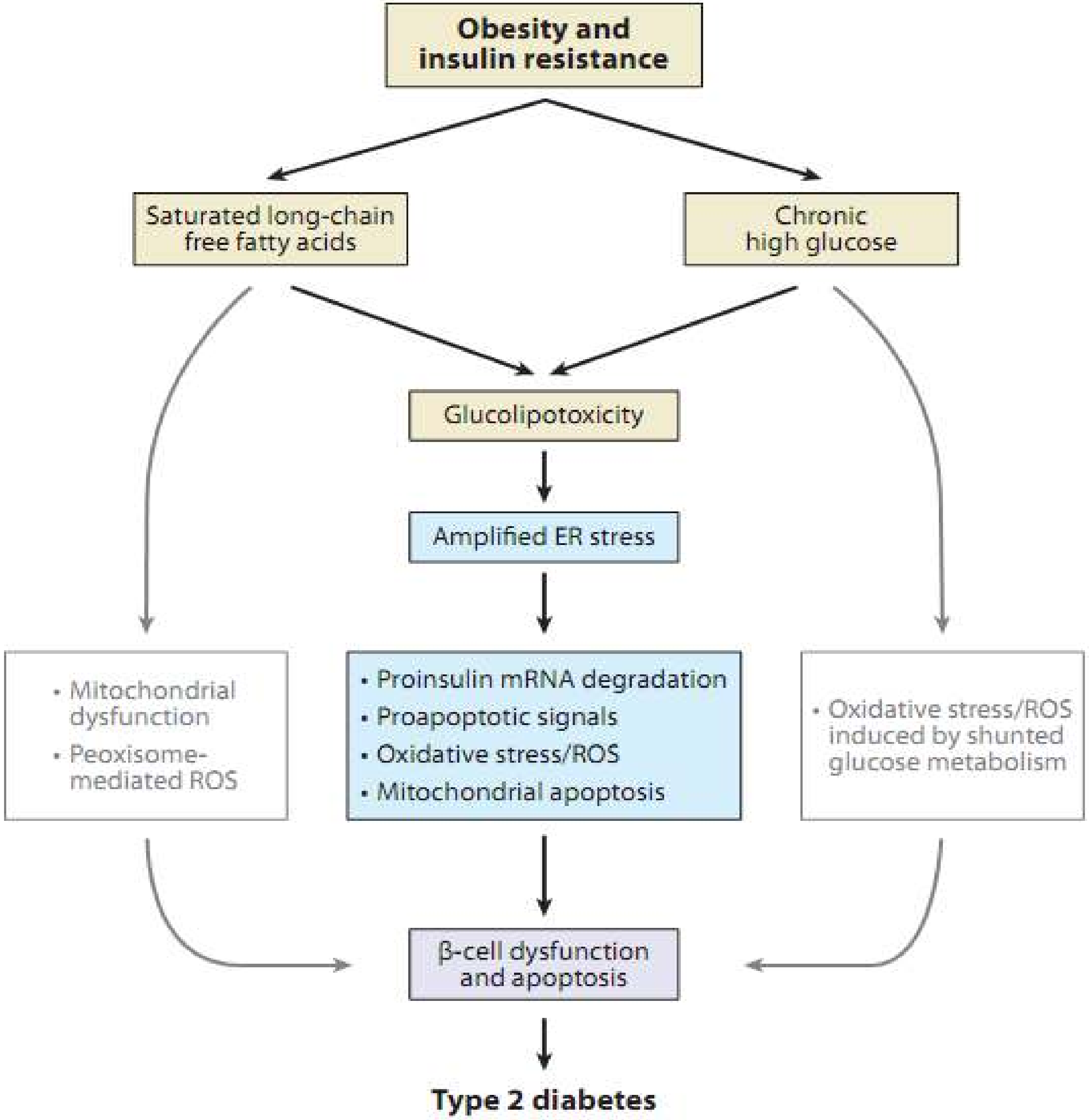
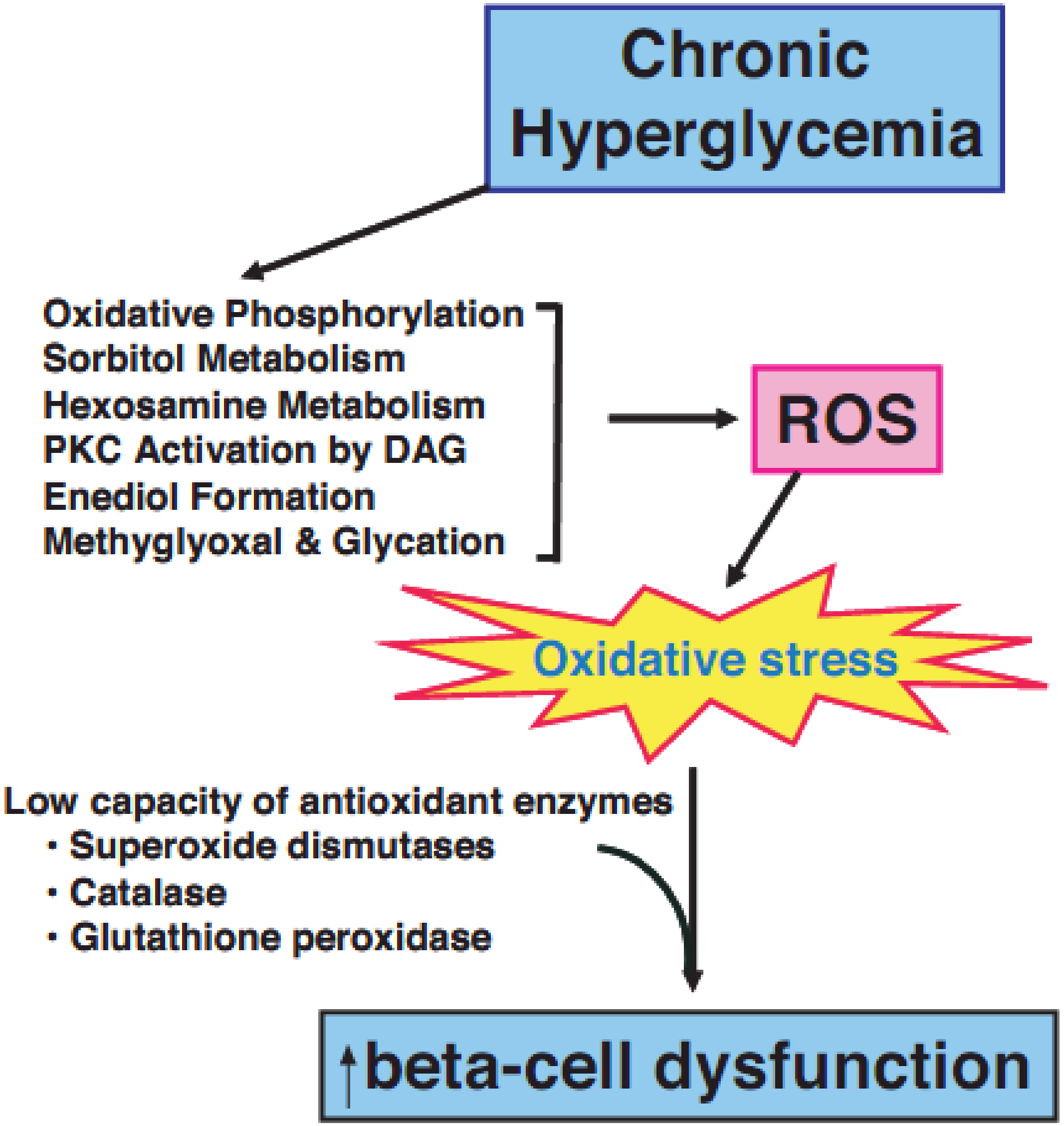
Mechanisms Regulating B cell Mass in Type 2 DM



Biochemical pathways through which elevated levels of glucose can form excessive levels of reactive oxygen species



Chronic Hyperglycemia

- Oxidative Phosphorylation
- Sorbitol Metabolism
- Hexosamine Metabolism
- PKC Activation by DAG
- Enediol Formation
- Methyglyoxal & Glycation

ROS

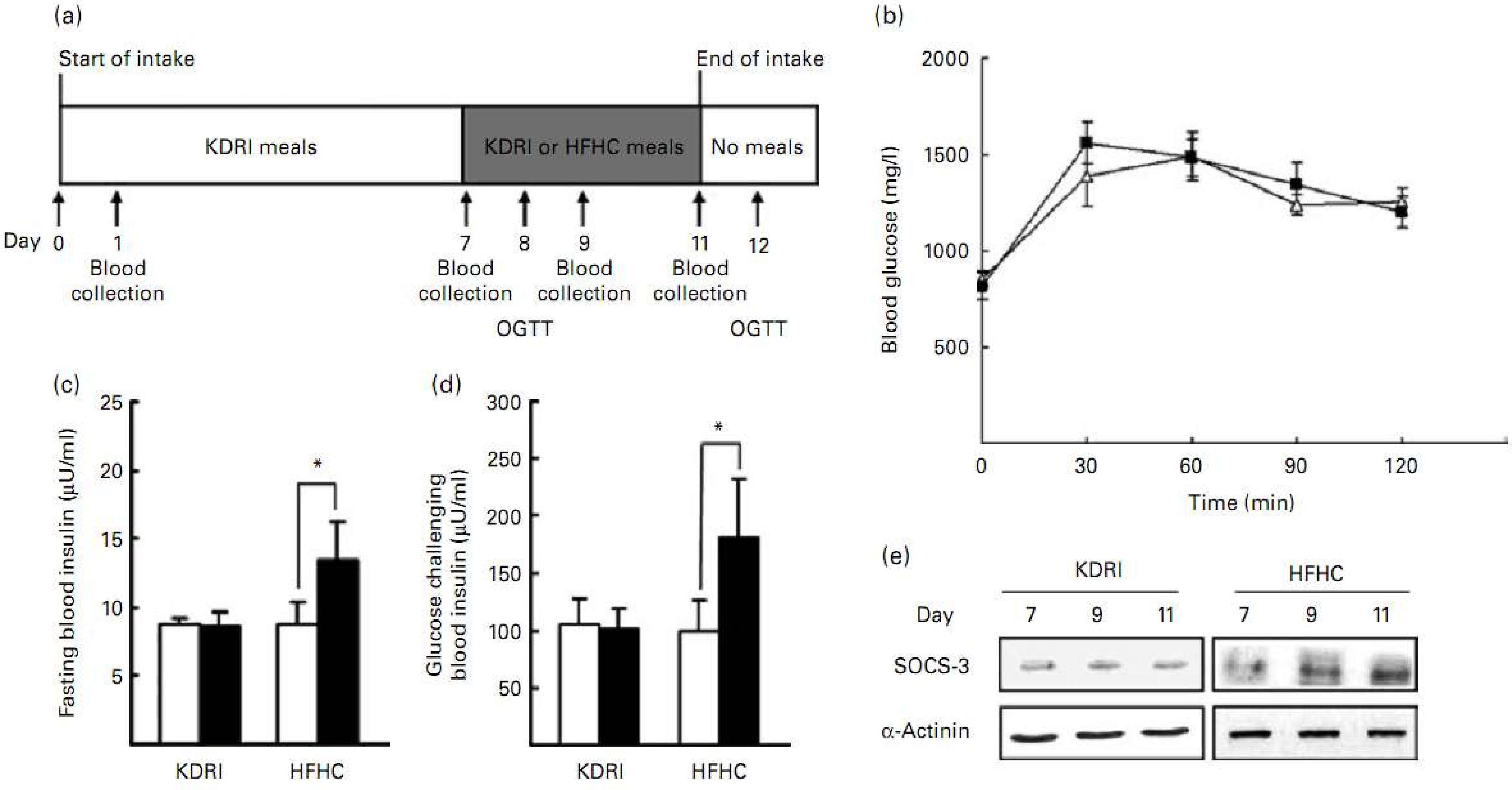
Oxidative stress

Low capacity of antioxidant enzymes
  - Superoxide dismutases
  - Catalase
  - Glutathione peroxidase

↑beta-cell dysfunction

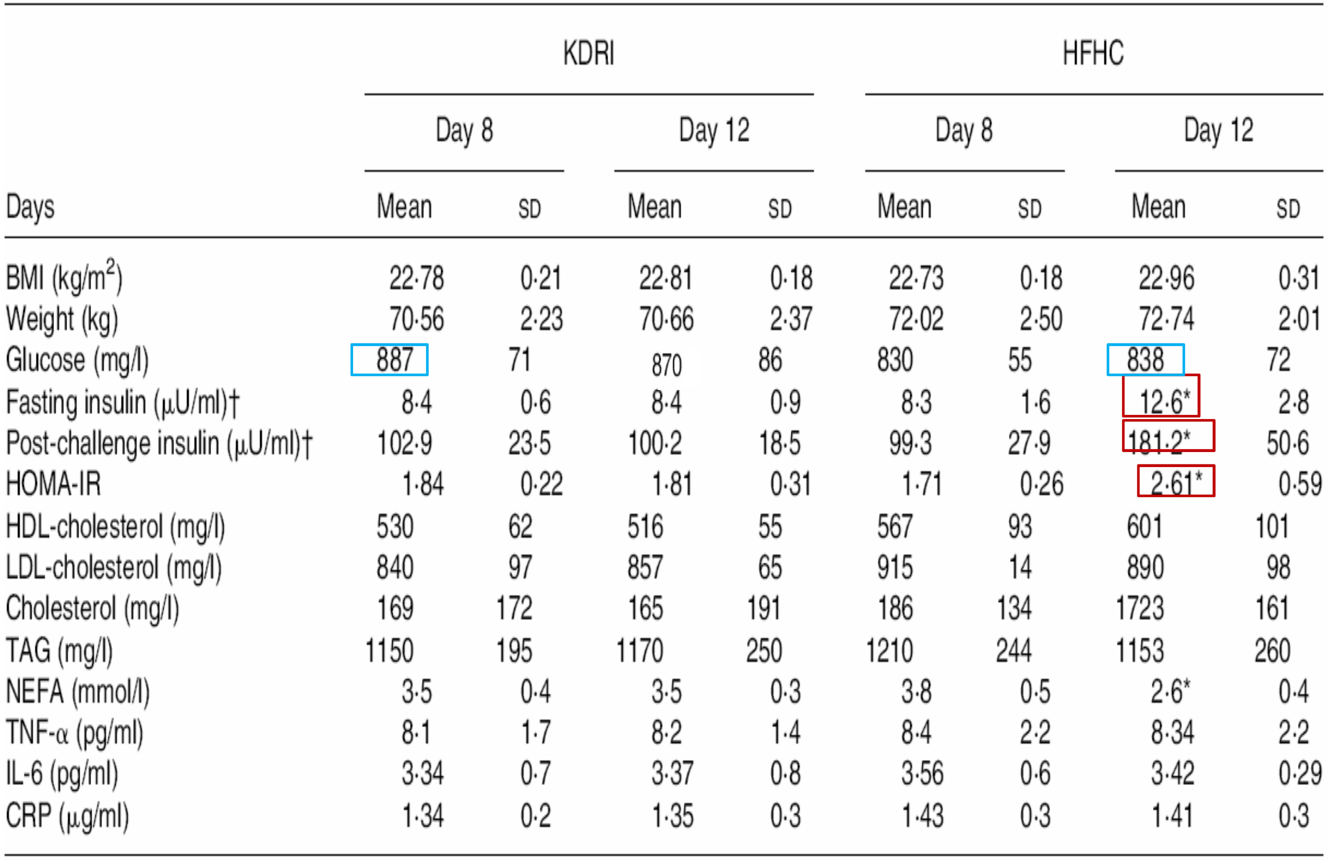
Vincent Poitout and R. Paul Robertson
Endocr Rev;29(3):351-366

Hyperinsulinaemia and insulin resistance after repeated intake of high-fat, high-carbohydrate meals



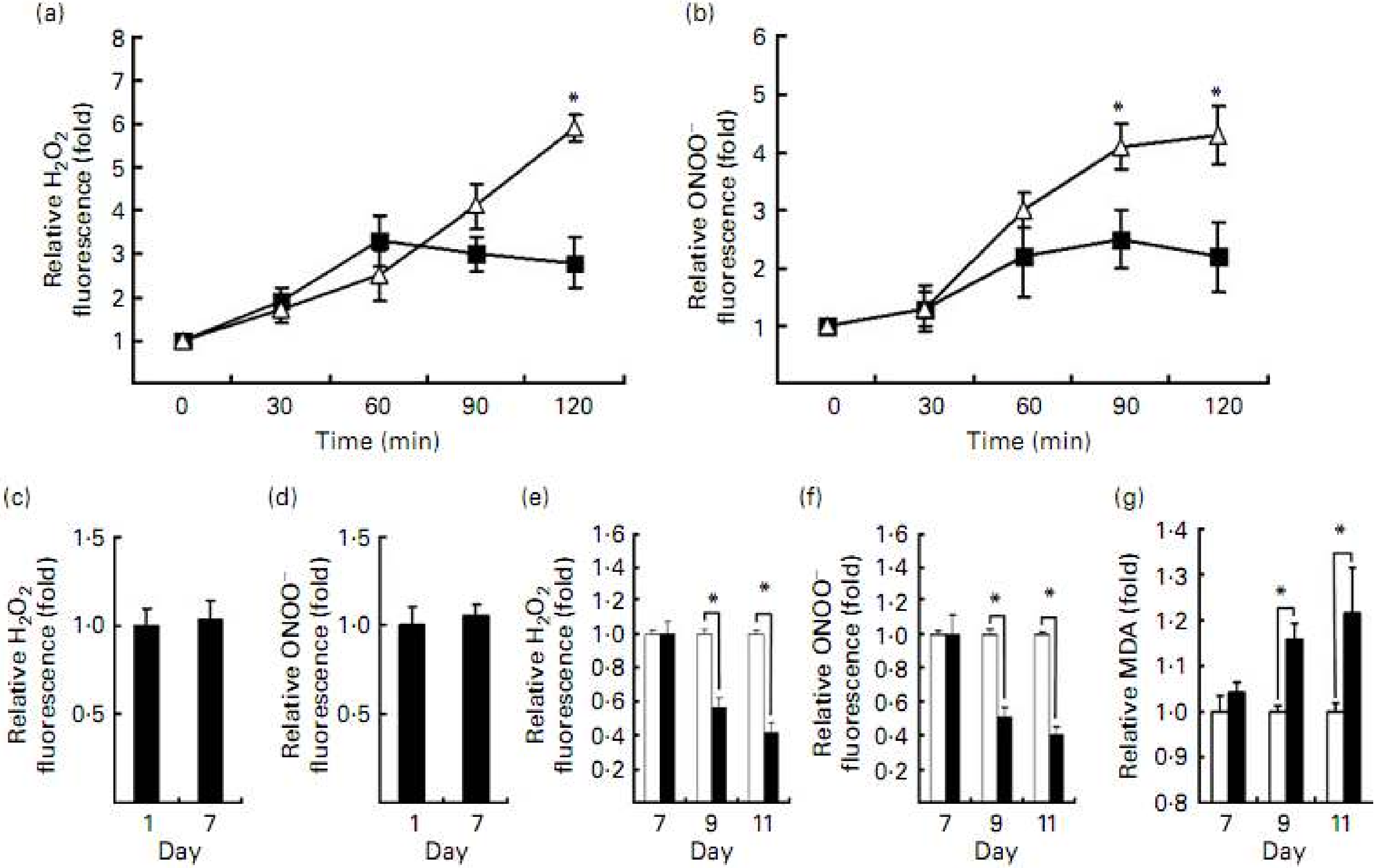
[Lim S et al. British Journal of Nutrition](#) 28 November 2011

Metabolic changes in normal lean individuals following the dietary reference intake for Koreans (KDRI) or consuming HFHC meals



	KDRI				HFHC			
	Day 8		Day 12		Day 8		Day 12	
Days	Mean	SD	Mean	SD	Mean	SD	Mean	SD
BMI (kg/m^2)	22·78	0·21	22·81	0·18	22·73	0·18	22·96	0·31
Weight (kg)	70·56	2·23	70·66	2·37	72·02	2·50	72·74	2·01
Glucose (mg/l)	887	71	870	86	830	55	838	72
Fasting insulin (μU/ml)†	8·4	0·6	8·4	0·9	8·3	1·6	12·6*	2·8
Post-challenge insulin (μU/ml)†	102·9	23·5	100·2	18·5	99·3	27·9	181·2*	50·6
HOMA-IR	1·84	0·22	1·81	0·31	1·71	0·26	2·61*	0·59
HDL-cholesterol (mg/l)	530	62	516	55	567	93	601	101
LDL-cholesterol (mg/l)	840	97	857	65	915	14	890	98
Cholesterol (mg/l)	169	172	165	191	186	134	1723	161
TAG (mg/l)	1150	195	1170	250	1210	244	1153	260
NEFA (mmol/l)	3·5	0·4	3·5	0·3	3·8	0·5	2·6*	0·4
TNF-α (pg/ml)	8·1	1·7	8·2	1·4	8·4	2·2	8·34	2·2
IL-6 (pg/ml)	3·34	0·7	3·37	0·8	3·56	0·6	3·42	0·29
CRP (μg/ml)	1·34	0·2	1·35	0·3	1·43	0·3	1·41	0·3

Oxidative stress after the intake of high-fat, high-carbohydrate meals



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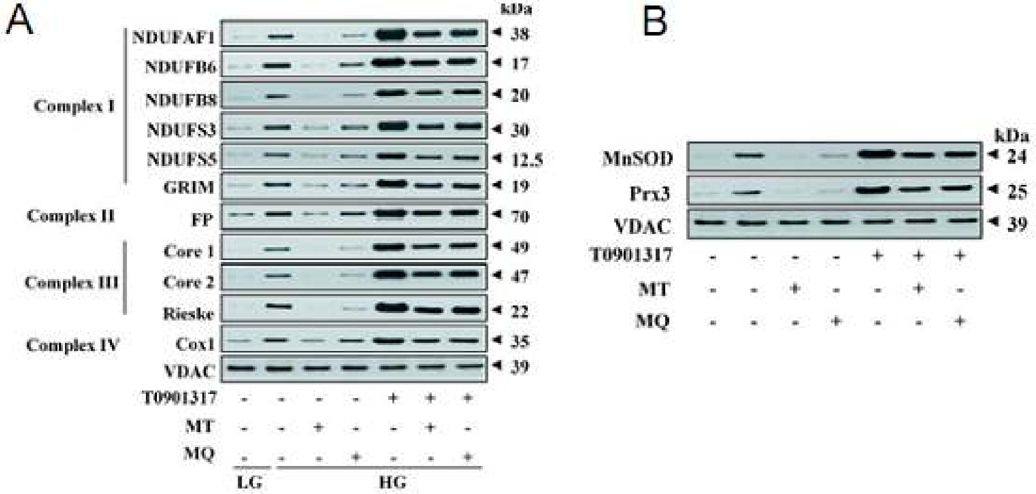
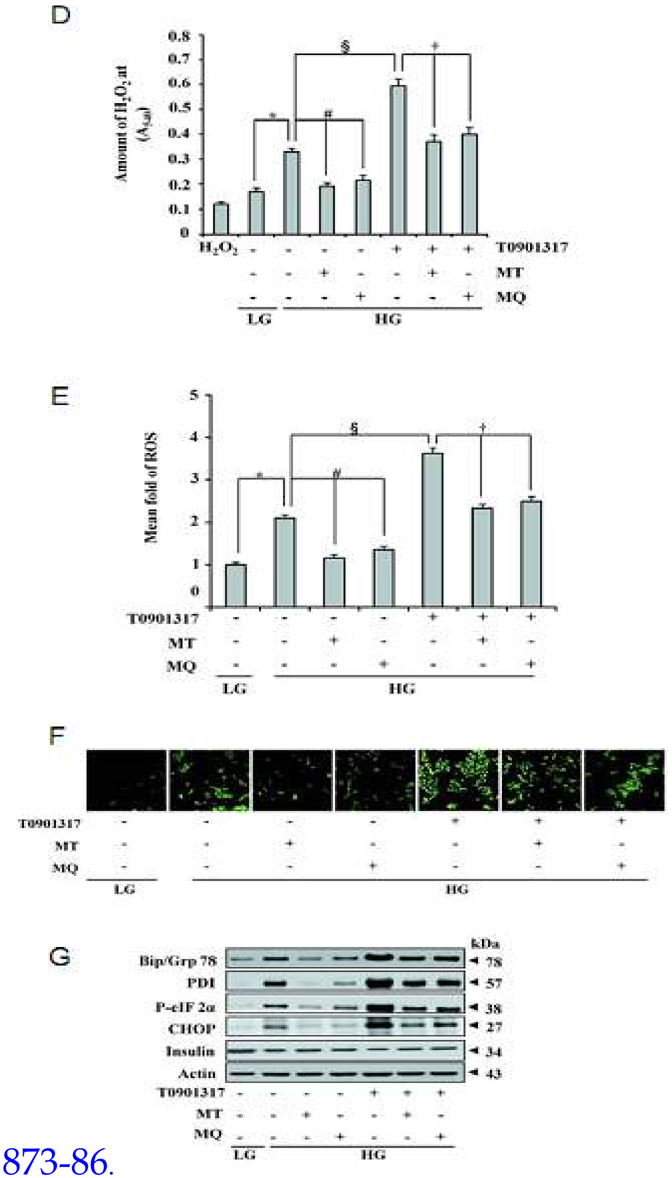
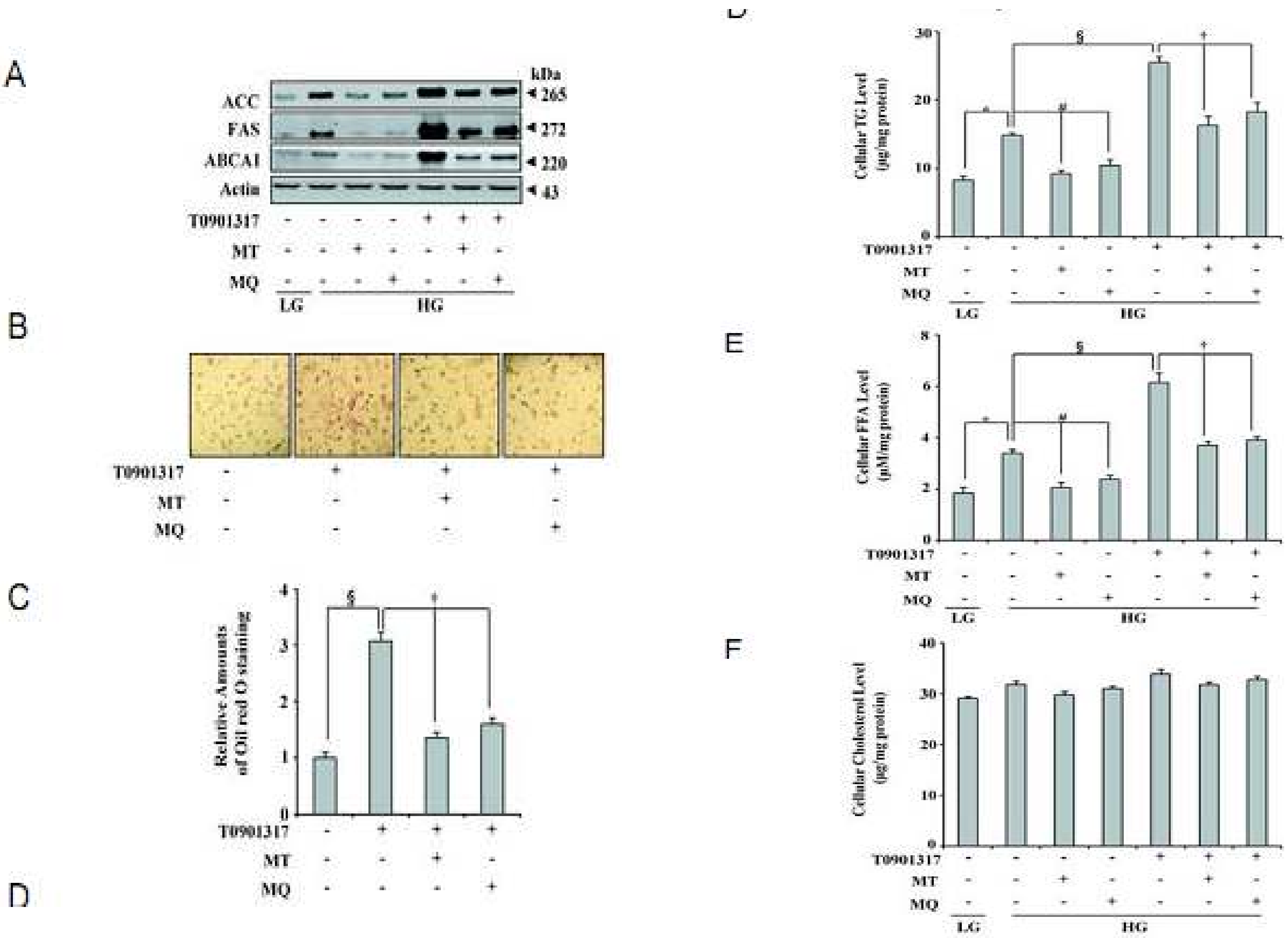
Mitochondria-targeted antioxidants attenuate the increases in mETC complexes, ROS and ER stress in beta cells





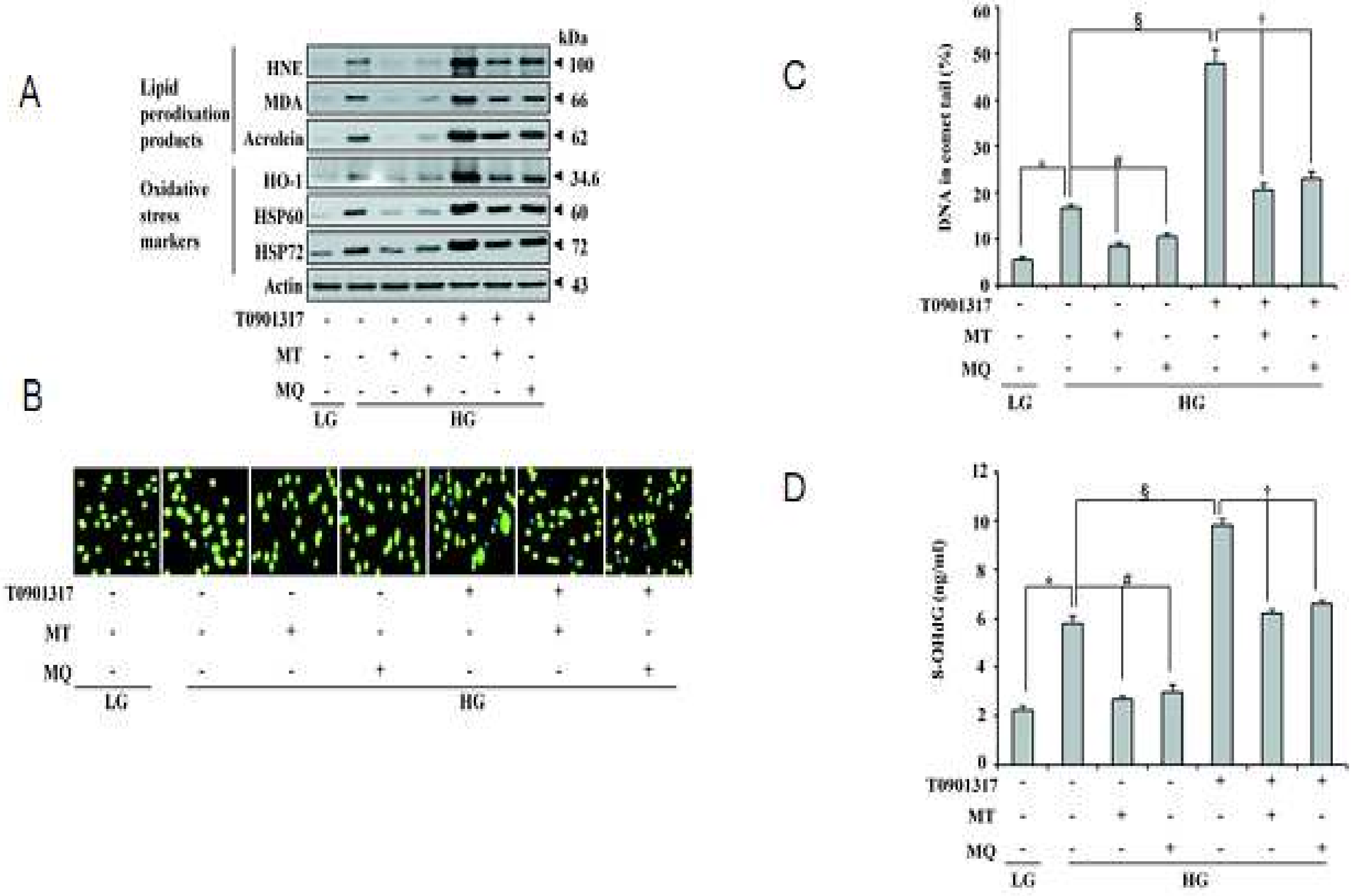
Lim S. et al Cell Physiol Biochem. 2011;28(5):873-86.

Mitochondria-targeted antioxidants attenuate lipogenesis and lipid accumulation under glucotoxic and glucolipotoxic conditions



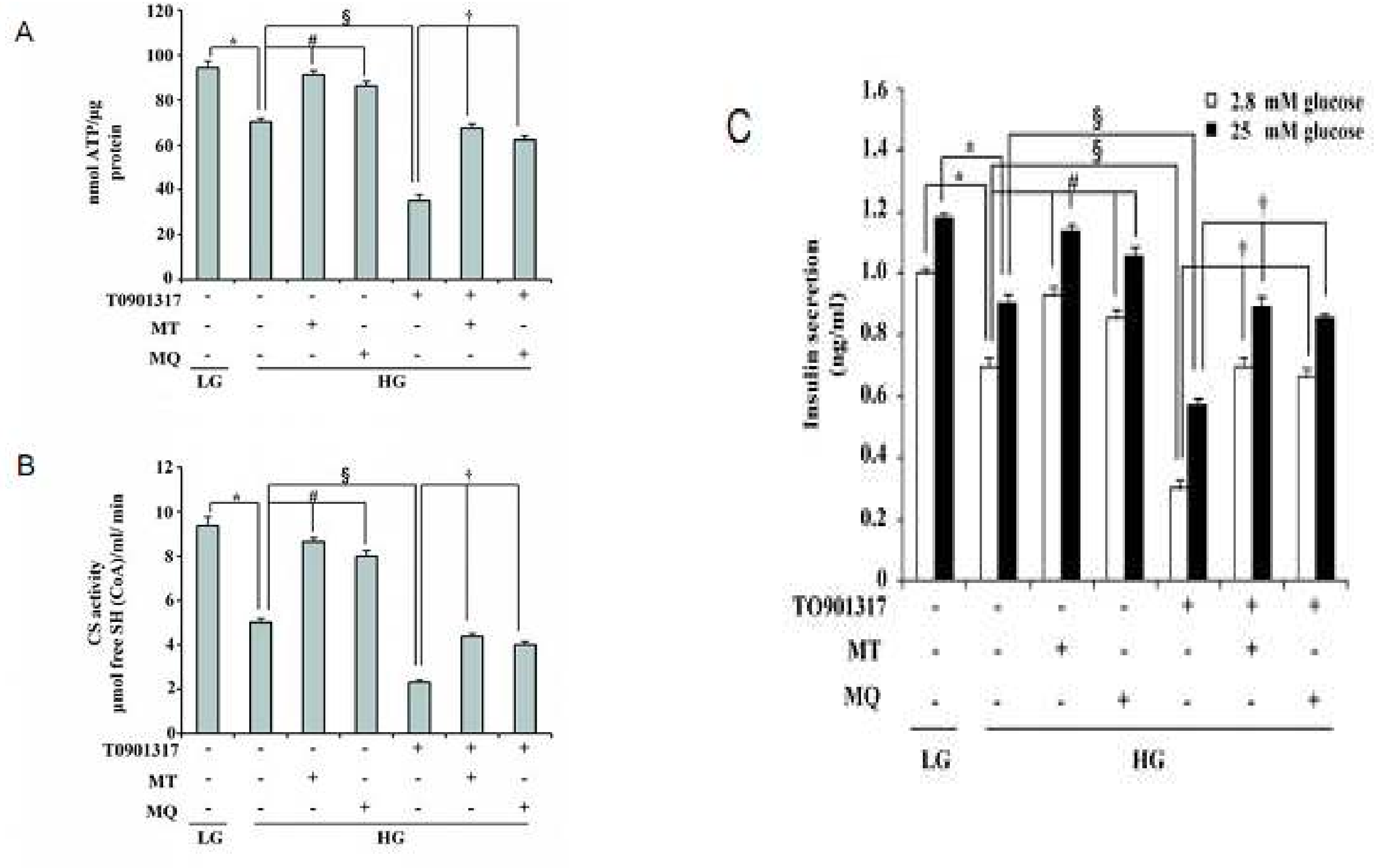
Lim S. et al Cell Physiol Biochem. 2011;28(5):873-86.

Mitochondria-targeted antioxidants attenuate lipid peroxidation and DNA damage



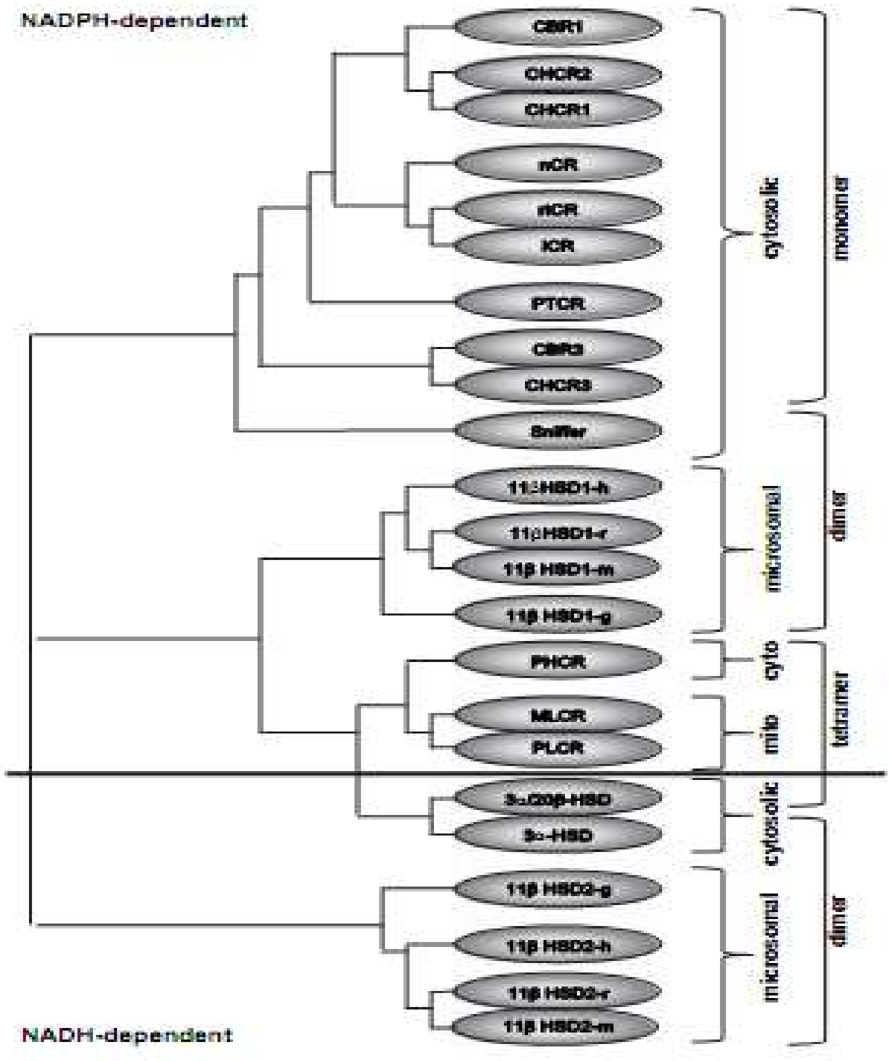
Lim S. et al Cell Physiol Biochem. 2011;28(5):873-86.

Mitochondria-targeted antioxidants restore ATP content, citrate synthase activity and GSIS

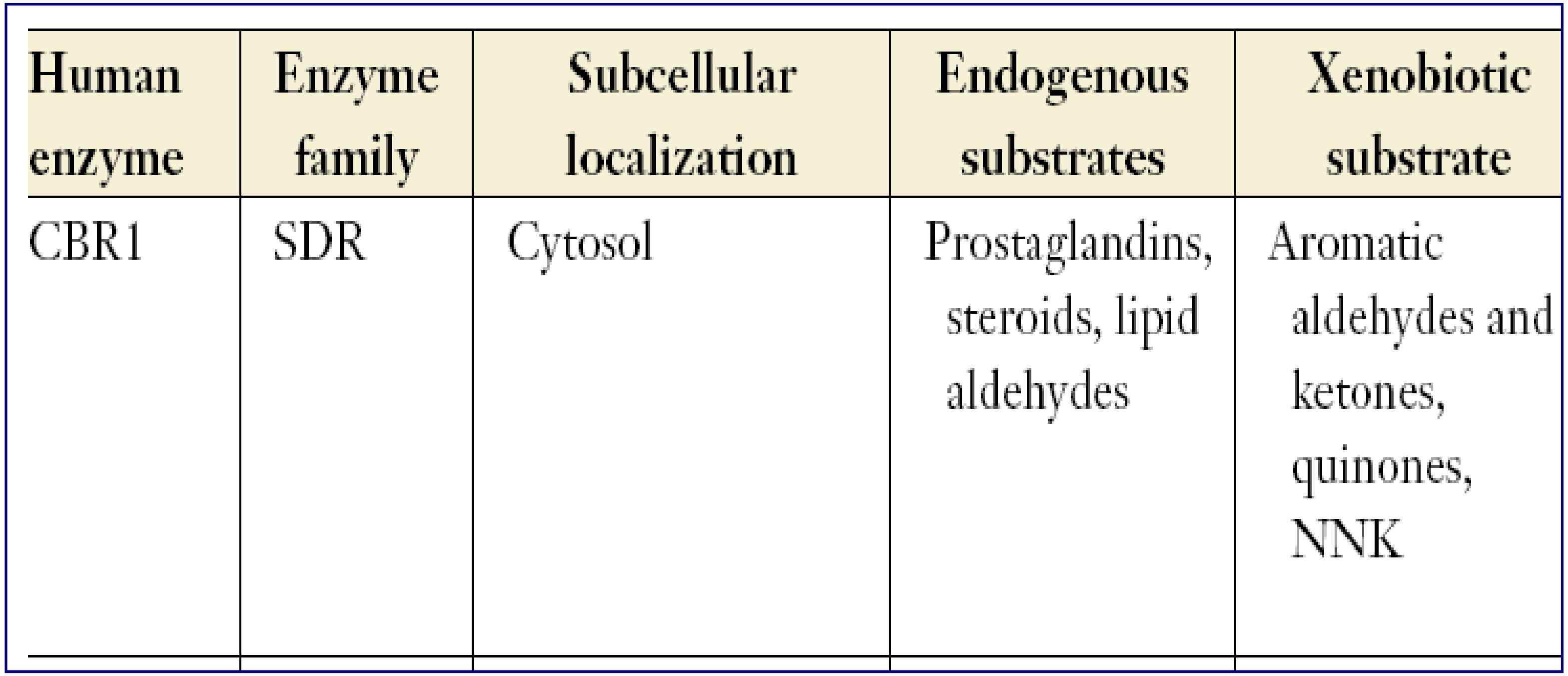


Lim S. et al Cell Physiol Biochem. 2011;28(5):873-86.

Evolutionary Tree of Carbonyl Reducing Enzymes



Carbonyl Reductase 1



Human enzyme	Enzyme family	Subcellular localization	Endogenous substrates	Xenobiotic substrate
CBR1	SDR	Cytosol	Prostaglandins, steroids, lipid aldehydes	Aromatic aldehydes and ketones, quinones, NNK

Lipid peroxidation

Reactive oxygen species
(ROS)

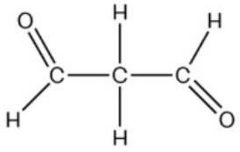
↓

Membrane lipids

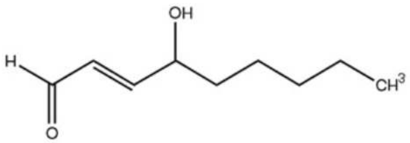
↓ Lipid peroxidation

Reactive carbonyl compounds
(aldehydes,ketones)

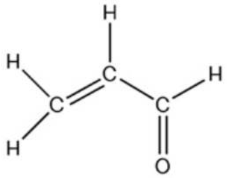
<u>Reactive aldehydes</u>



Malondialdehyde(MDA)

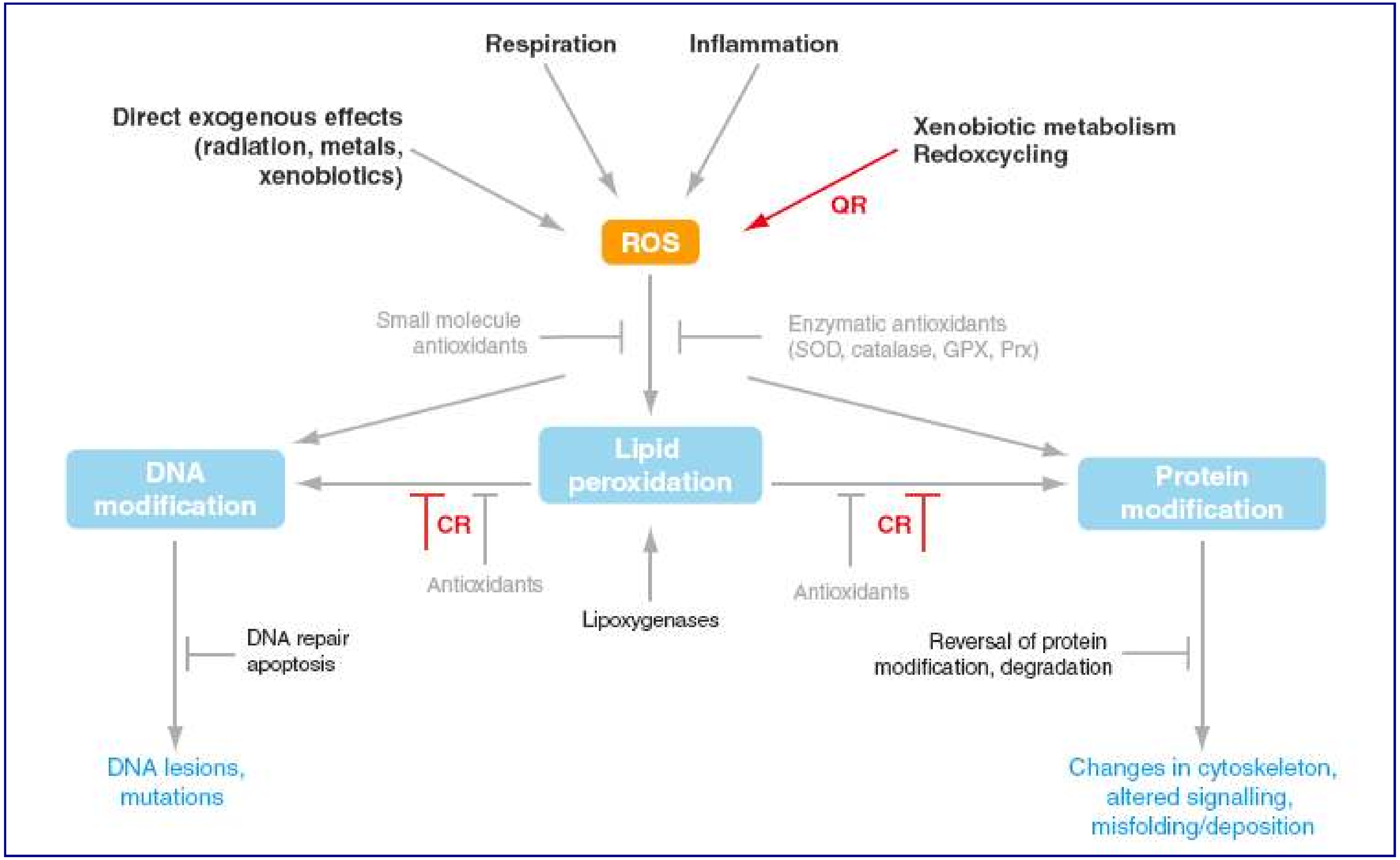


4-hydroxynonenal(HNE)

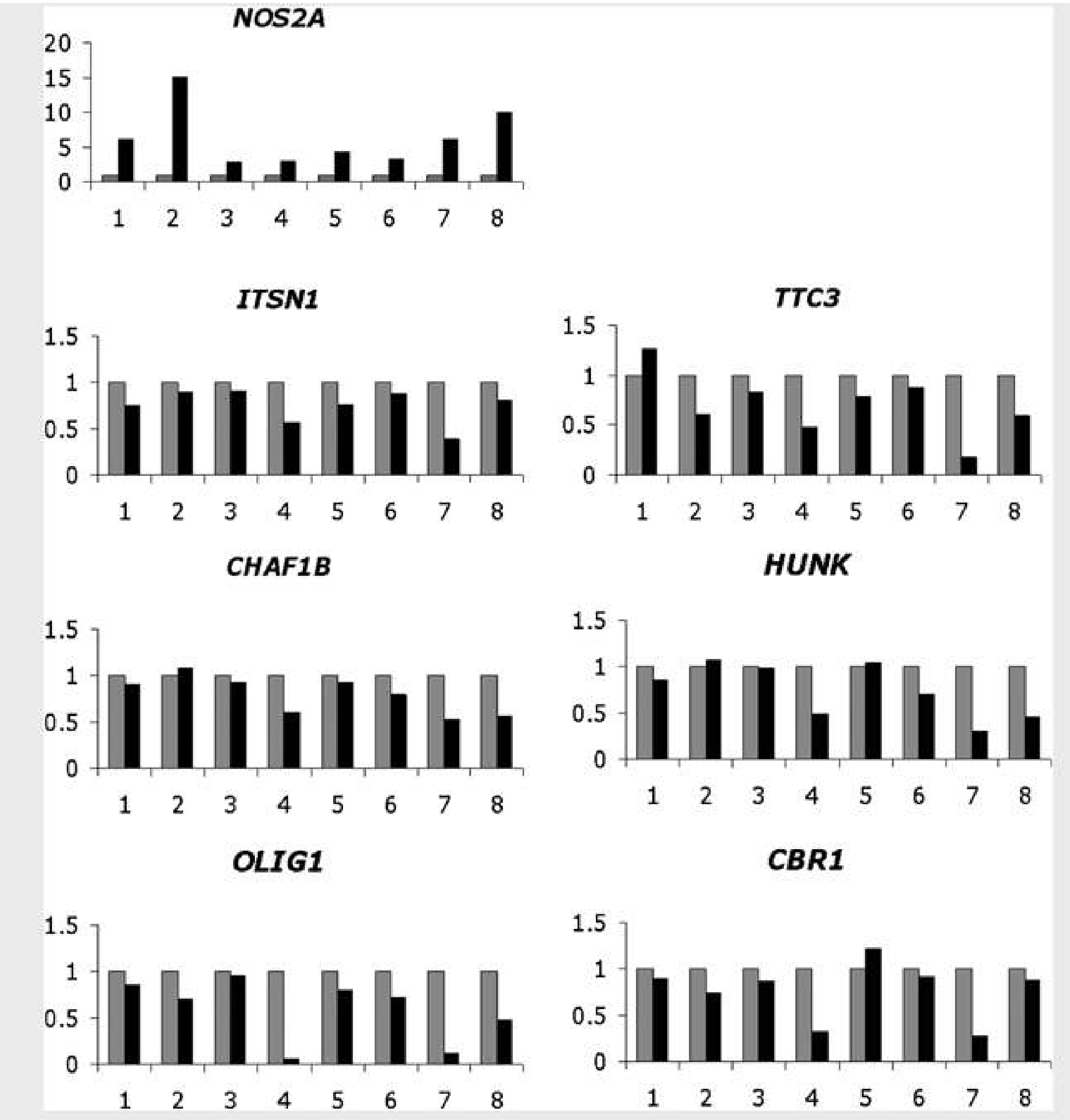


Acrolein

Schematic overview of carbonyl reductases in oxidative stress



Expression levels of differentially expressed genes in human pancreatic islets stimulated by a mixture of cytokines, consisting of TNF(5000 U/ml), IFN(750 U/ml) and IL-1 (75 U/ml)



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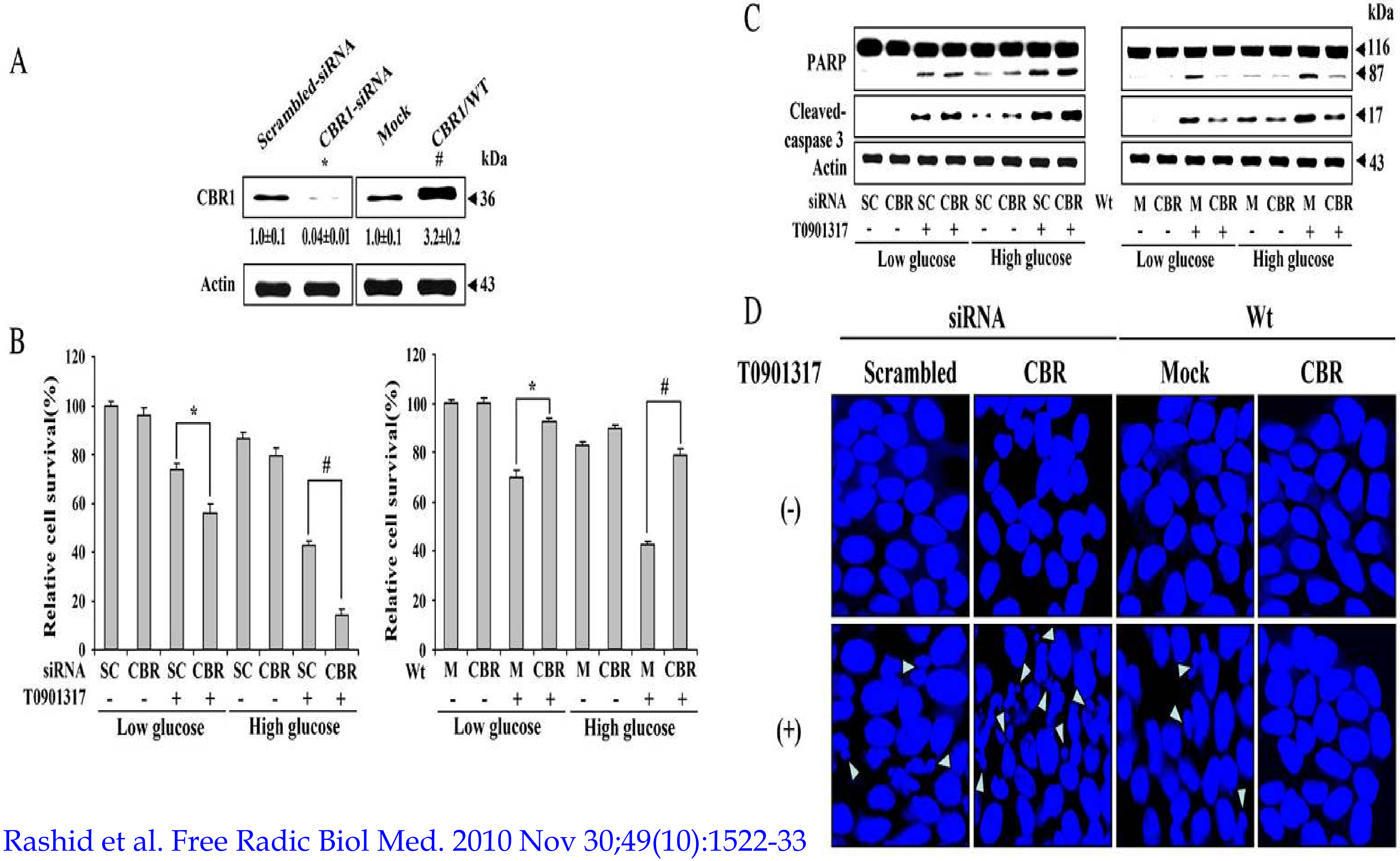
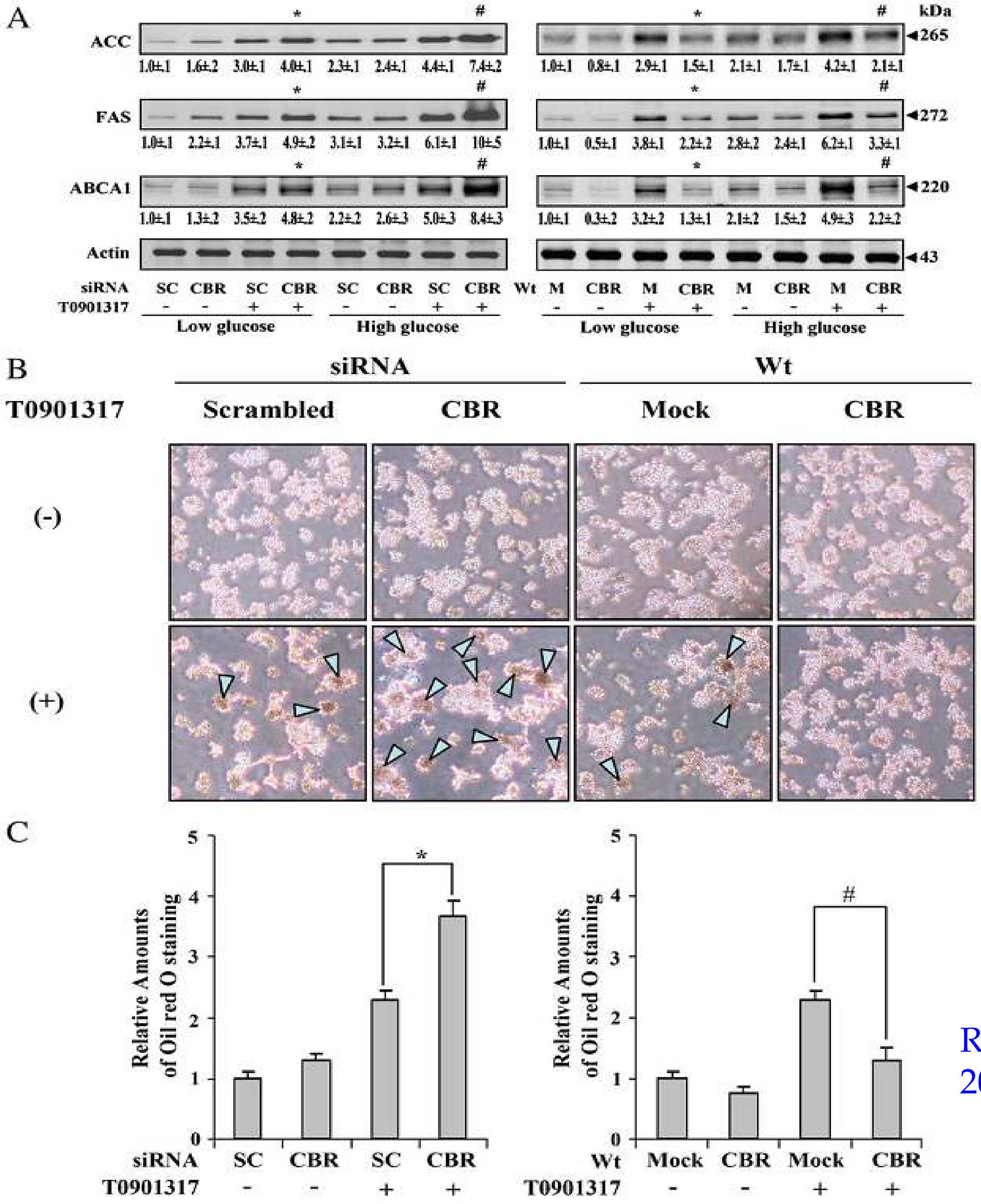
Regulation of pancreatic β-cell survival by CBR1



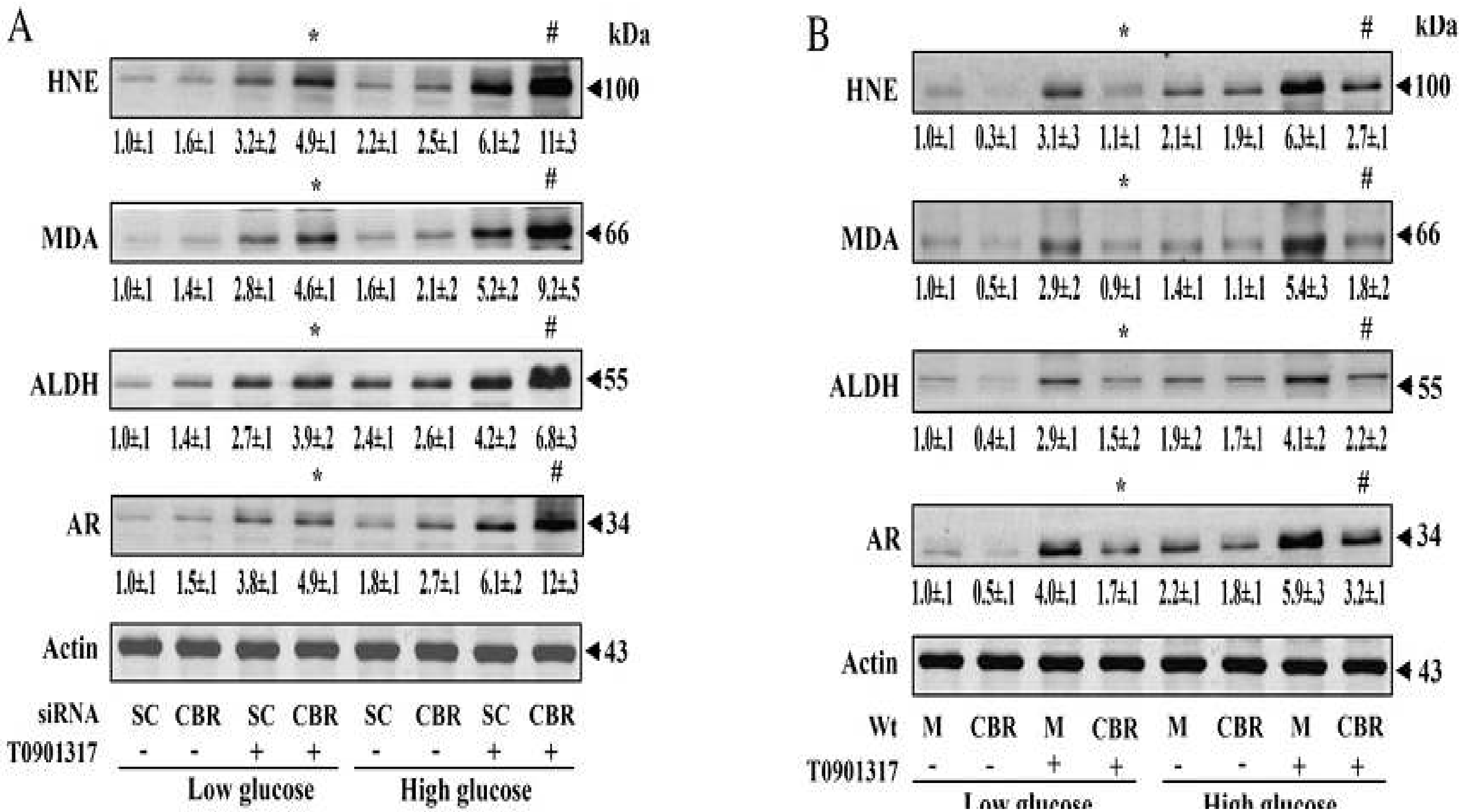
Rashid et al. Free Radic Biol Med. 2010 Nov 30;49(10):1522-33

Regulation of lipogenesis by CBR1 in pancreatic β-cells



Rashid et al. Free Radic Biol Med.
2010 Nov 30;49(10):1522-33

CBR1 attenuates lipid peroxidation in pancreatic β-cells



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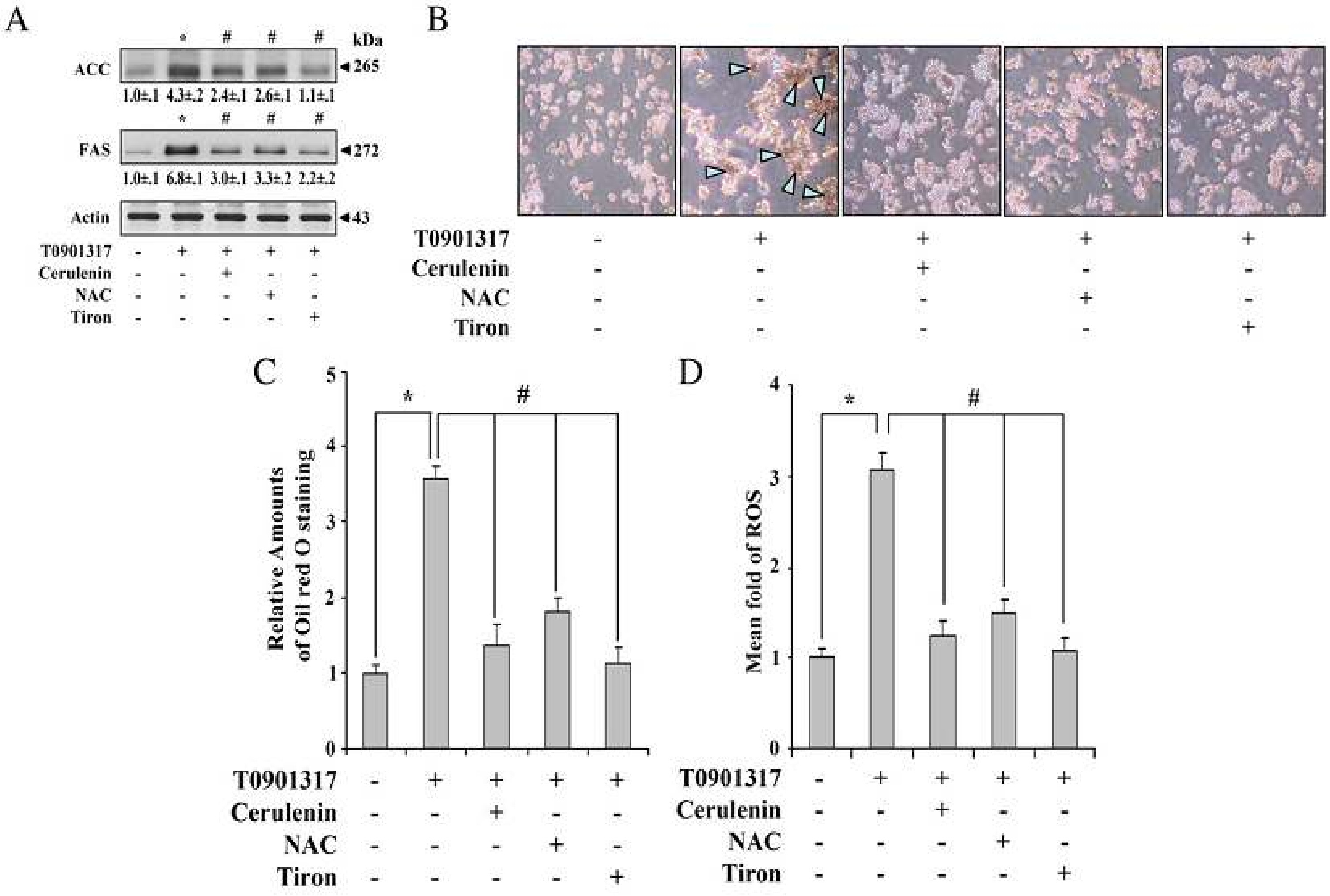
Attenuation of lipogenesis and ER stress by antioxidants in CBR1-knockdown cells



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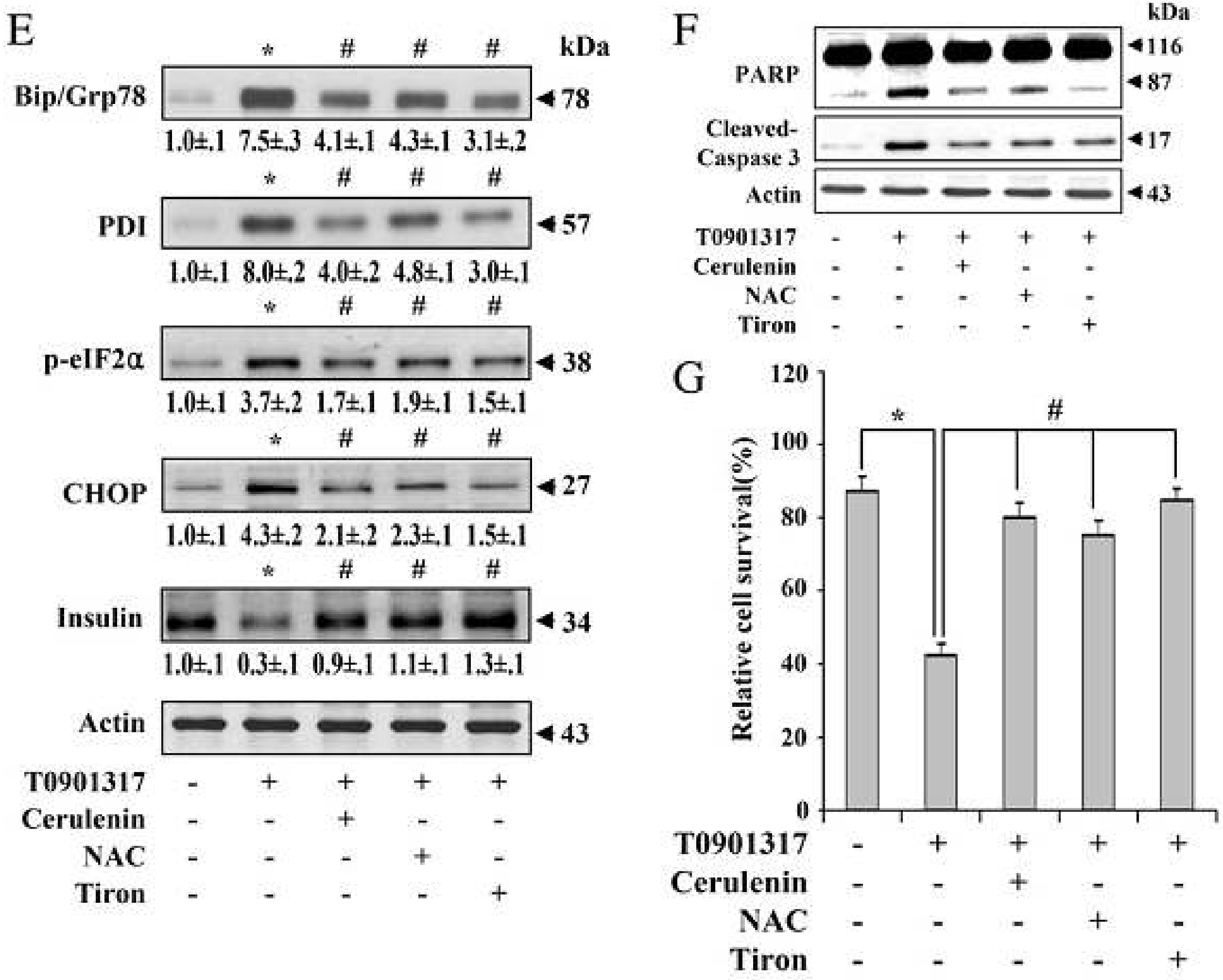
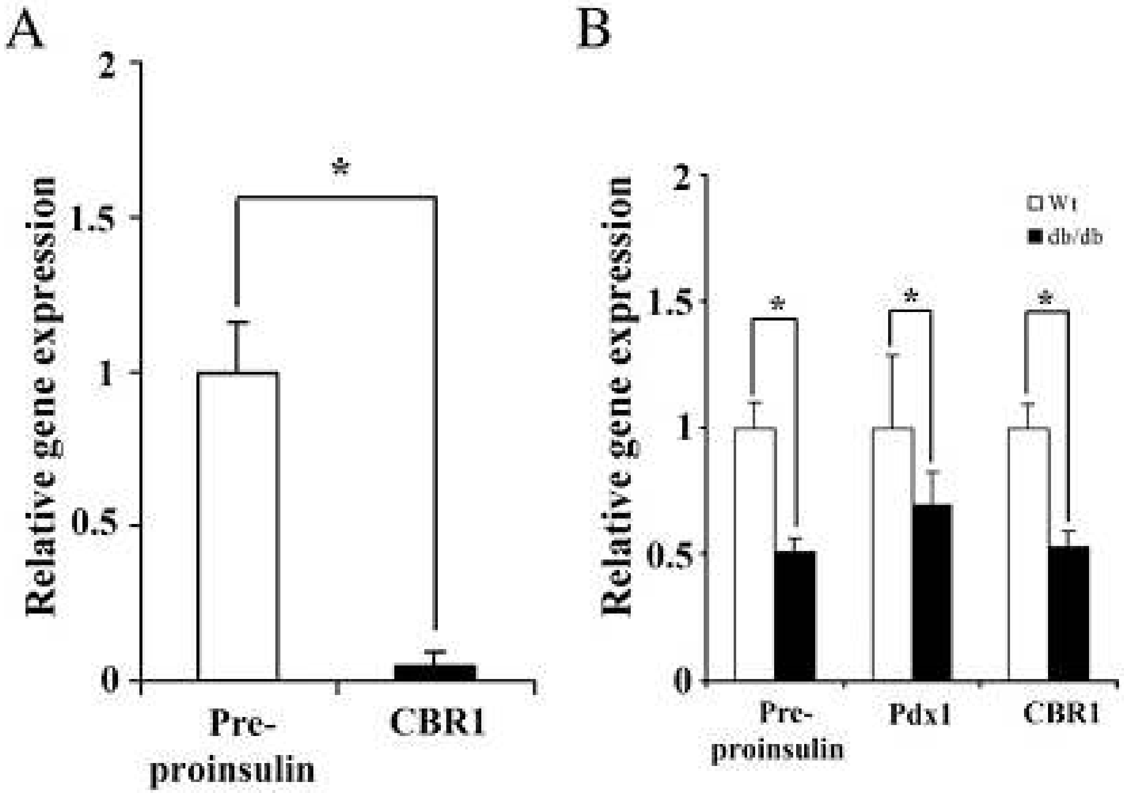
Attenuation of lipogenesis and ER stress by antioxidants in CBR1-knockdown cells



Rashid et al. Free Radic Biol Med. 2010 Nov 30;49(10):1522-33

Decreased CBR1 expression in pancreatic islets of *db/db* mice



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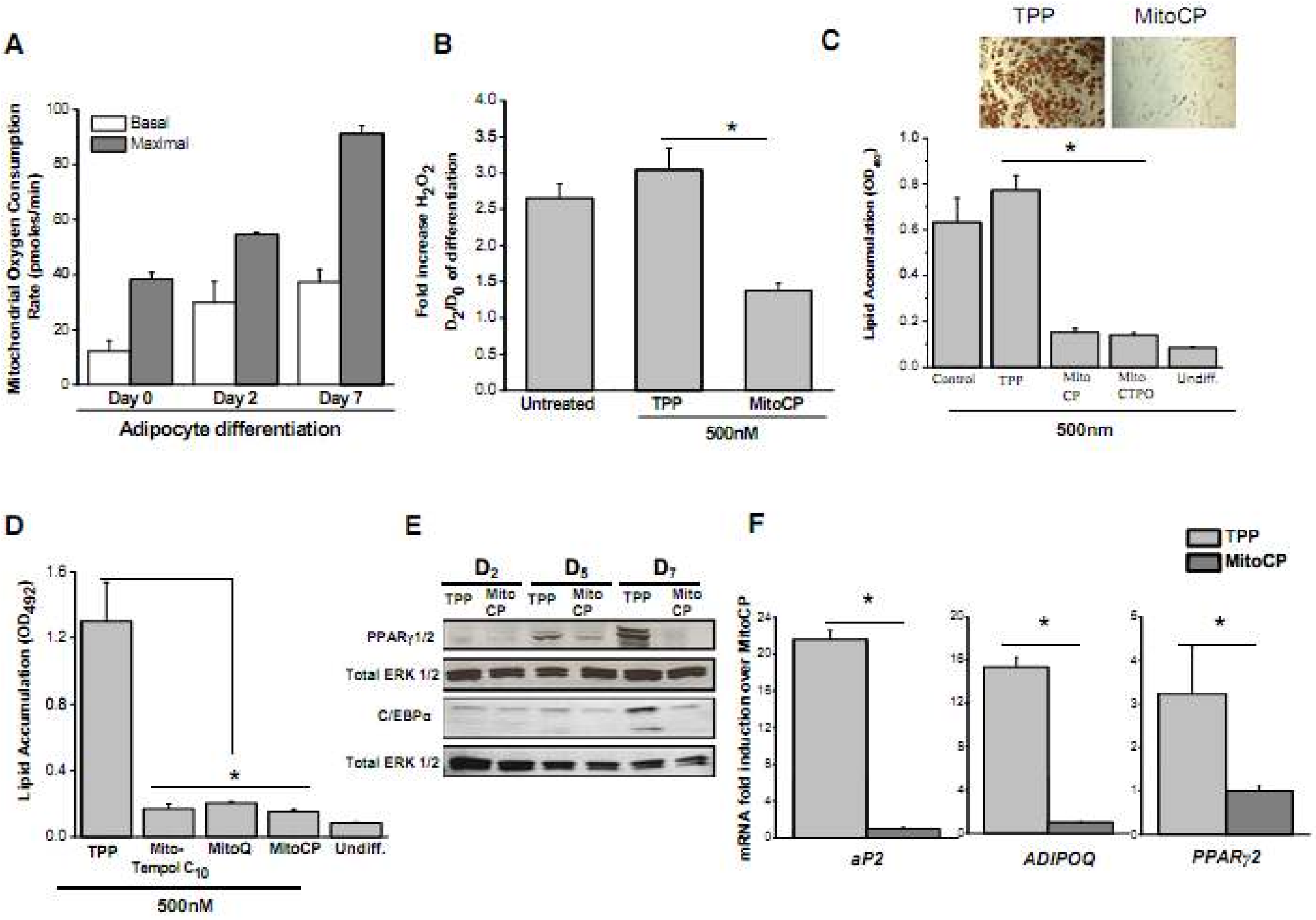
Mitochondrial complex III ROS regulate adipocyte differentiation. Tormos KV, Anso E, Hamanaka RB, Eisenbart J, Joseph J, Kalyanaraman B, **Chandel NS**. Cell Metab. 2011 Oct 5;14(4):537-44.



CONCLUSION

1. HFHC diet induces insulin resistance in a very short period of time.

2. Mitochondrial targeted antioxidants may be good candidate drugs for type 2 DM.

3. Human carbonyl reductase 1 may play an imoprtant role in the development of type 2 DM.

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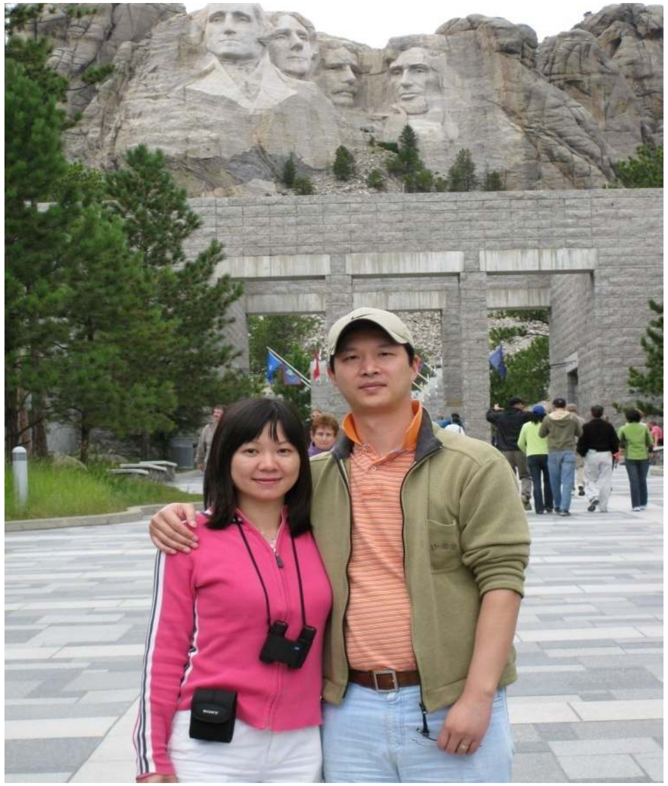

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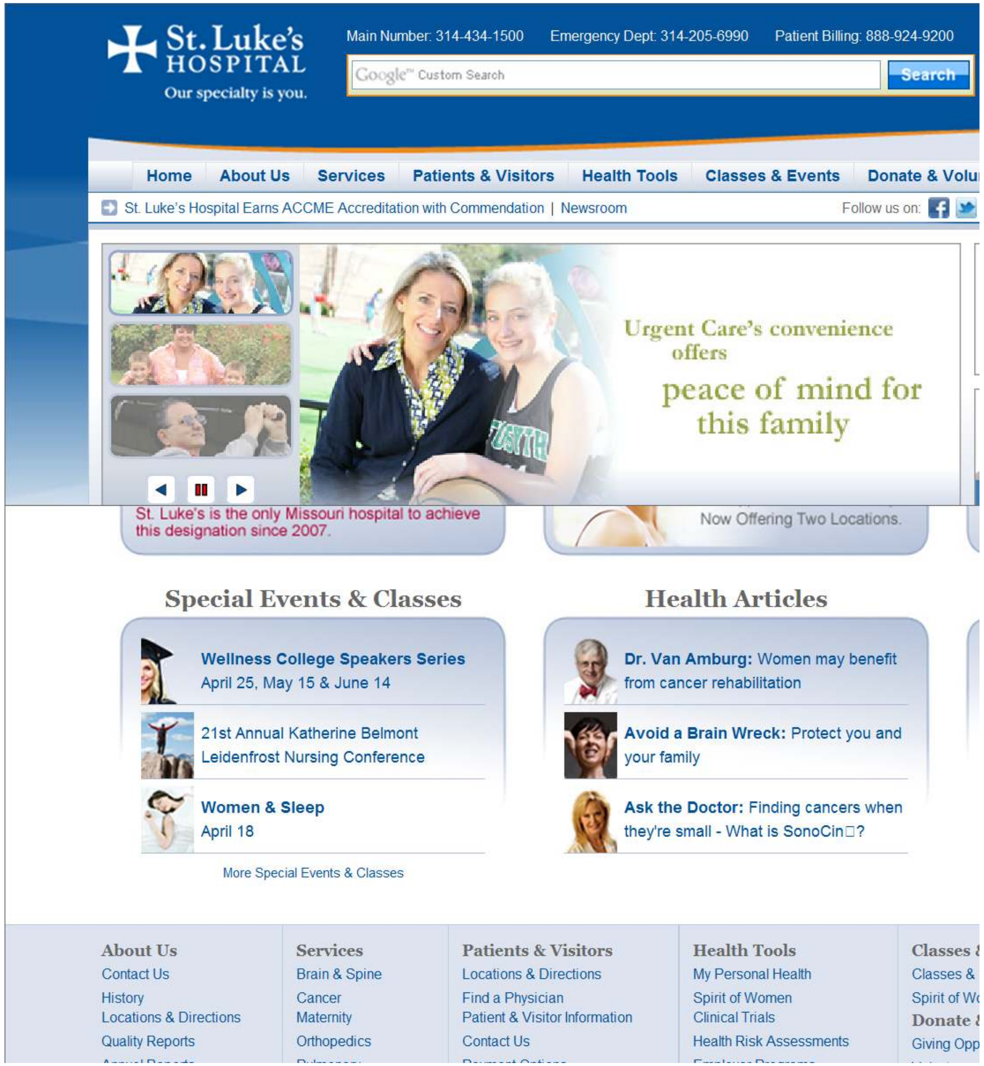

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