Novel Physiological Role of Caveolin-1 in Aging and Aging-related Diseases

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Lee Gil Ya Cancer and Diabetes Institute

Primarily I asked questions on biological issues on aging

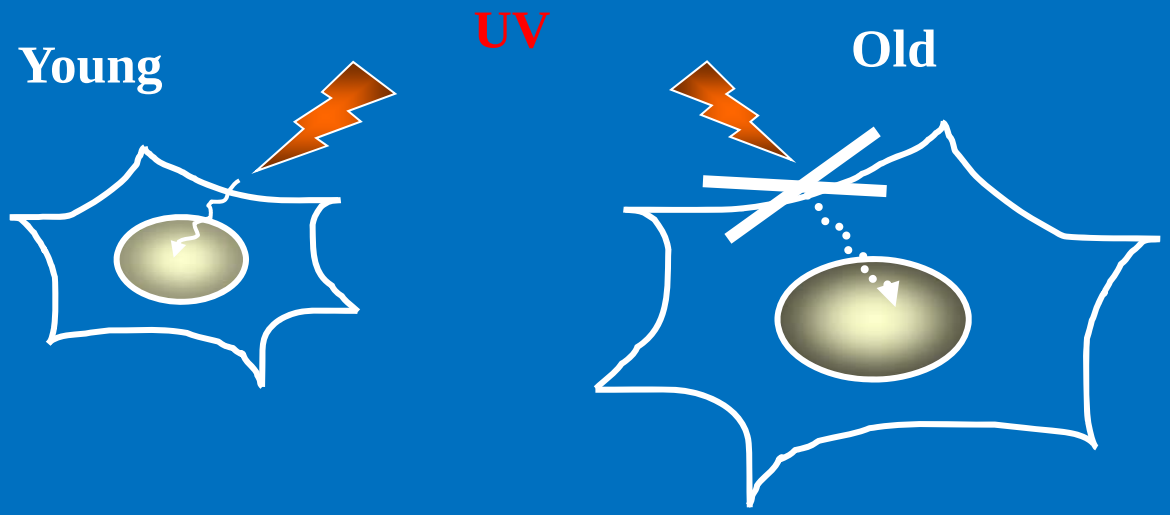
Parenchymal loss

Functional loss

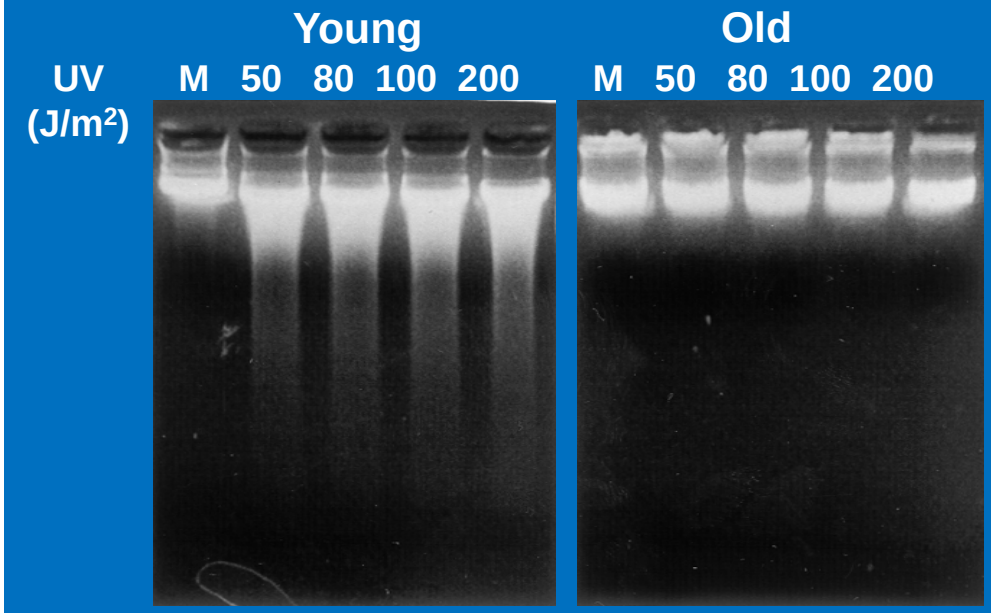
Morphological alteration

Question 1

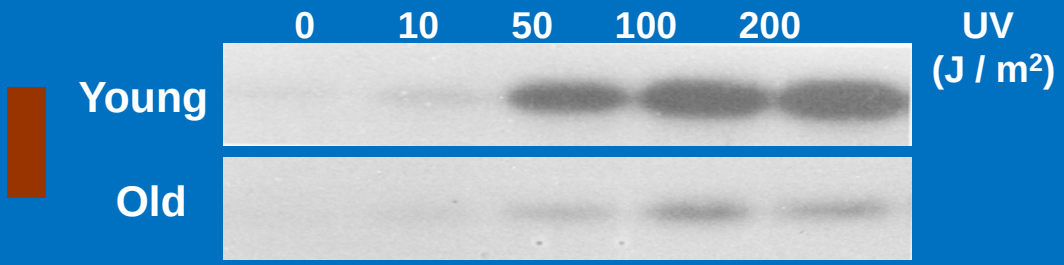
Apoptosis for parenchymal loss



• DNA Fragmentation by UV-irradiation

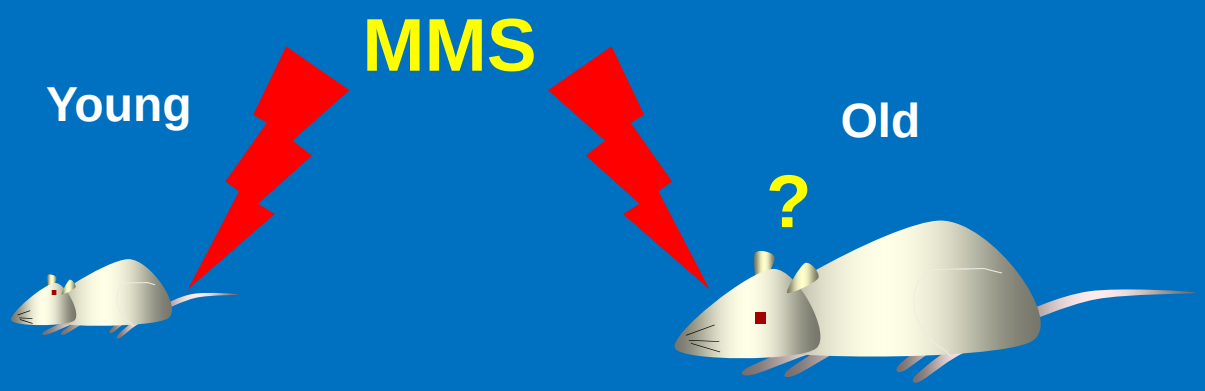


• UV-Induced Activation of SAPK/JNK

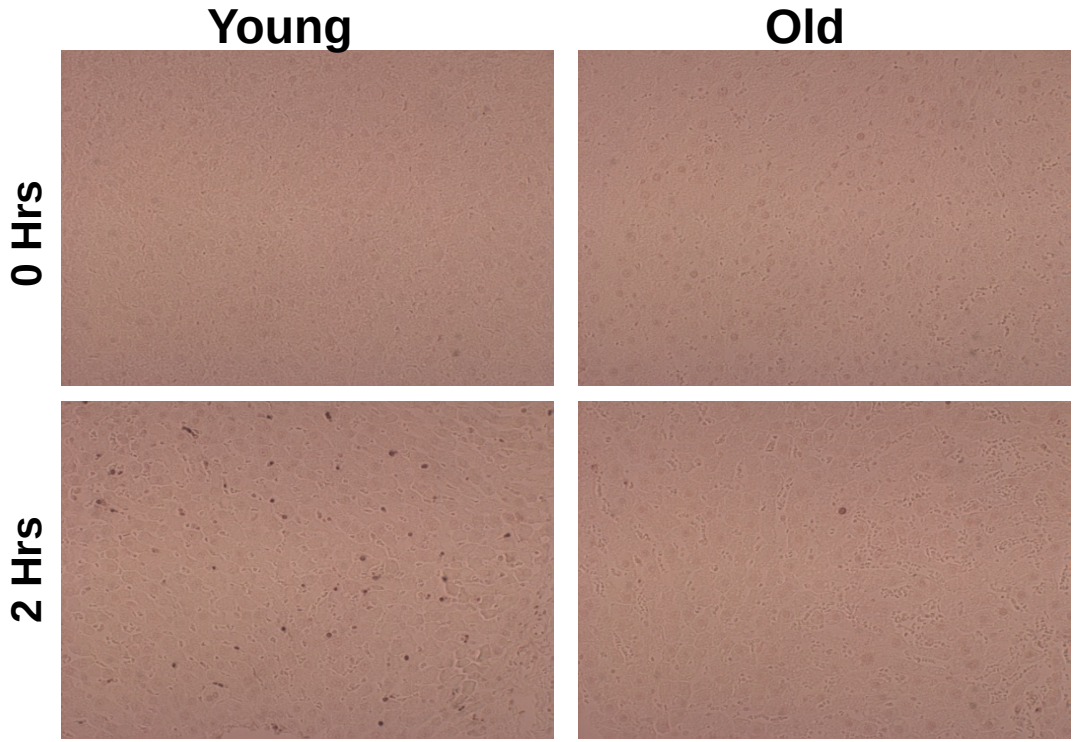


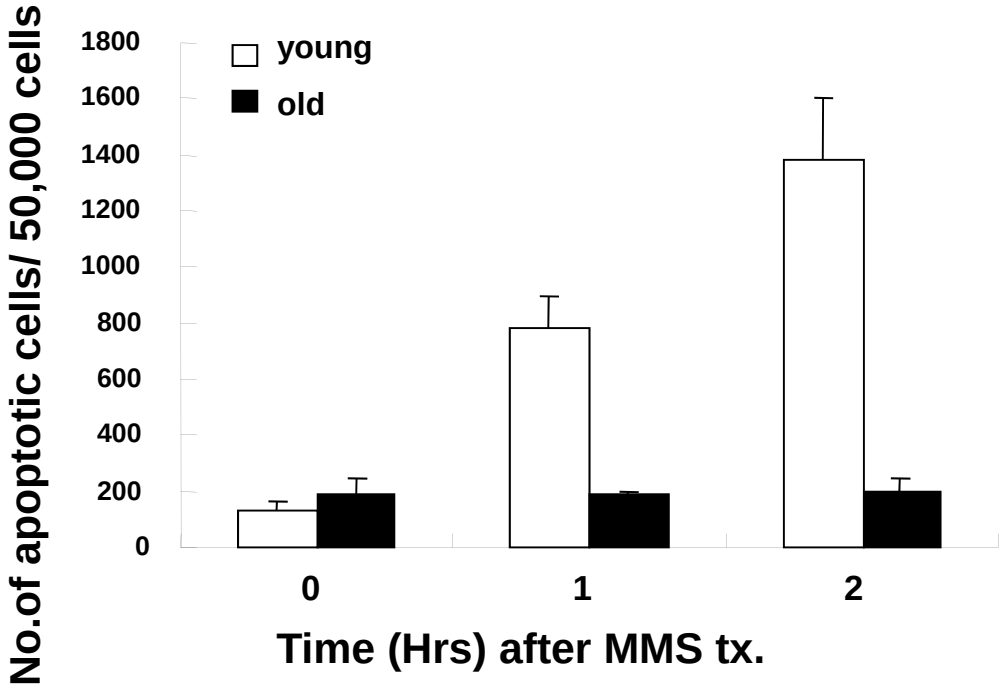
Yeo et al, Mol. Cell 10. 415. 2000

Suh et al.NatureMedicine,2002,8,3

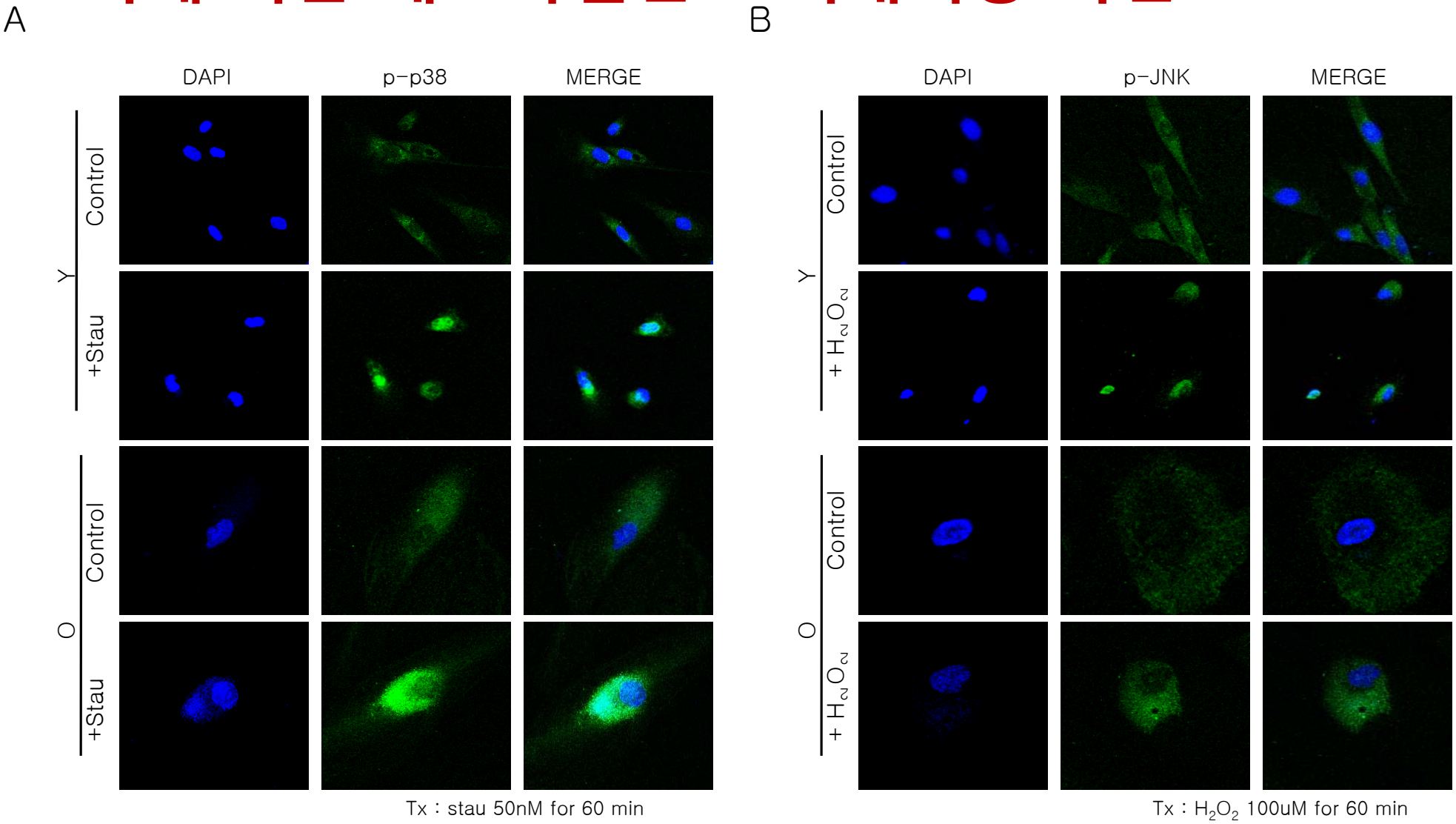


• Absence of Apoptotic Response to MMS in vivo

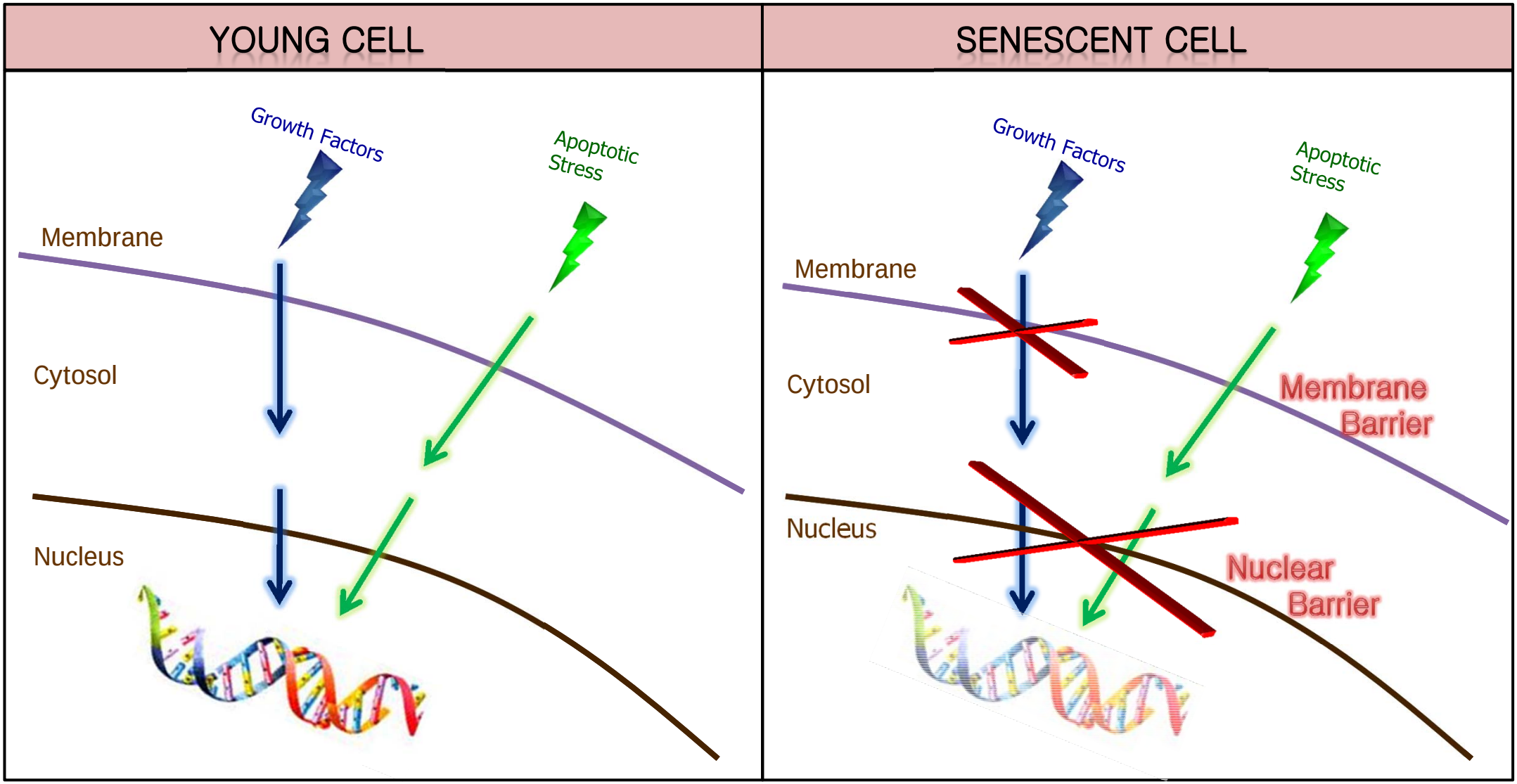




노화에 따른 세포사멸신호 핵내이동 차단



Nuclear Barrier Hypothesis of Aging

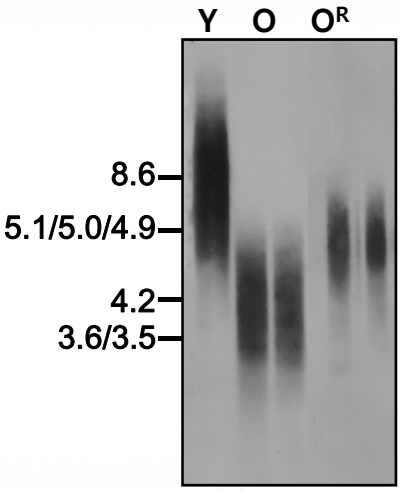


노화현상의
비가역성과 불가피성의
생물학적 근거

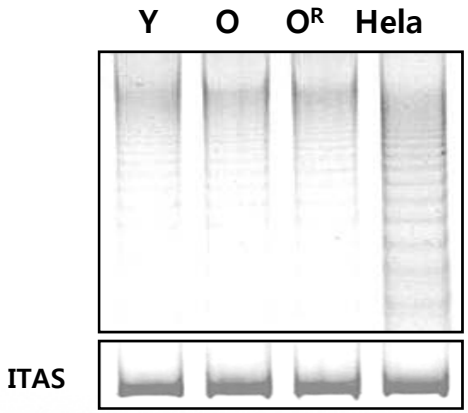
텔로미어 단축
노화색소 축적
생체분자의 손상

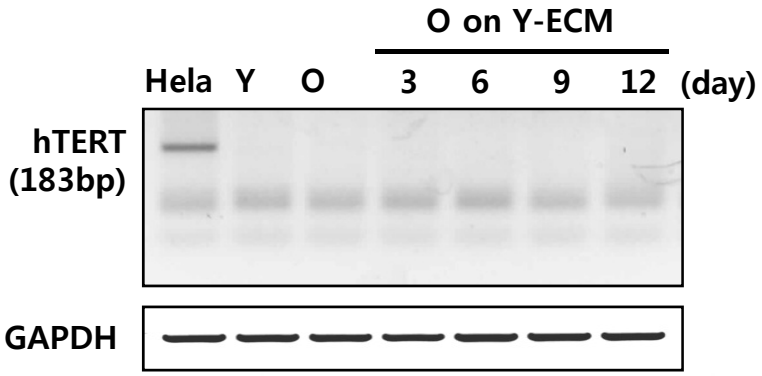
Telomere length recovery

C

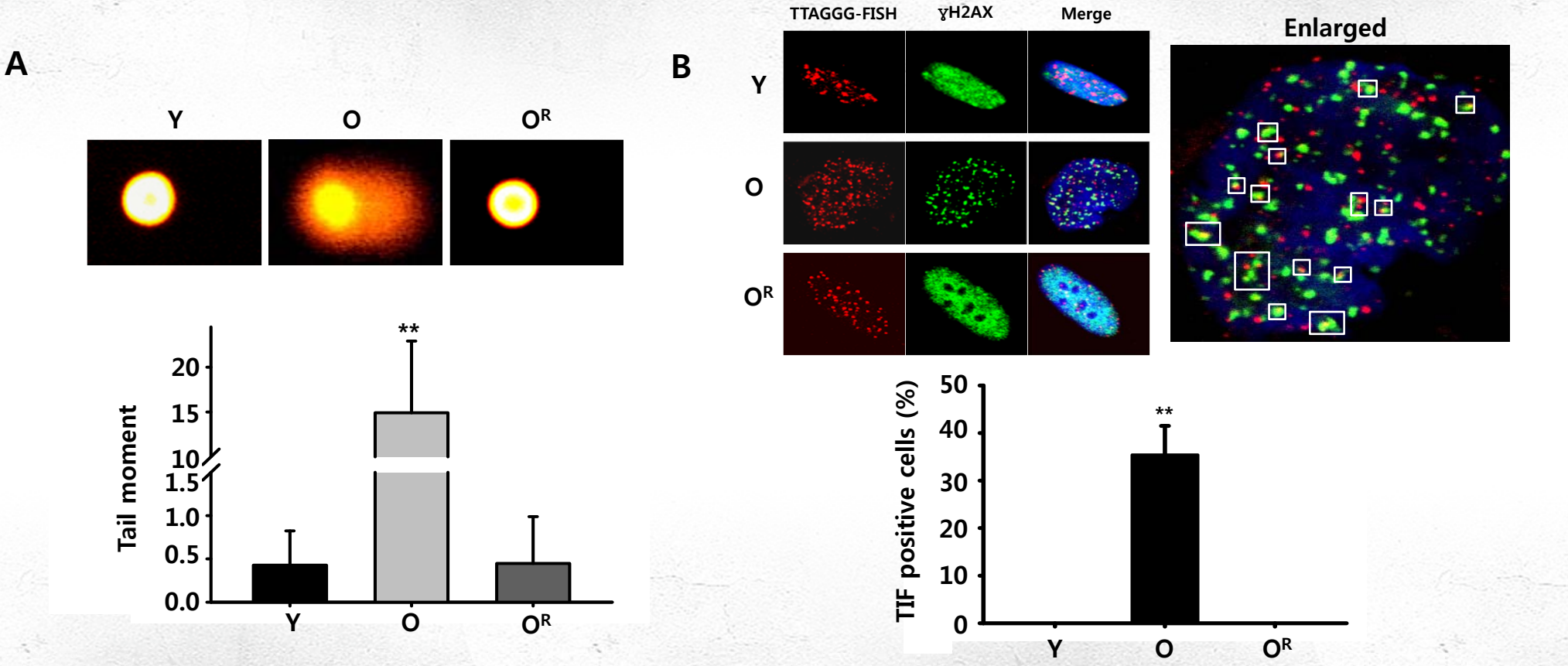


D





DNA damage repair in restoration



노화현상의
비가역성과 불가피성의
생물학적 근거 : 부정되고 있음

텔로미어 단축 : 제어가능

노화색소 축적 : 제어가능

생체분자의 손상 : 제어가능

Aging phenotype is
an adaptive response
for Survival
toward environmental stress through
resistance to apoptotic stress

Possibility of Restore Principle
Instead of Replace Principle

Question 2

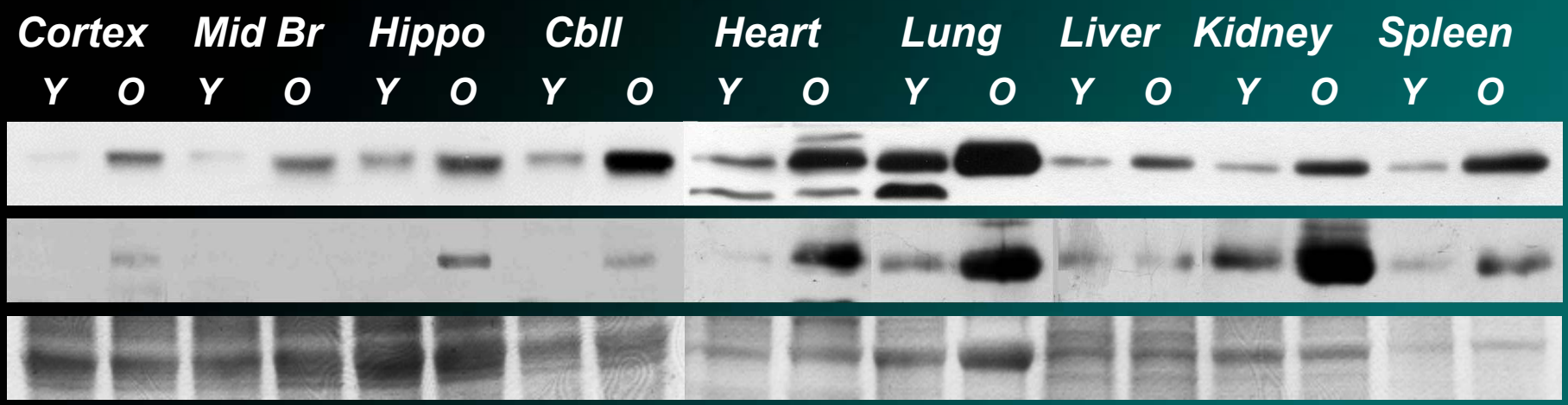
Loss of Functional Efficiency

Senescence-associated cellular responses

1. Metabolic response
   stability essential
2. Stress response
   unstable response
3. Mitogenic response
   No response or low response

Major source of irreversibility nature of aging

Aging effect on Caveolin expression



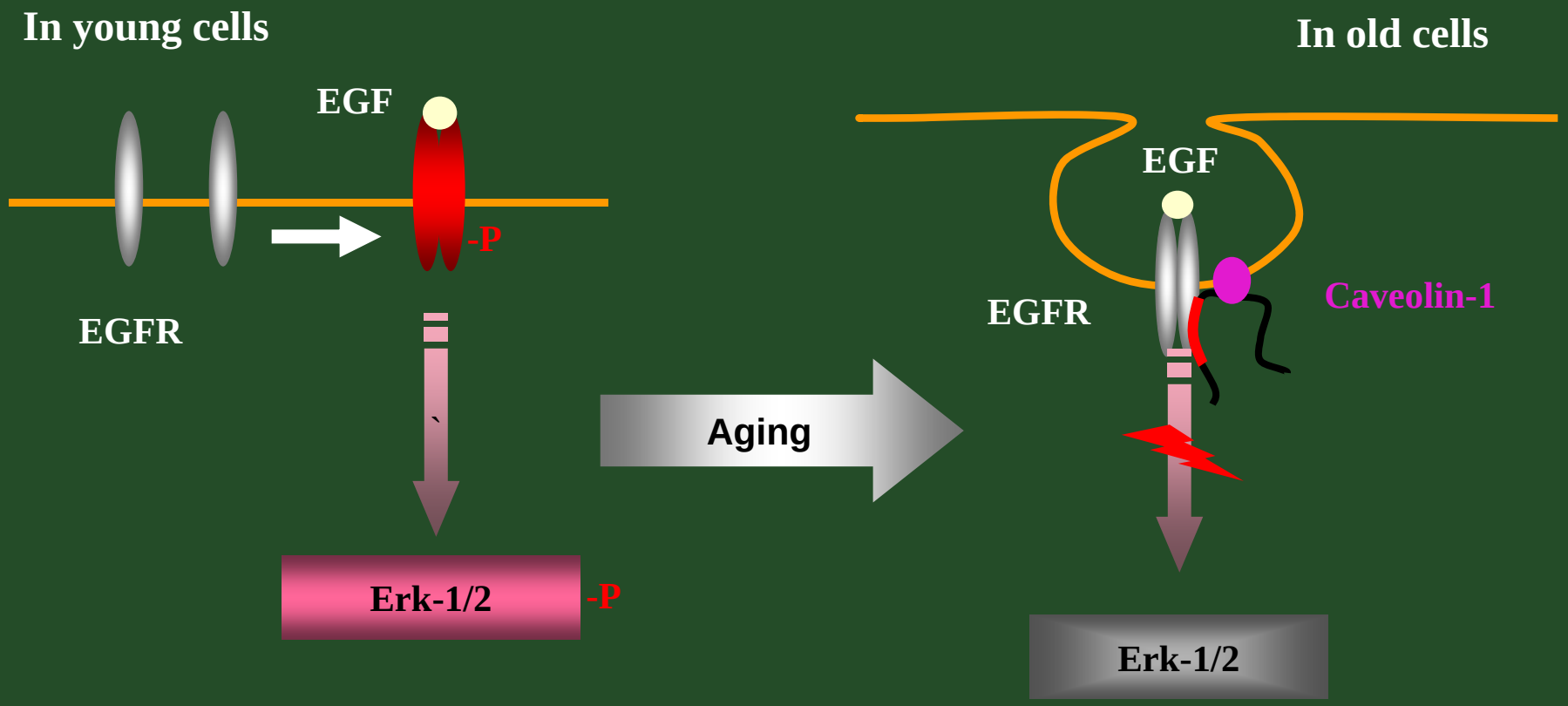
Park et al JBC 2000

Up-regulation of caveolin attenuates epidermal growth factor signaling in senescent cells.

Park, et al. (2000) J Biol Chem. 275, 20847

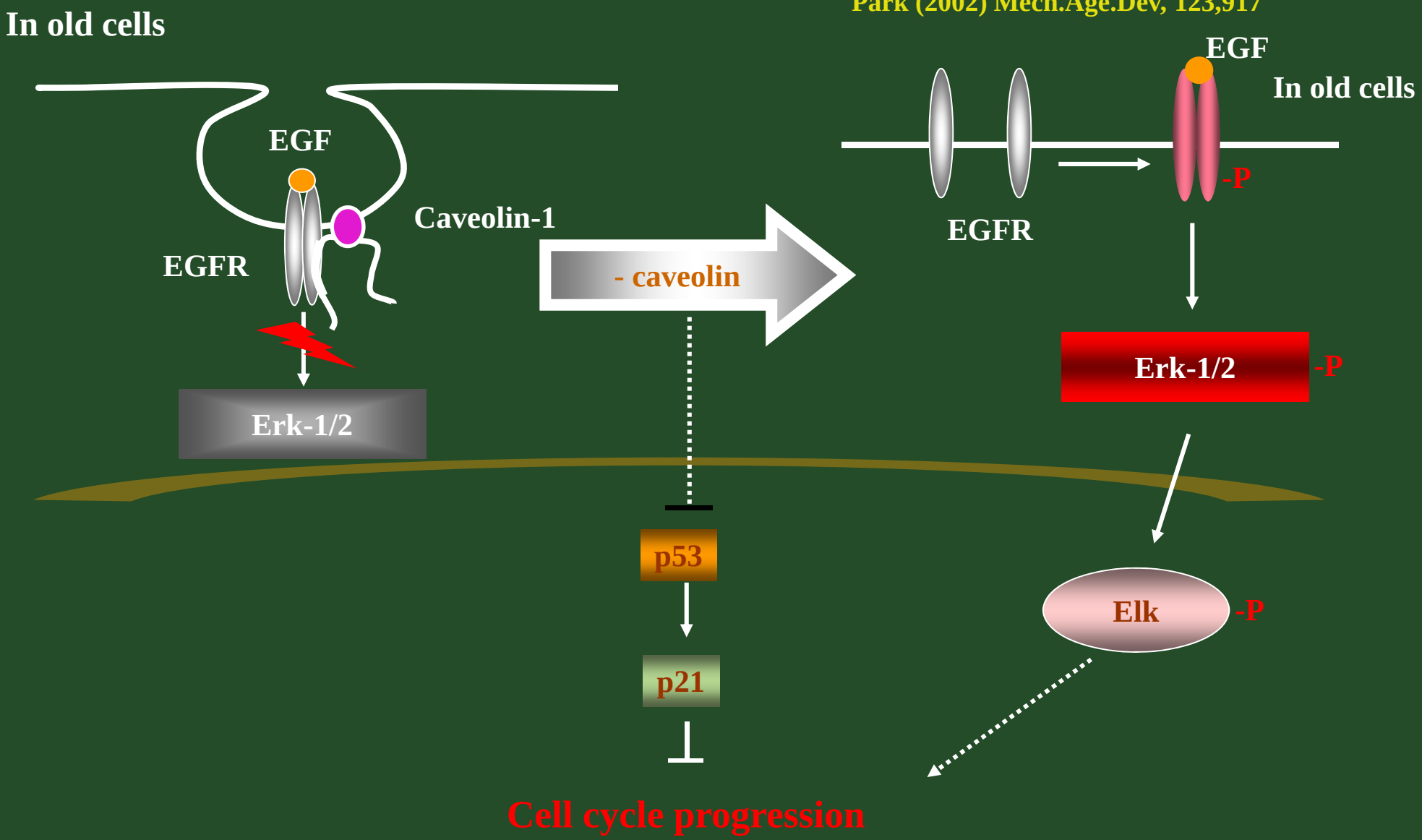
Park et al(2001) Ann NYAcad Sc, 2001,928,79

Park et al(2002)Ann NYAcad Sc, 2002,959,45



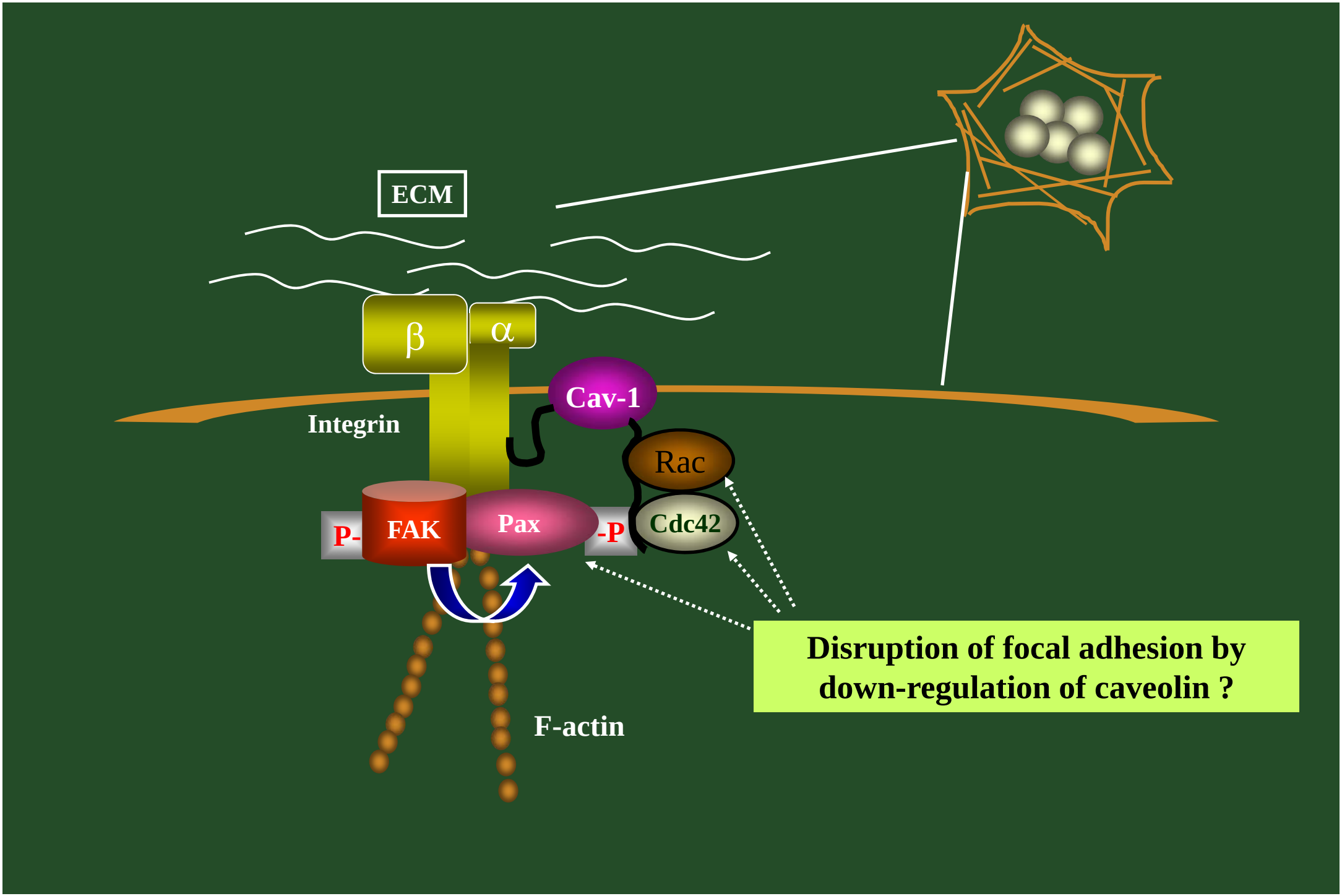
Senescent phenotype can be reversed by reduction of caveolin status

Cho et al. (2003) J Biol Chem. 278(30):27789
Park (2002) Mech.Age.Dev, 123,917

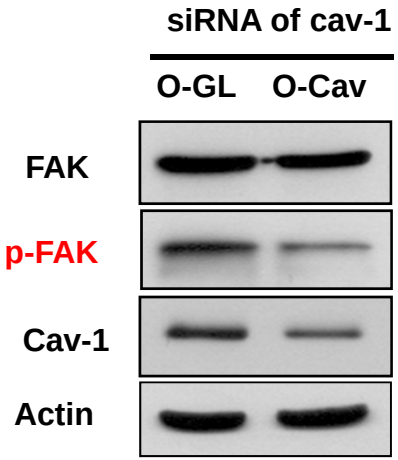


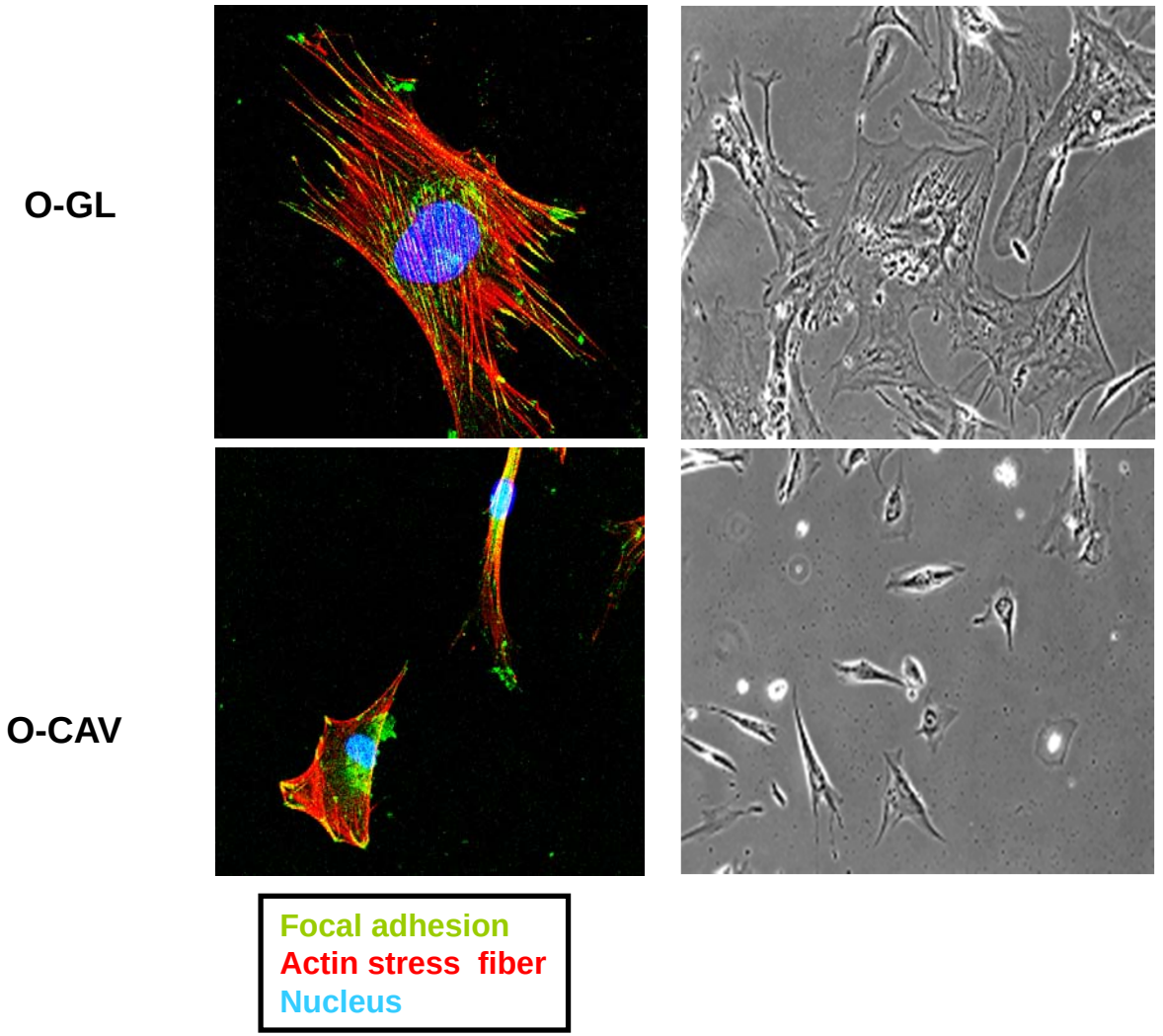
Question 3

Morphological alteration


ECM
β
α
Integrin
Cav-1
Rac
Cdc42
P-
FAK
Pax
-P
F-actin
Disruption of focal adhesion by down-regulation of caveolin ?

Morphological adjustment of senescent cells





Cho et al., J Biol Chem. 2004; 279(40):42270

Morphological adjustment of the senescent cells can be induced by simple modulation of the caveolin status

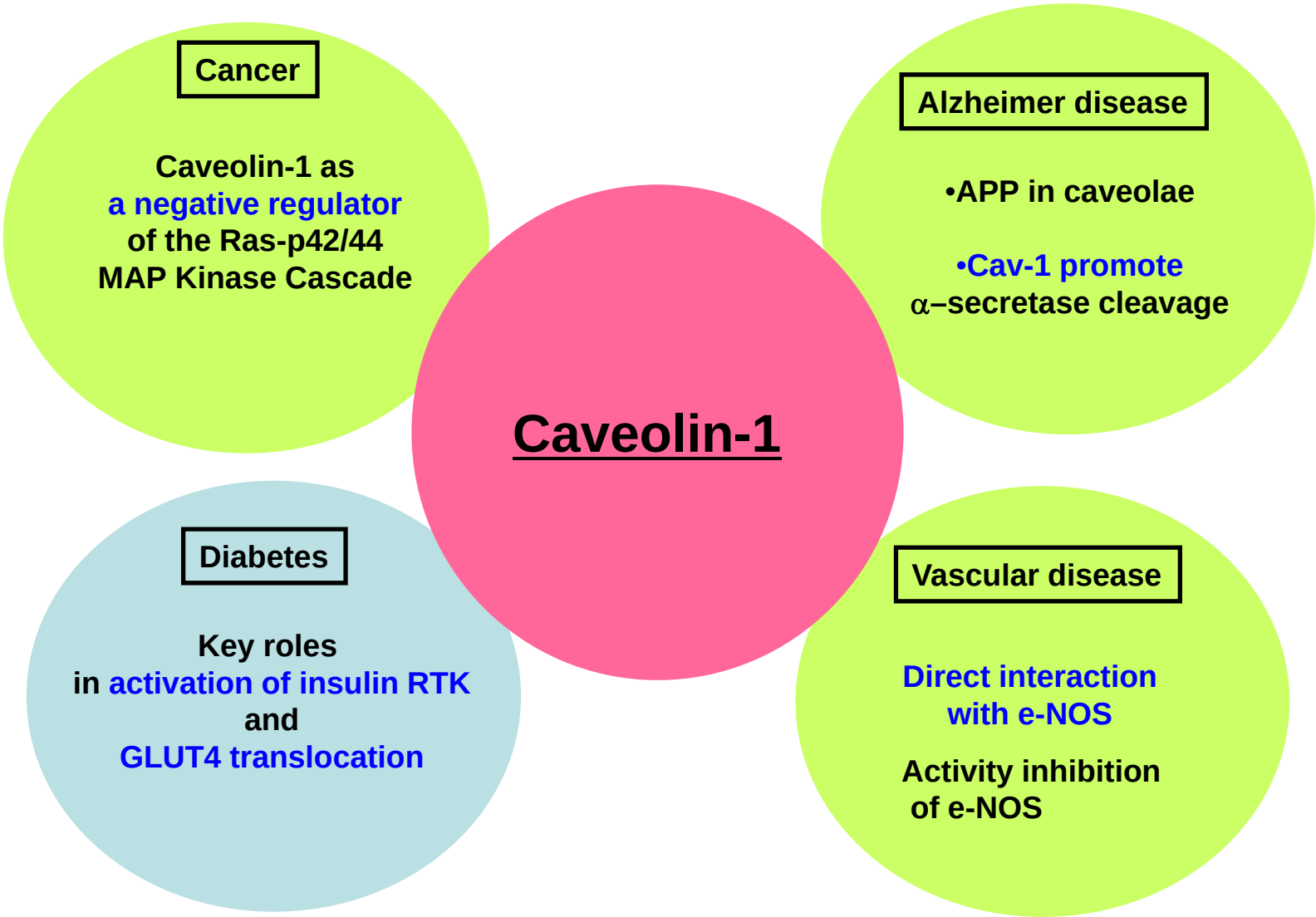
Structural restoration of the senescent cells by crosstalk between determinants of function and morphology

***Caveolin* in signal regulation, intracellular trafficking, polarity, migration, endocytosis and *More* !!**

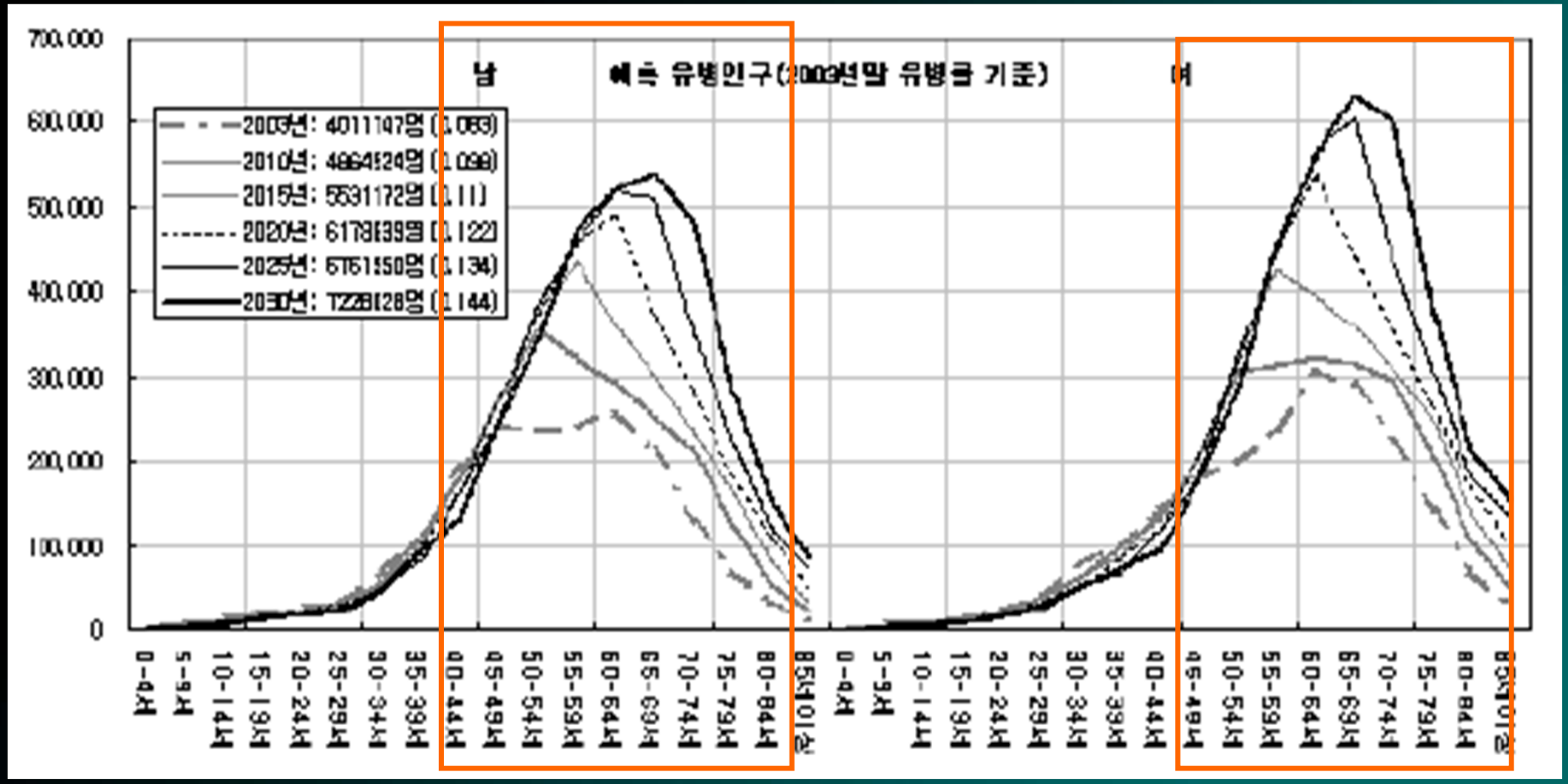
Question 4

Organ pathology level
Diabetes
Stem cell differentiation
Cancer cell differentiation,
Wound healing
Exercise

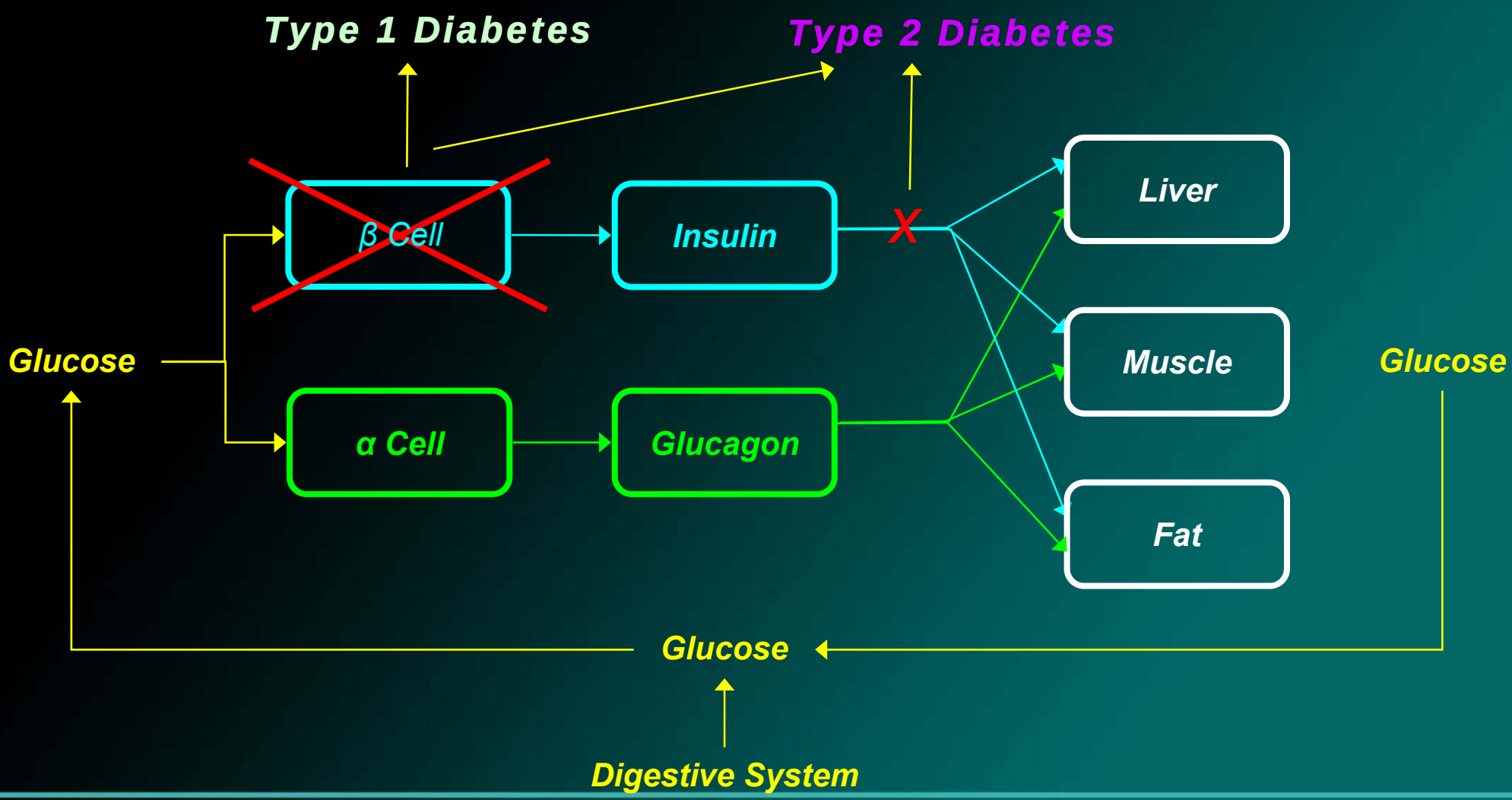
Caveolin-1 and Aging-related Diseases



Prevalence of Diabetes



Control of blood glucose levels



Type II Diabetes

- *NIDDM (non-insulin dependent)*
  90-95% of DM
  Obese type and Lean type (65 %)

- *Insulin resistance*

- *Mainly occurs in adults*

Is Ageing itself related with Type II DM ?

Why no adequate
Age dependent lean type DM model ?

Type II D.M Animal models

GK

OLETF

Ageing independent

ob/ob

ZDF

obese

Few studies on obesity independent or age dependent lean type D.M

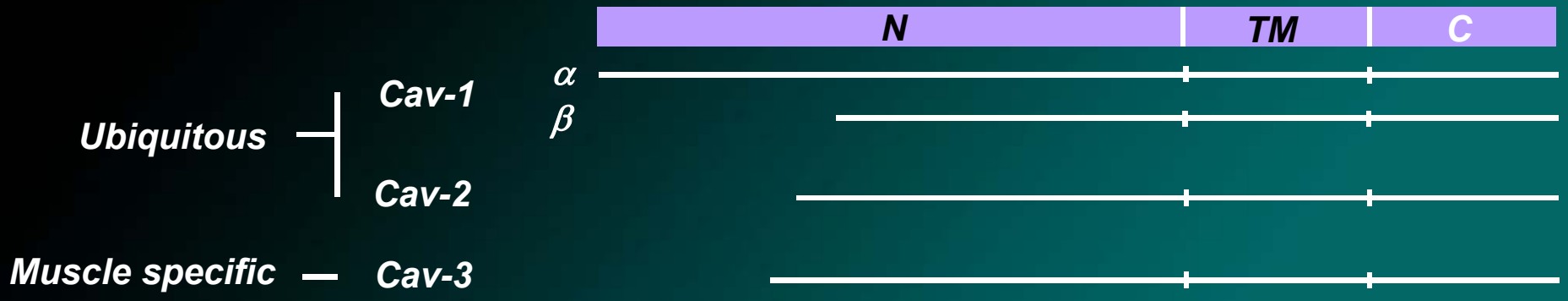
Roles of Caveolin-1

in Muscle Tissues ?

Caveolae

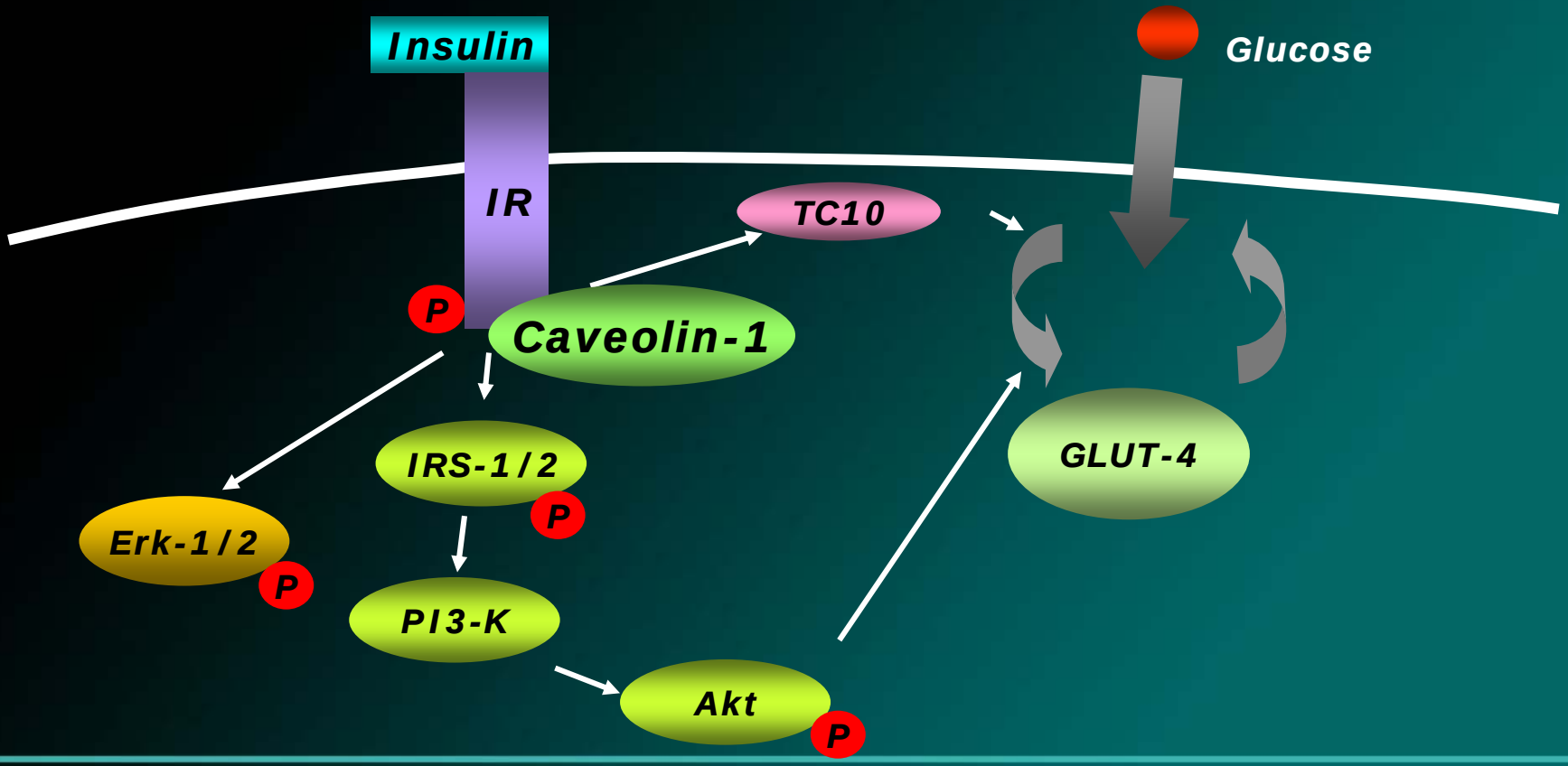
- ***Small vesicular organelles of cell membrane***
- ***Signaling molecules enriched in caveolae;***

  G-protein subunits, EGFR and related receptor tyrosine kinases
- ***Caveolin, marker protein of caveolae***



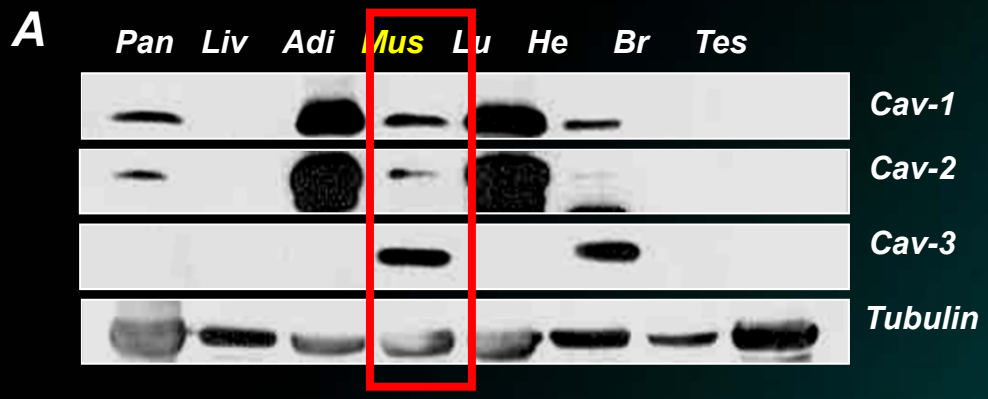
Caveolin & insulin sensitivity in adipocytes

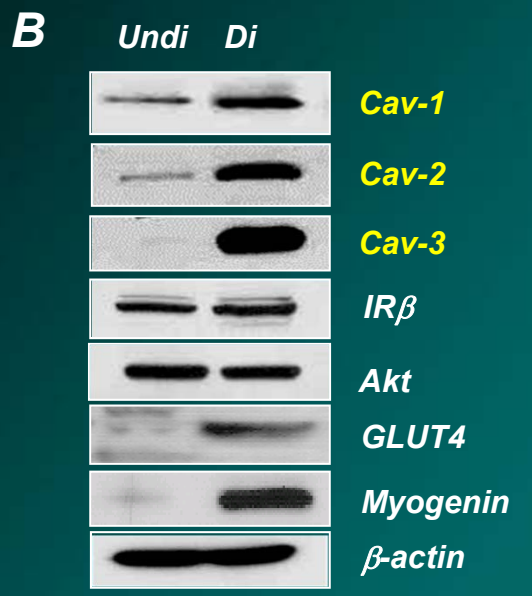
Relationship of caveolin with insulin signaling

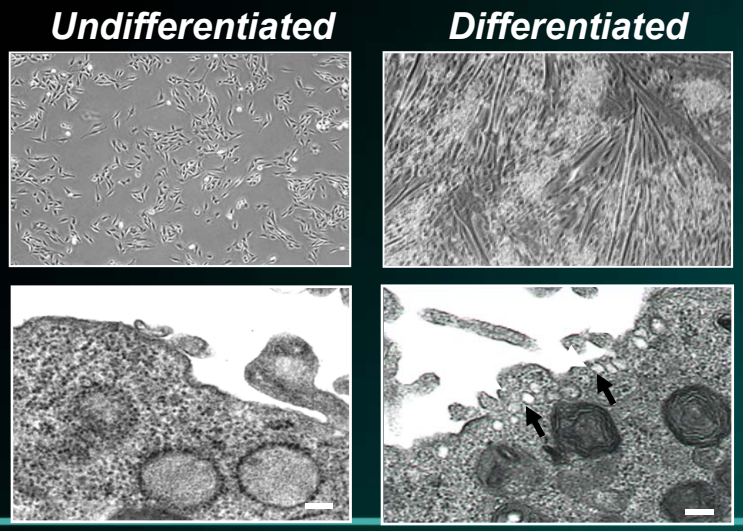


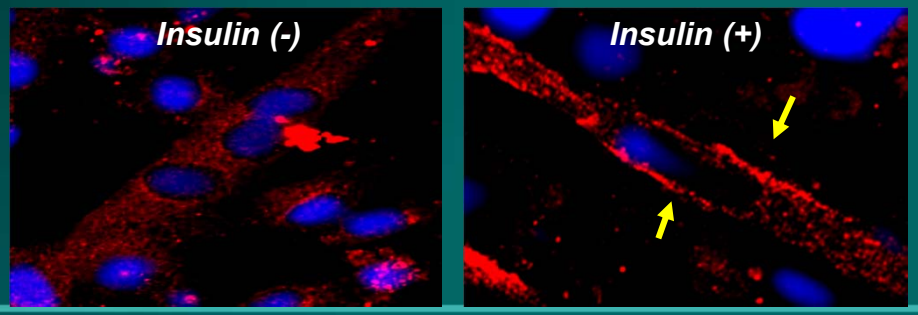
Can caveolins regulate the insulin signaling in skeletal muscle cells as in adipocytes?

Expression of caveolins during differentiation

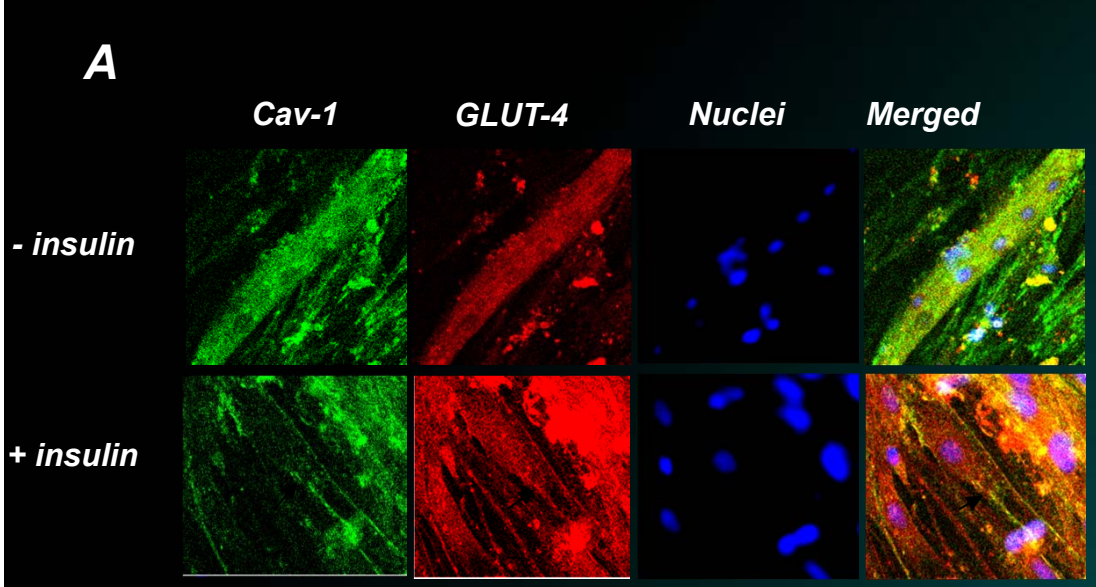






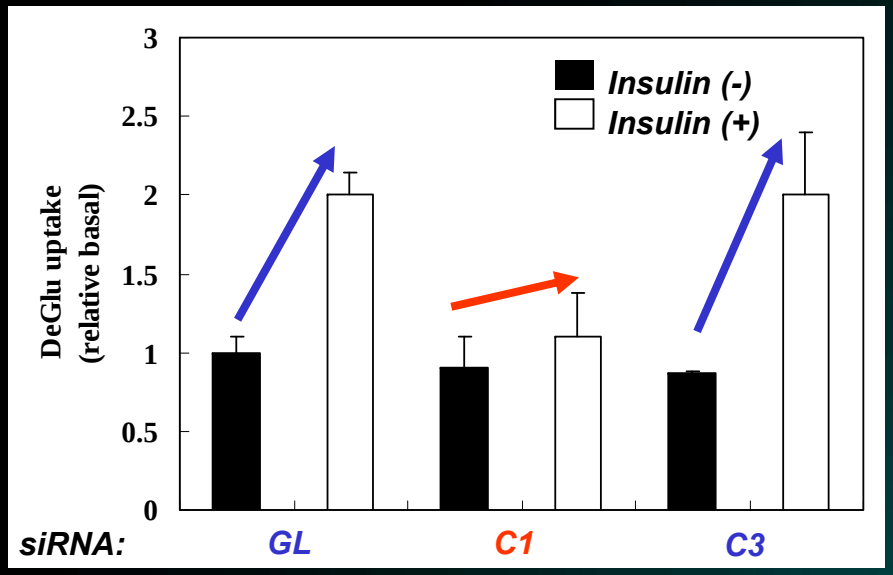


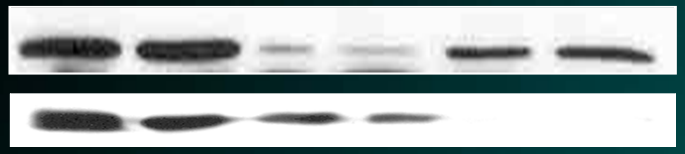
Caveolins and GLUT-4



Role of caveolins in glucose uptake

A





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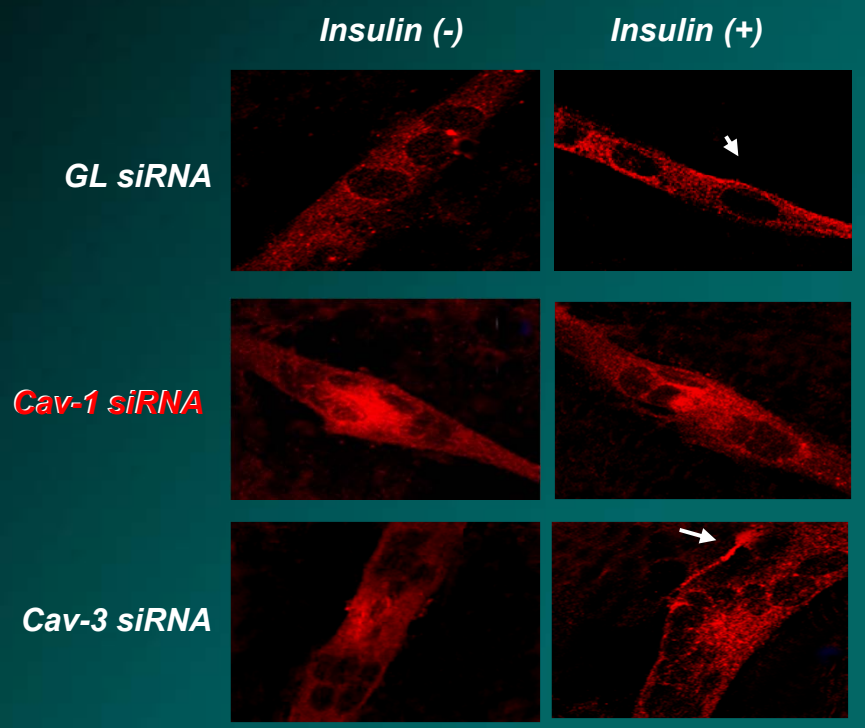
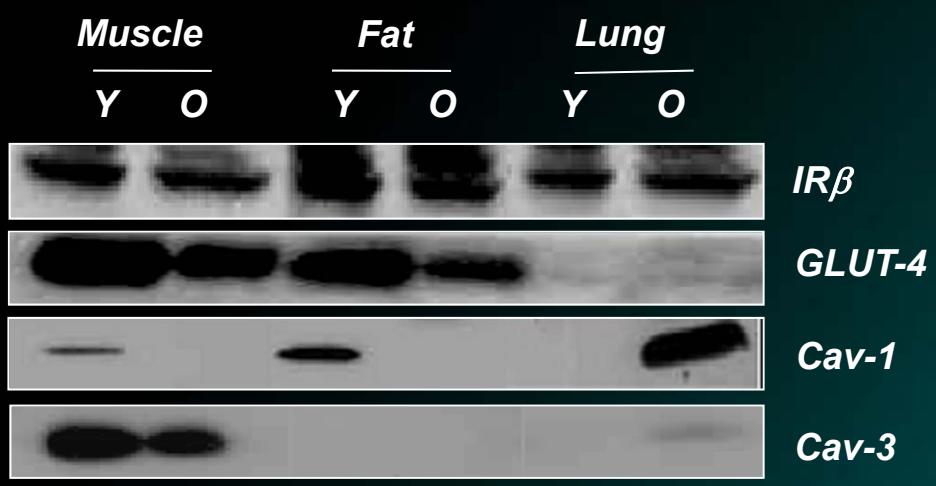
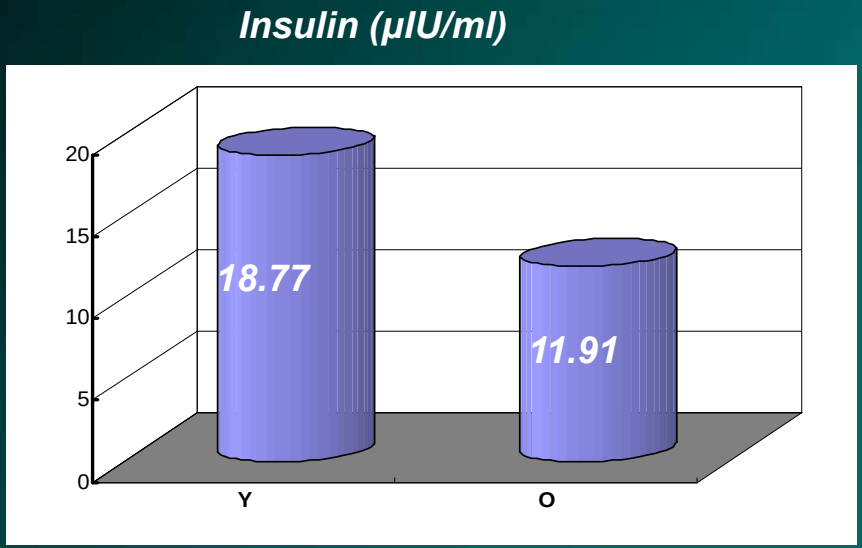


Caveolin-1

in Muscle Aging ?

Aging Effect on Caveolin-1 Status in Muscle and Fat Tissues





Common nature of muscle and fat tissue would be the insulin-sensitivity

NEW ASSUMPTION

AGE DEPENDENT LOSS OF CAVEOLIN-1 IN MUSCLE AND FAT TISSUE WOULD BE CAUSATIVE FOR NON-OBESE TYPE II DIABETES ?

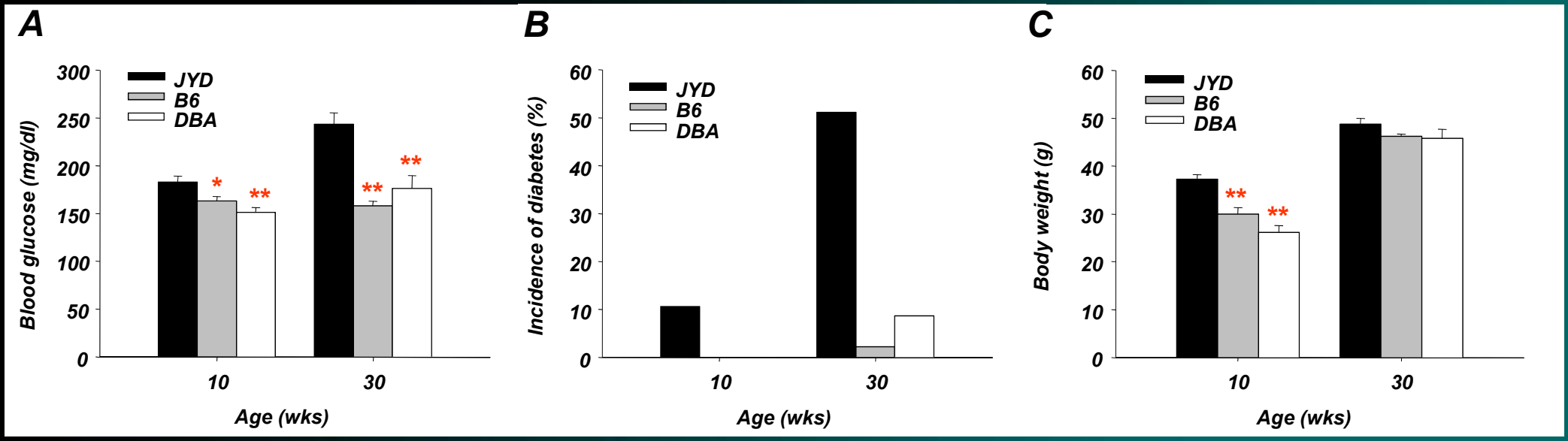
Caveolin-1 and Diabetes type II

JYD animal model

Collaboration with University of Calgary
(Dr. Ji-Won Yoon & Hee-Sook Jun)

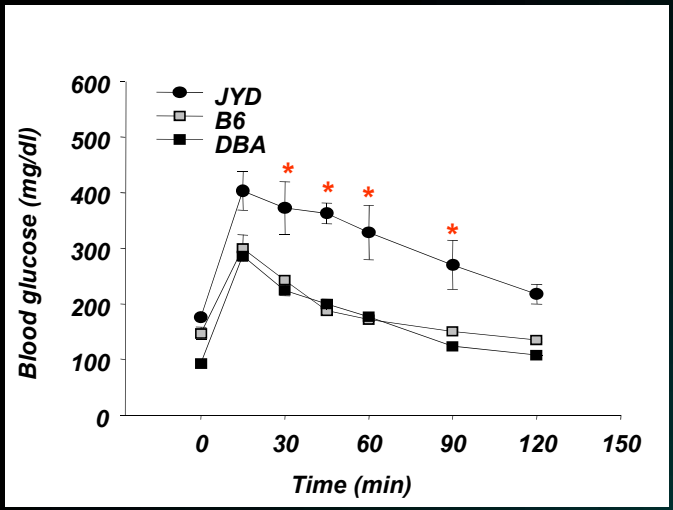
- *DBA X C57BL/6*
- *Age dependent phenotype*
- *Sex dependent diabetic phenotype*

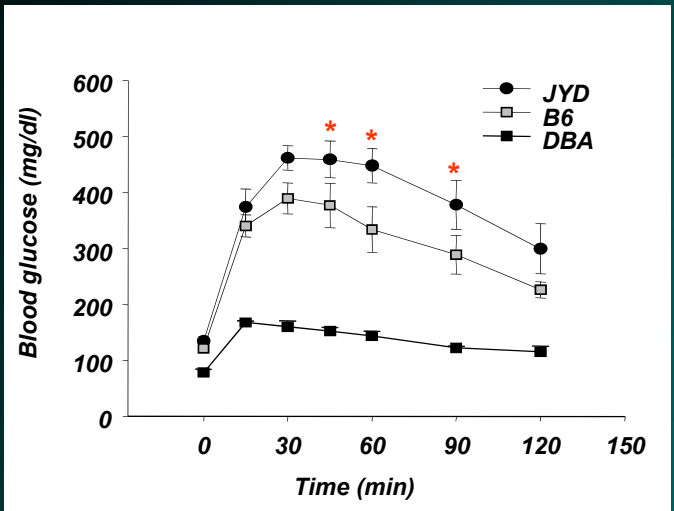
Blood glucose levels, incidence of diabetes, and body weight in male JYD mice

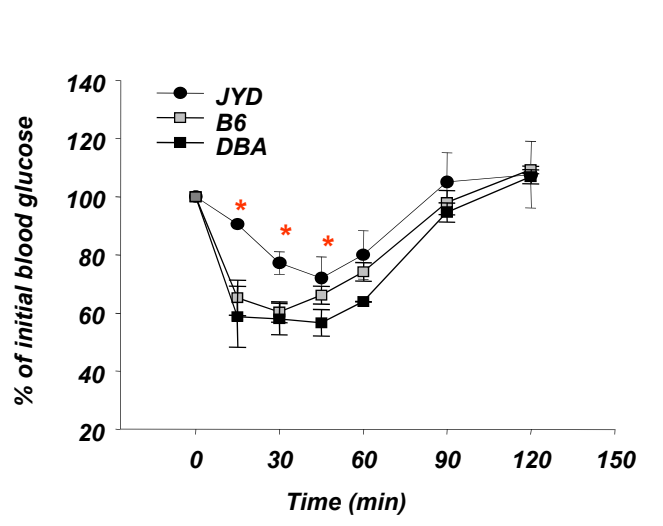


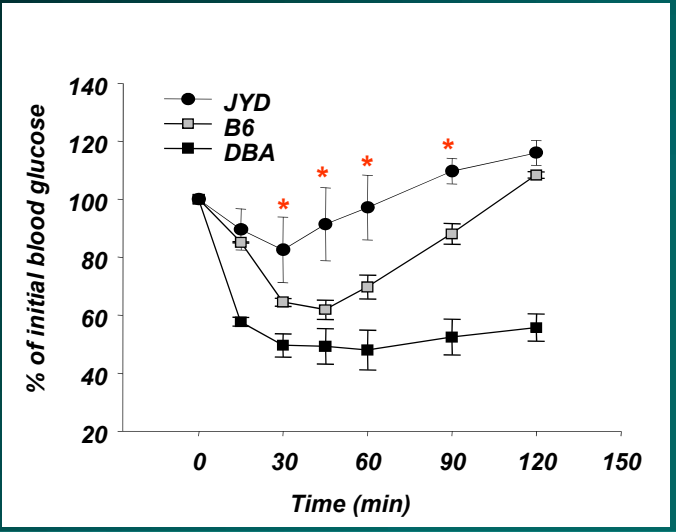
Glucose and insulin tolerance tests in male JYD mice

10 weeks



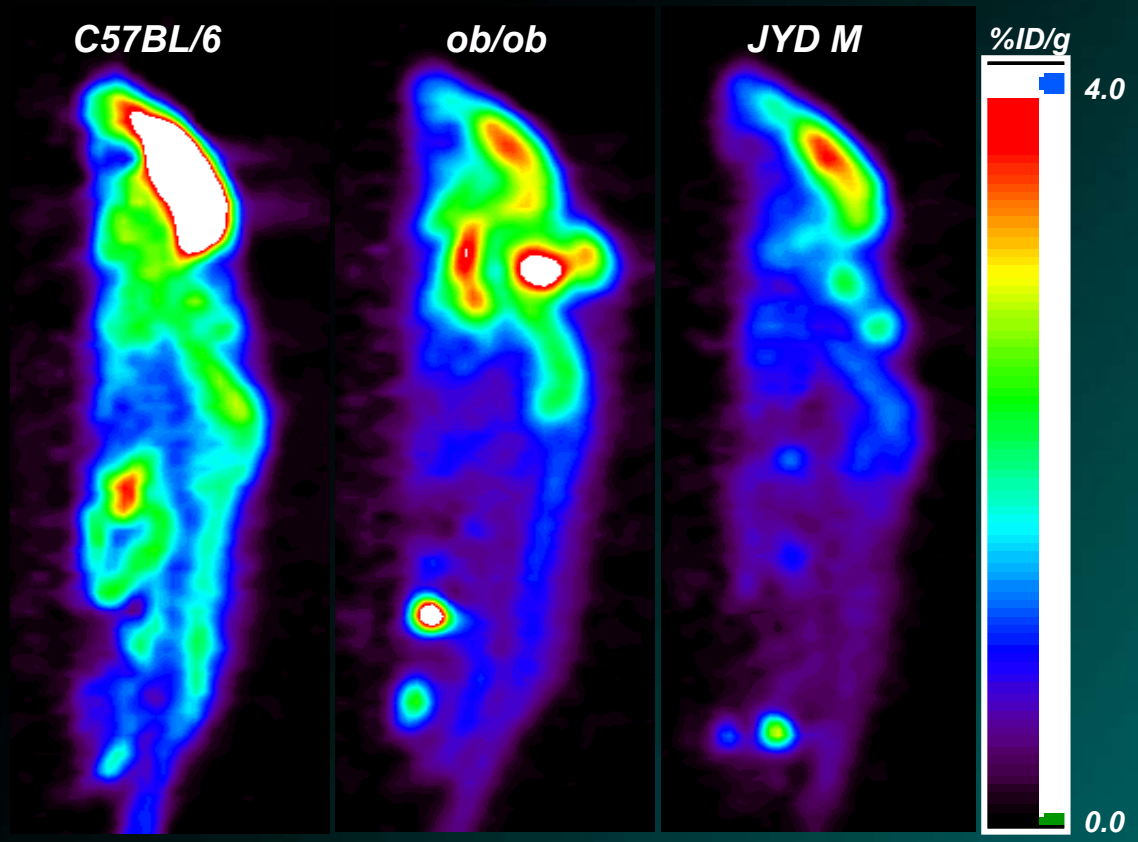


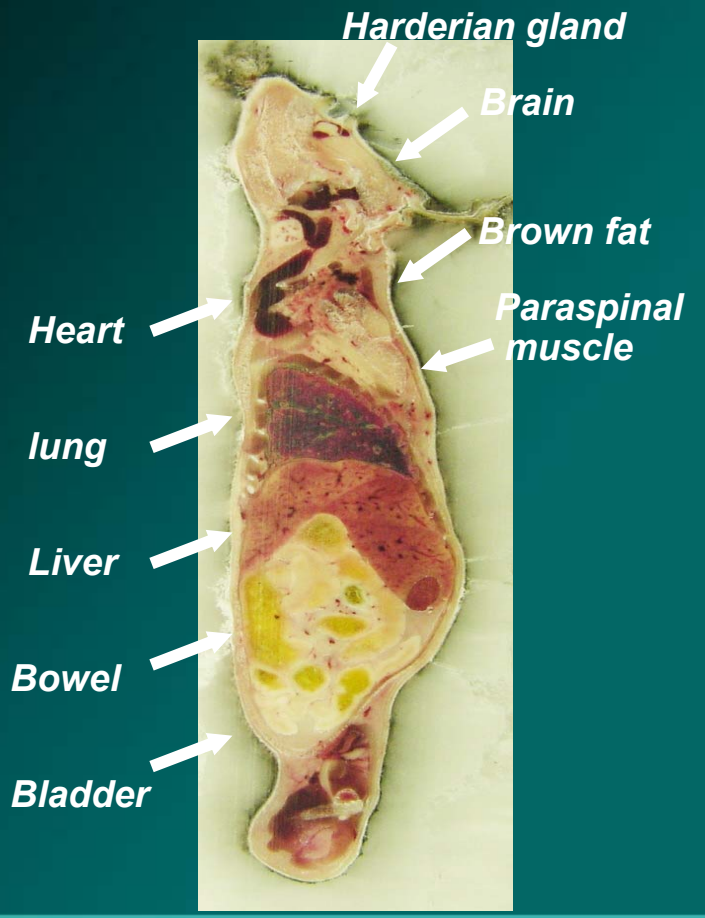




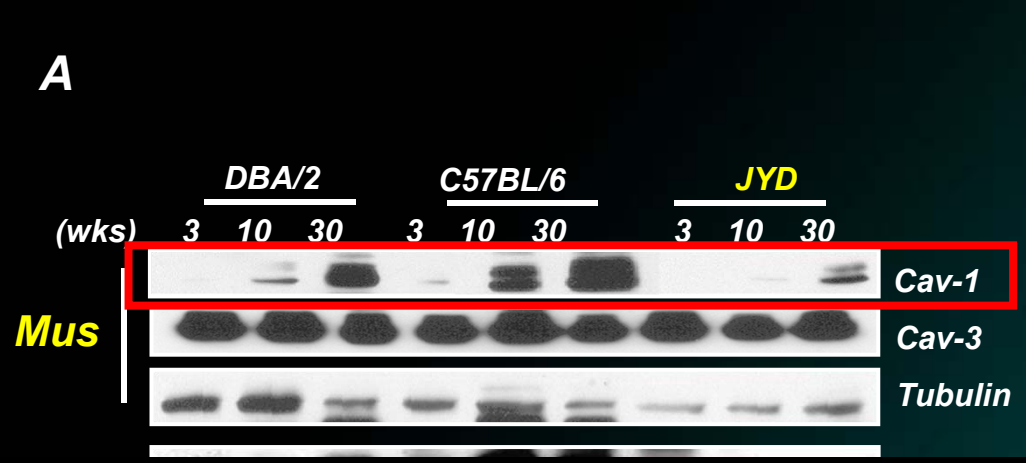
30 weeks

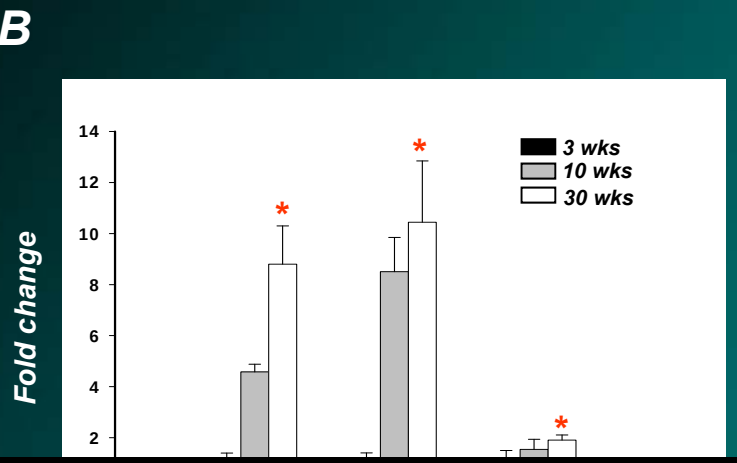
Whole-body ^{18}F-FDG PET images in JYD mice



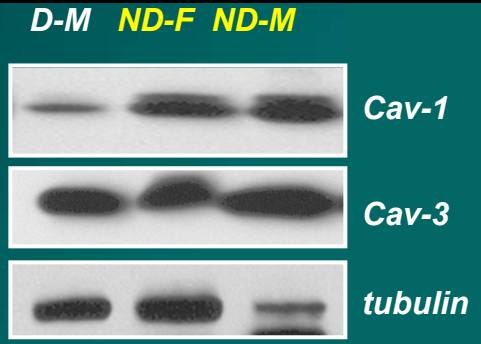


Expression of caveolins in skeletal muscle and other insulin responsive tissues



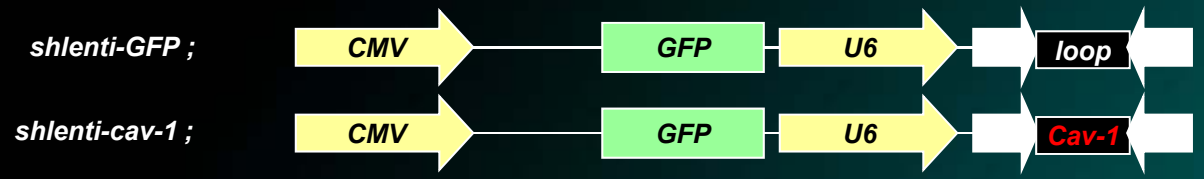


Can Caveolins regulate the insulin resistance in JYD model?

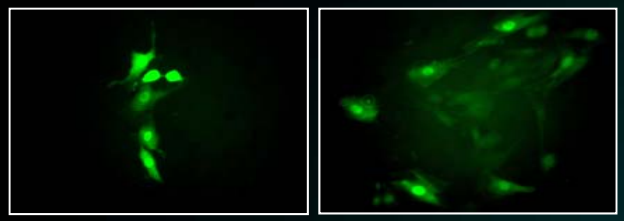


Down-regulation of caveolin-1 by shlenti-cav-1 viral vector

A

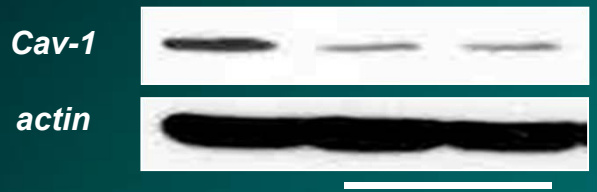


B



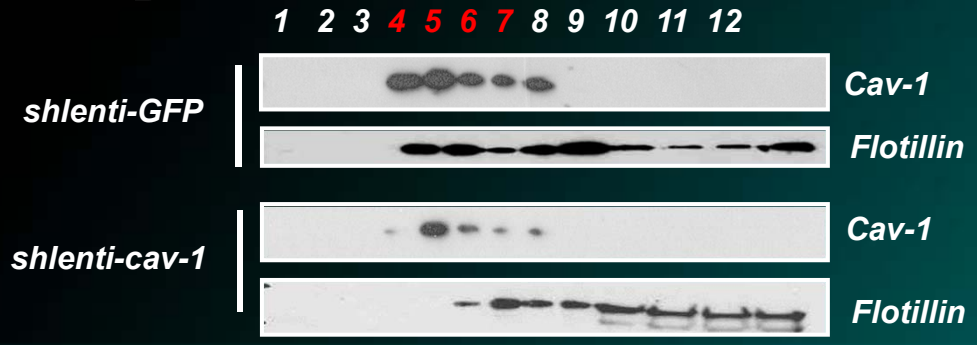
shlenti-GFP shlenti-cav-1

C

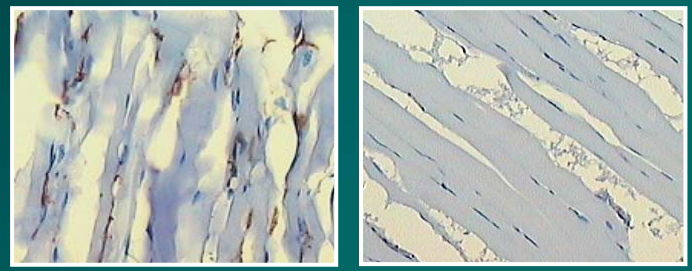


shlenti-GFP shlenti-cav-1

D

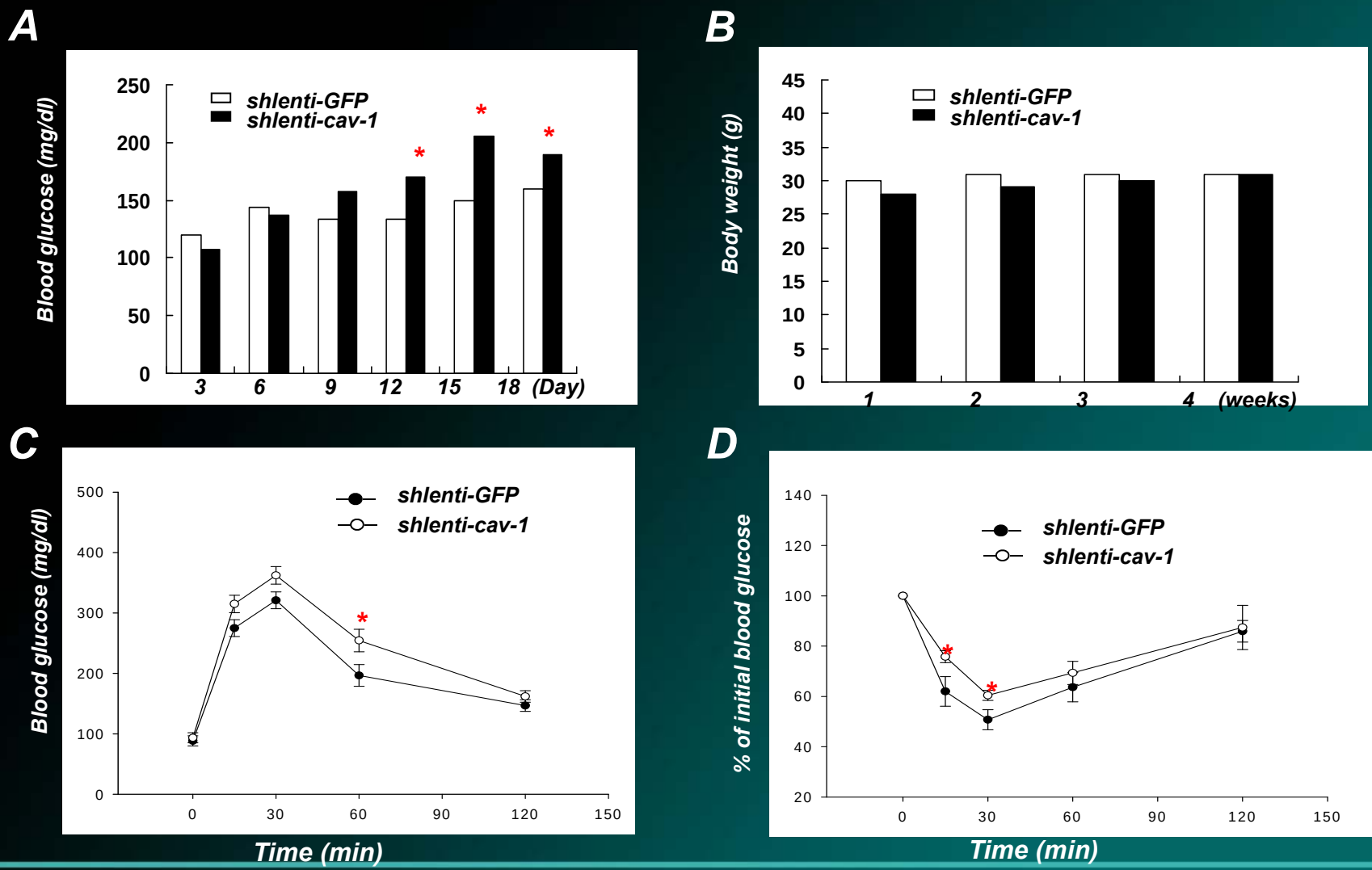


E

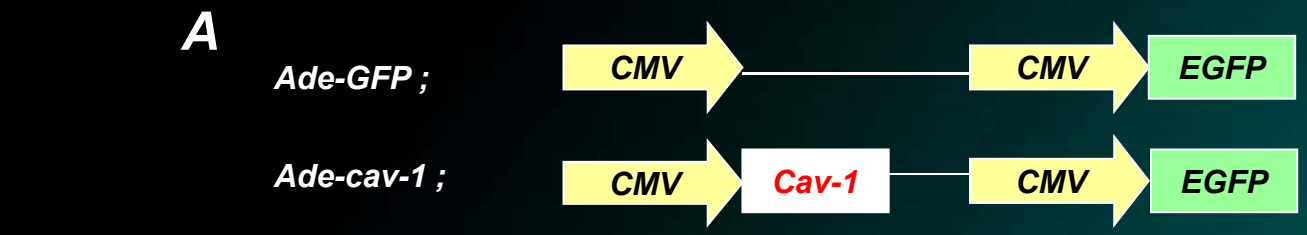


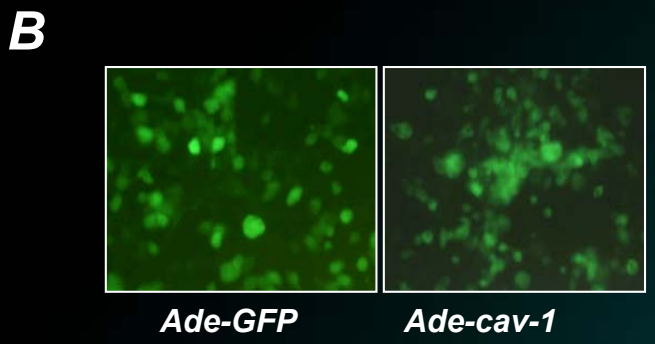
shlenti-GFP shlenti-cav-1

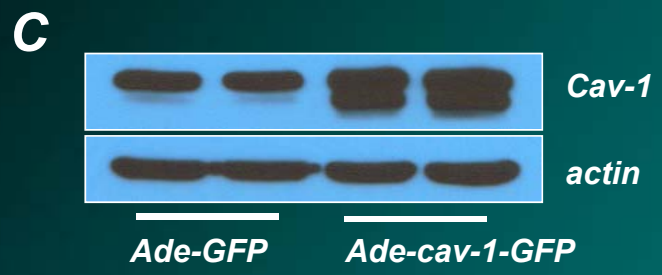
Impairment of glucose and insulin tolerance in shlenti-cav-1-injected C57BL/6 mice

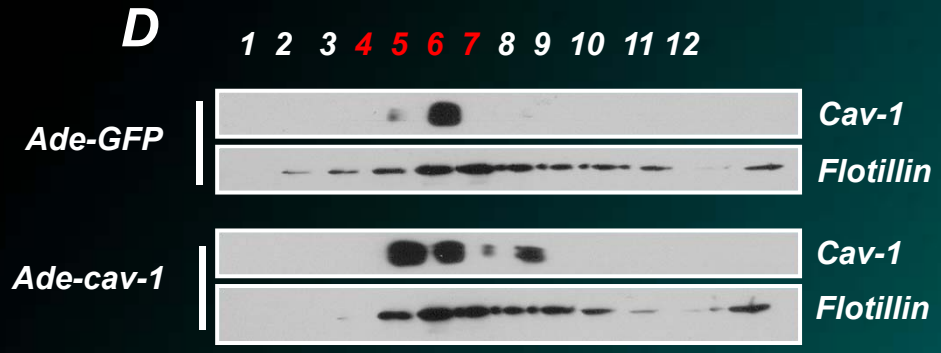


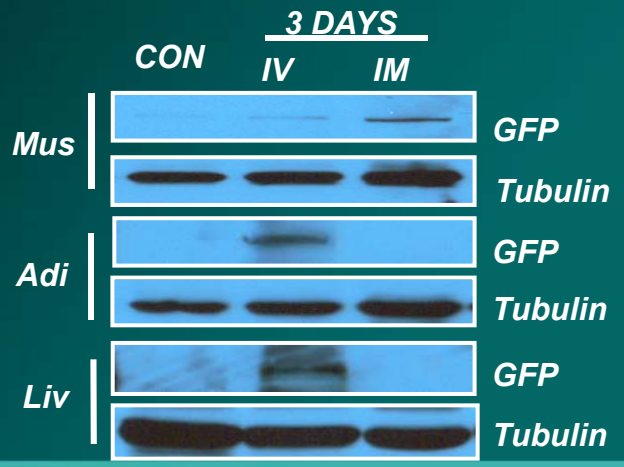
Overexpression of caveolin-1 by adenovirus-cav-1 viral vector





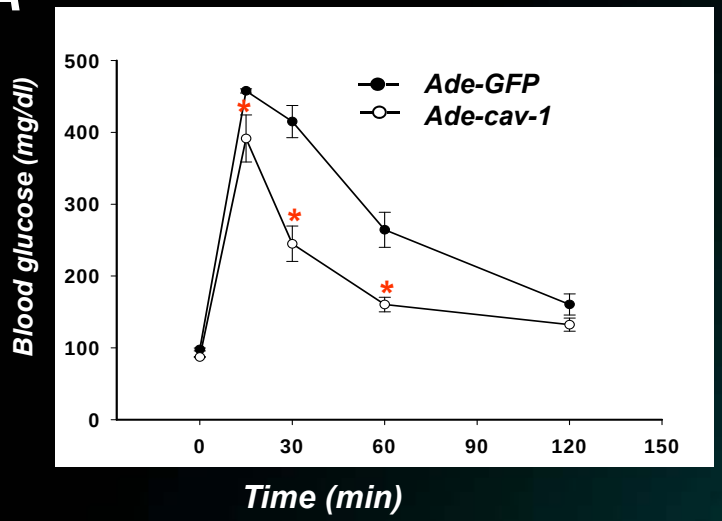






Improvement of glucose uptake and insulin tolerance in Ade-cav-1 injected JYD mice

A



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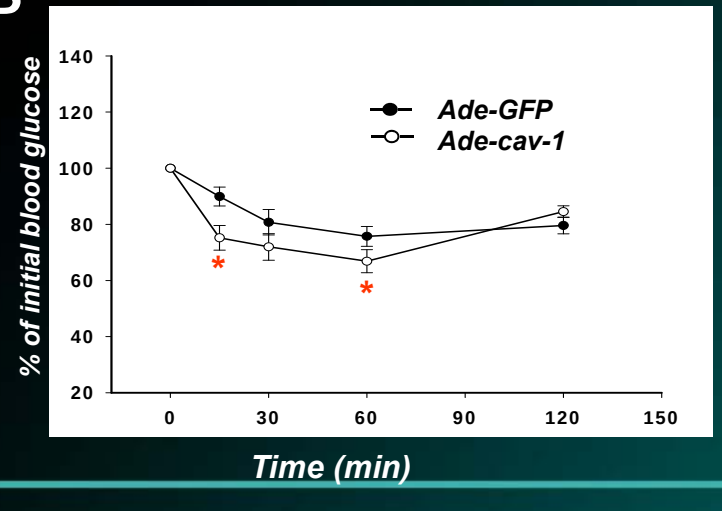

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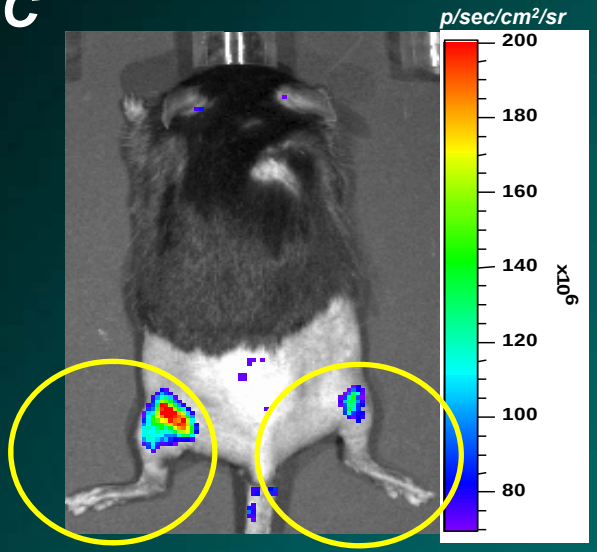

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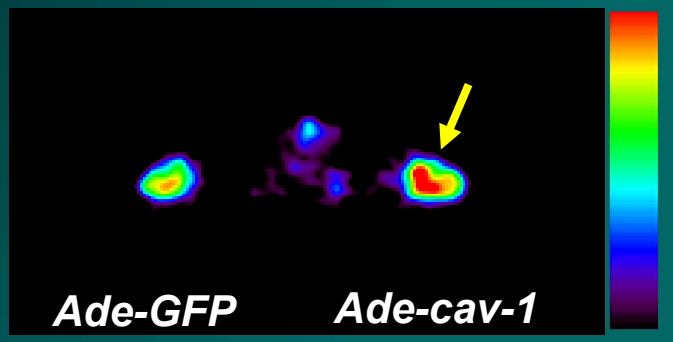


Caveolin-1 status** of the **skeletal muscle
might influence insulin sensitivity
in the aged organism
and
might contribute
to prevent or delay the appearance of
type 2 diabetes

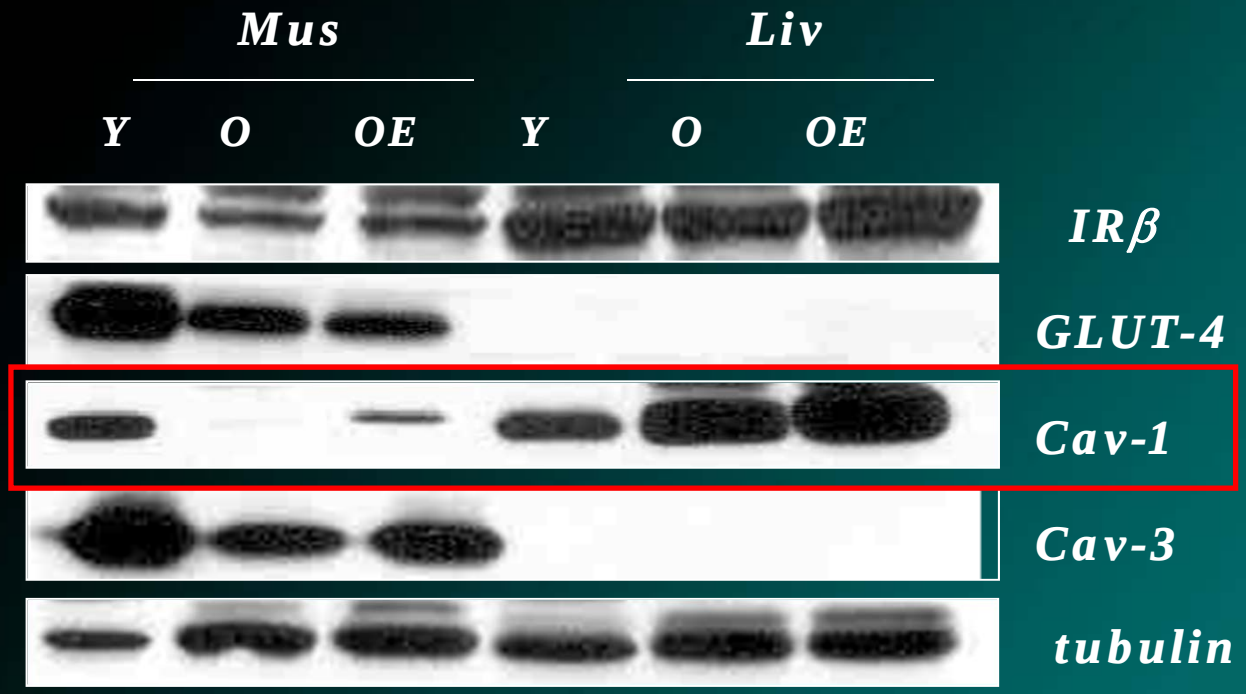
Exercise and

Caveolin-1 Status ?

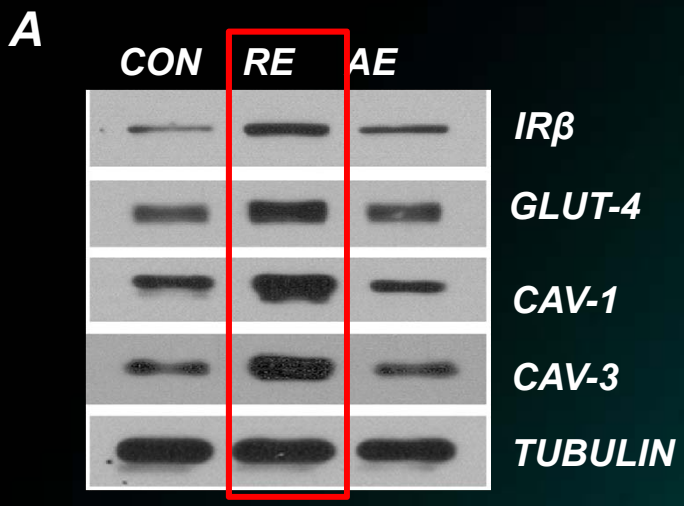
Can in vivo expression of caveolin-1 be increased by exercise training?

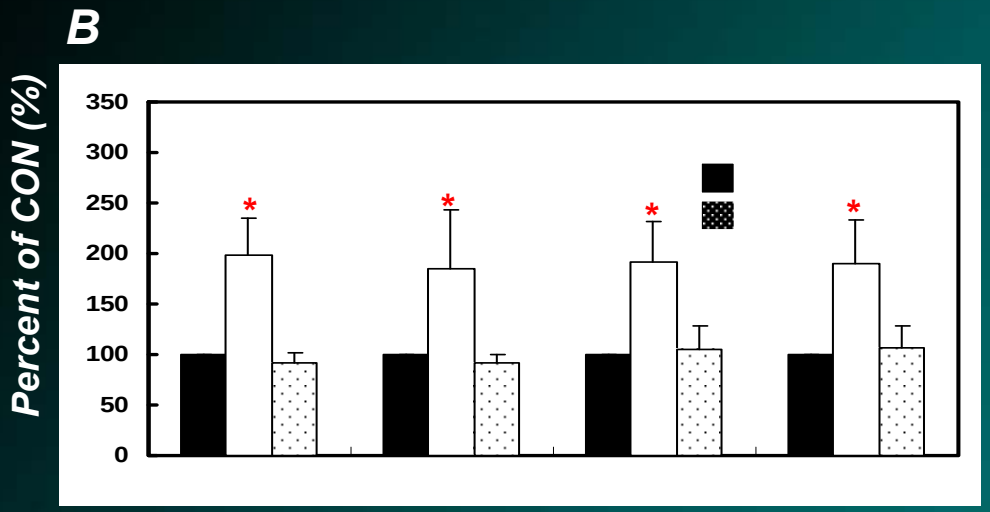
Exercised C57BL/6

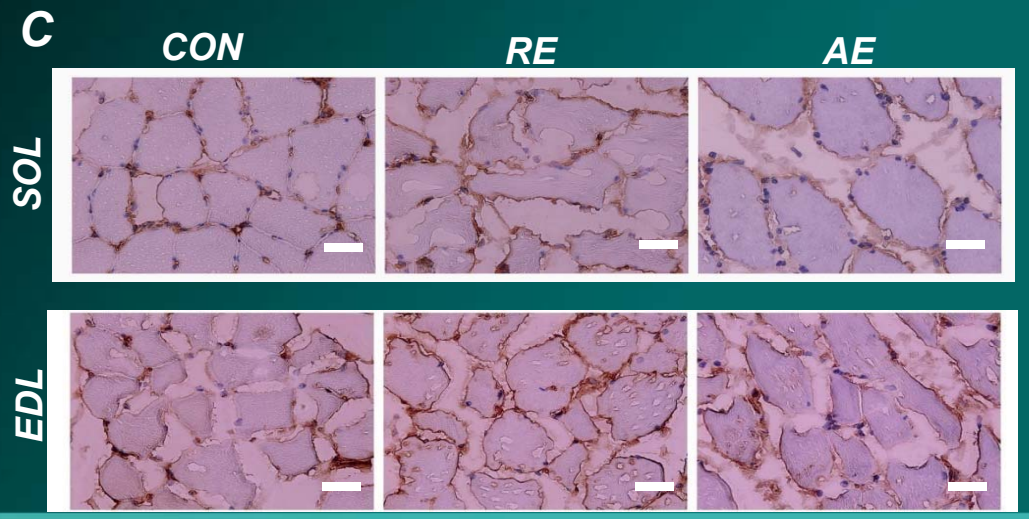
Y (6-8 wks), O (68-75 wks), O-ex (68-75 wks)



Expression of caveolins and insulin related proteins in EDL muscle during resistance exercise







Effect of exercise on caveolin-1 status in Human study

- Exercise type : 100m and 1500 m swimming
- Participants : 14 male penthlon athletes
- Samplings : Deltoid muscle and Vastus lateralis muscle biopsy before and after the exercise
- Purpose : modulation of glucose utilization

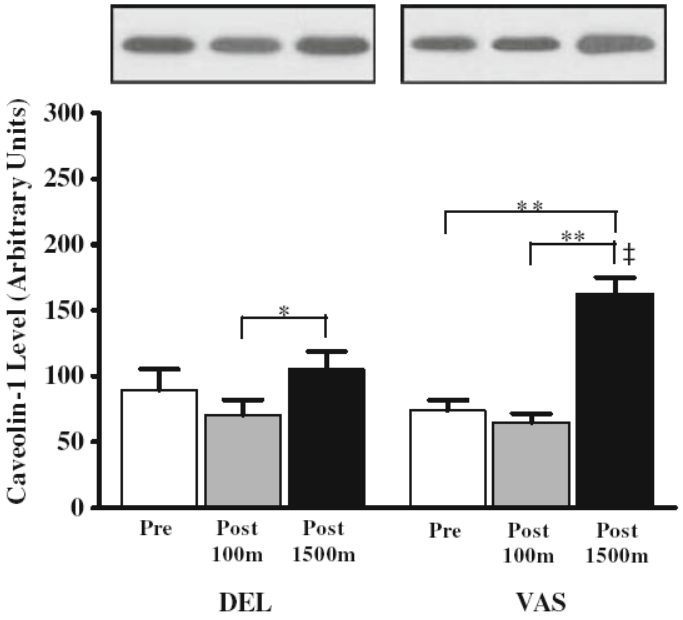


Fig. 1 Cav-1 content in deltoid (*DEL*) and vastus lateralis (*VAS*) following the 100 and 1,500 m swimming exercise. * and ** Significant difference between the swim trials with $P < 0.05$ and $P < 0.01$, respectively. ‡ Significant difference between *DEL* and *VAS* with $P < 0.01$

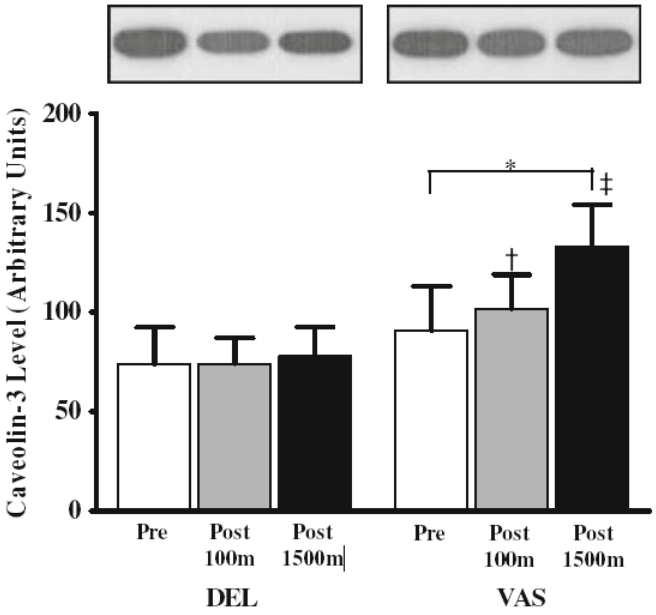


Fig. 2 Caveolin-3 levels in deltoid (*DEL*) and vastus lateralis (*VAS*) muscle following 100 and 1,500 m swimming exercise. * Significant difference between the 100 and 1,500 m swim trials with $P < 0.05$. † and ‡ Significant difference between *DEL* and *VAS* with $P < 0.05$ and $P < 0.01$, respectively

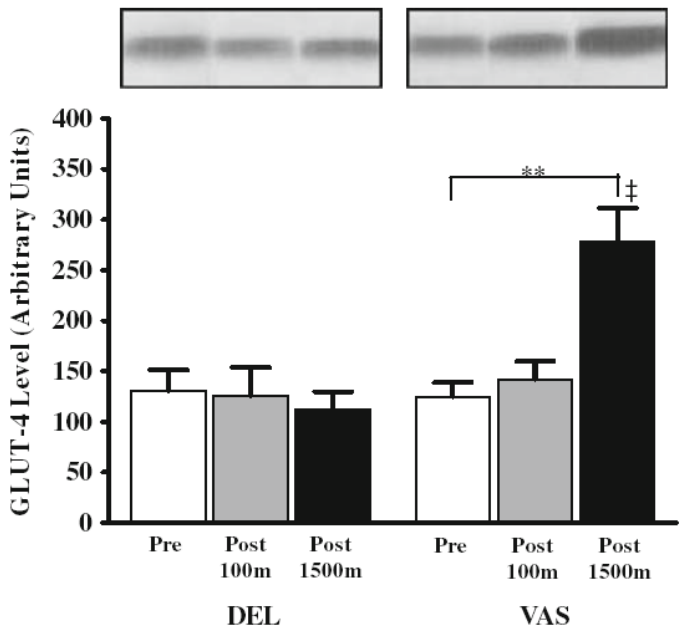
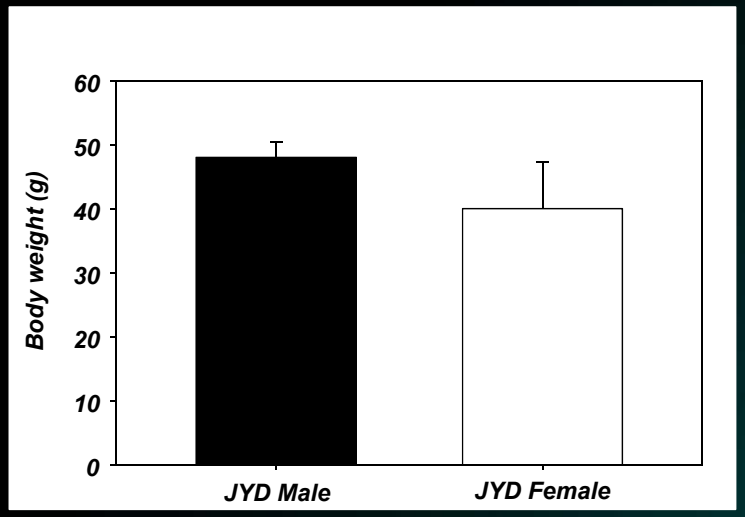


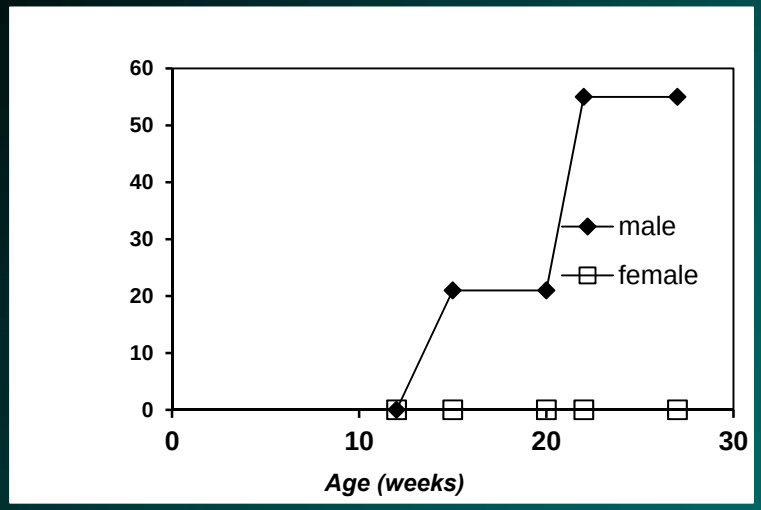
Fig. 3 GLUT4 levels in deltoid (*DEL*) and vastus lateralis (*VAS*) muscle following 100 and 1,500 m swimming exercise. ** Significant difference from the pre-exercise level with $P < 0.01$. ‡ Significant difference between *DEL* and *VAS* with $P < 0.01$

Caveolin-1 and Hormone Sensitivity ?

1. Sex hormone effects

Glucose and insulin tolerance test of male and female JYD mice





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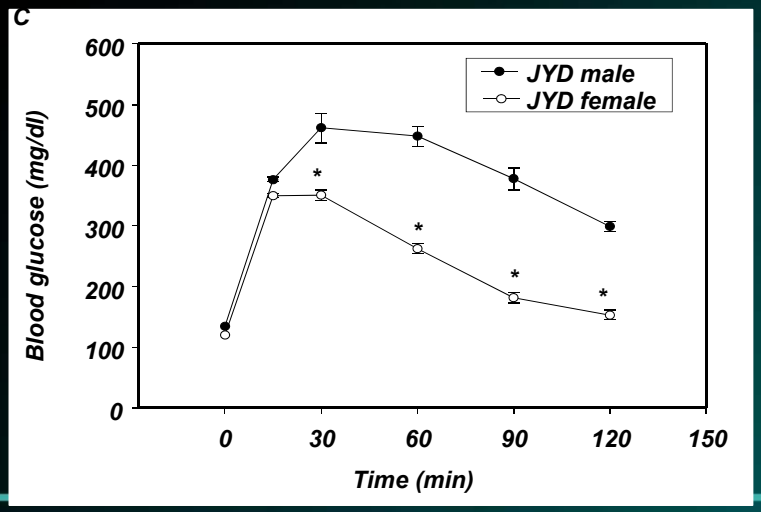
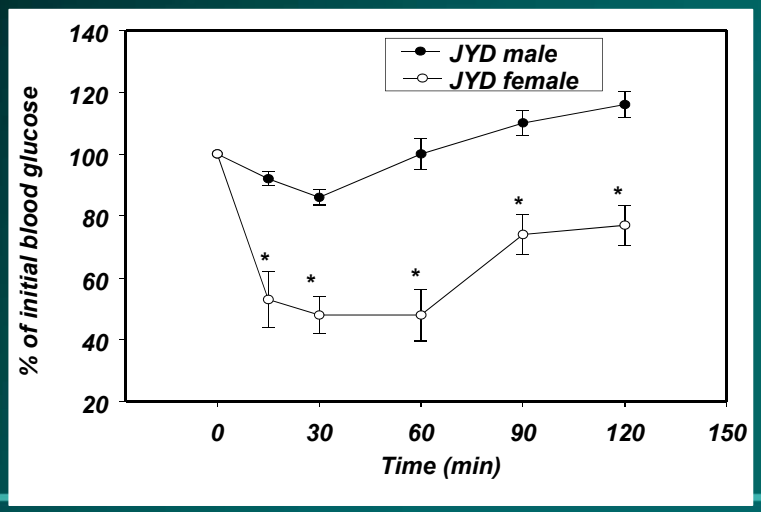
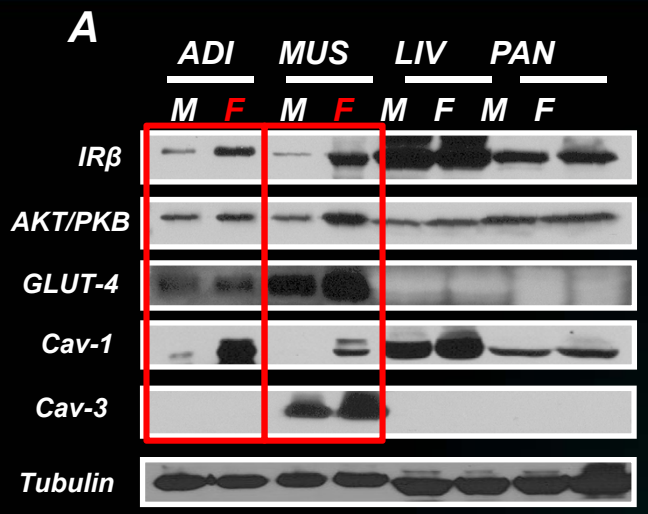
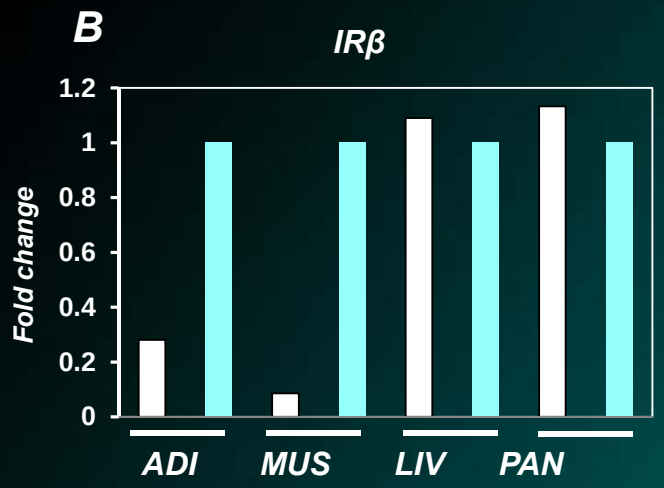
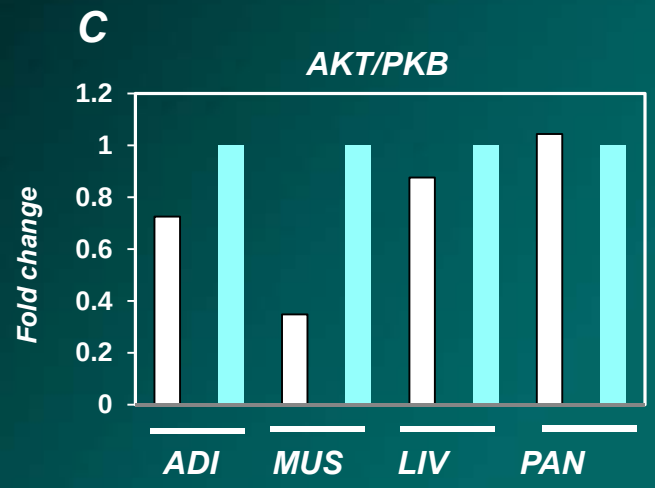


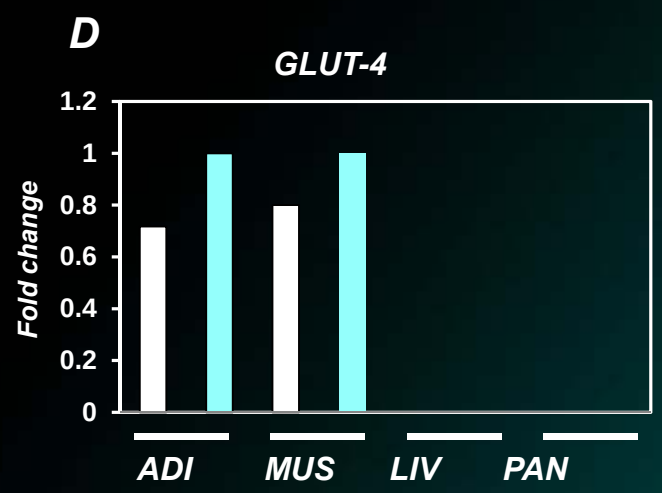


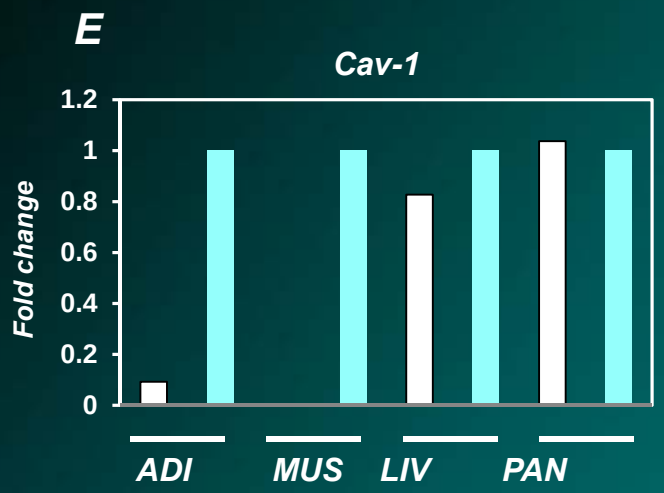
Expression level of insulin signaling molecules and caveolin in male and female JYD mice

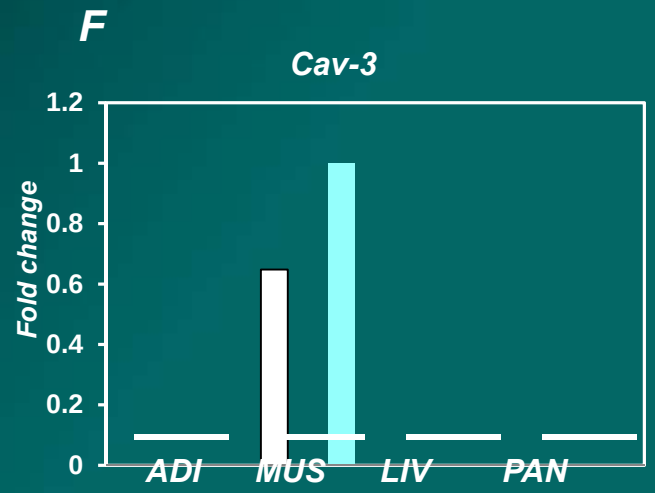




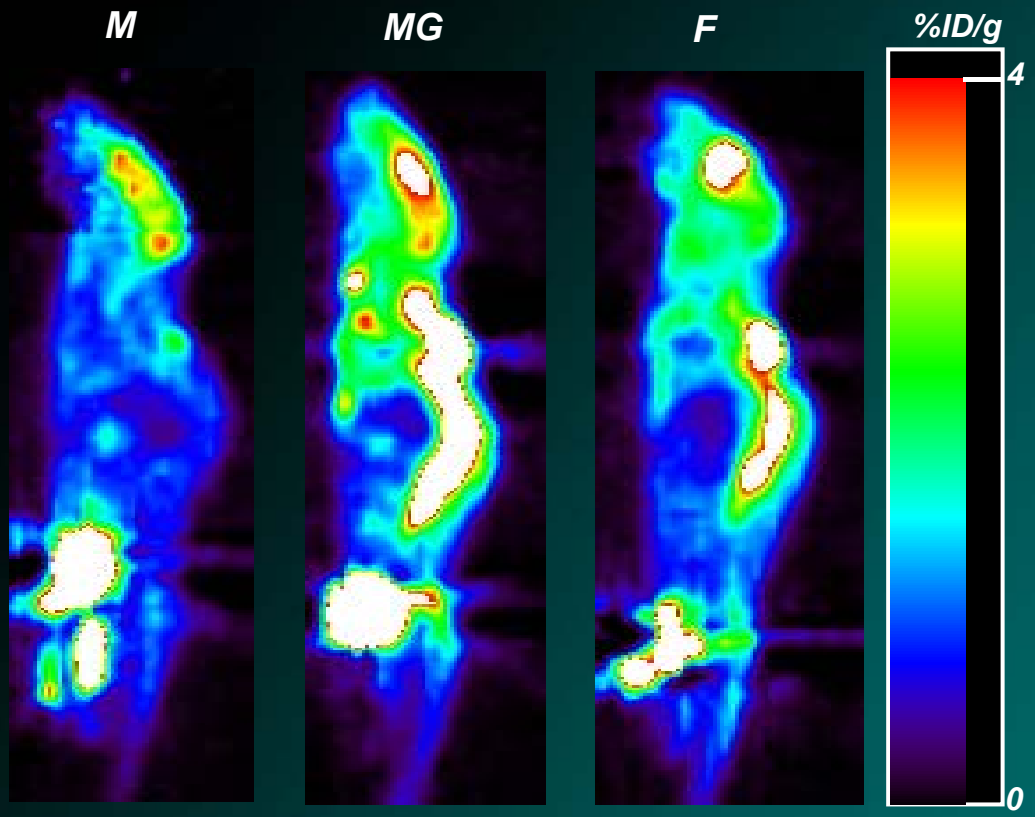








FDG-PET of whole body glucose uptake

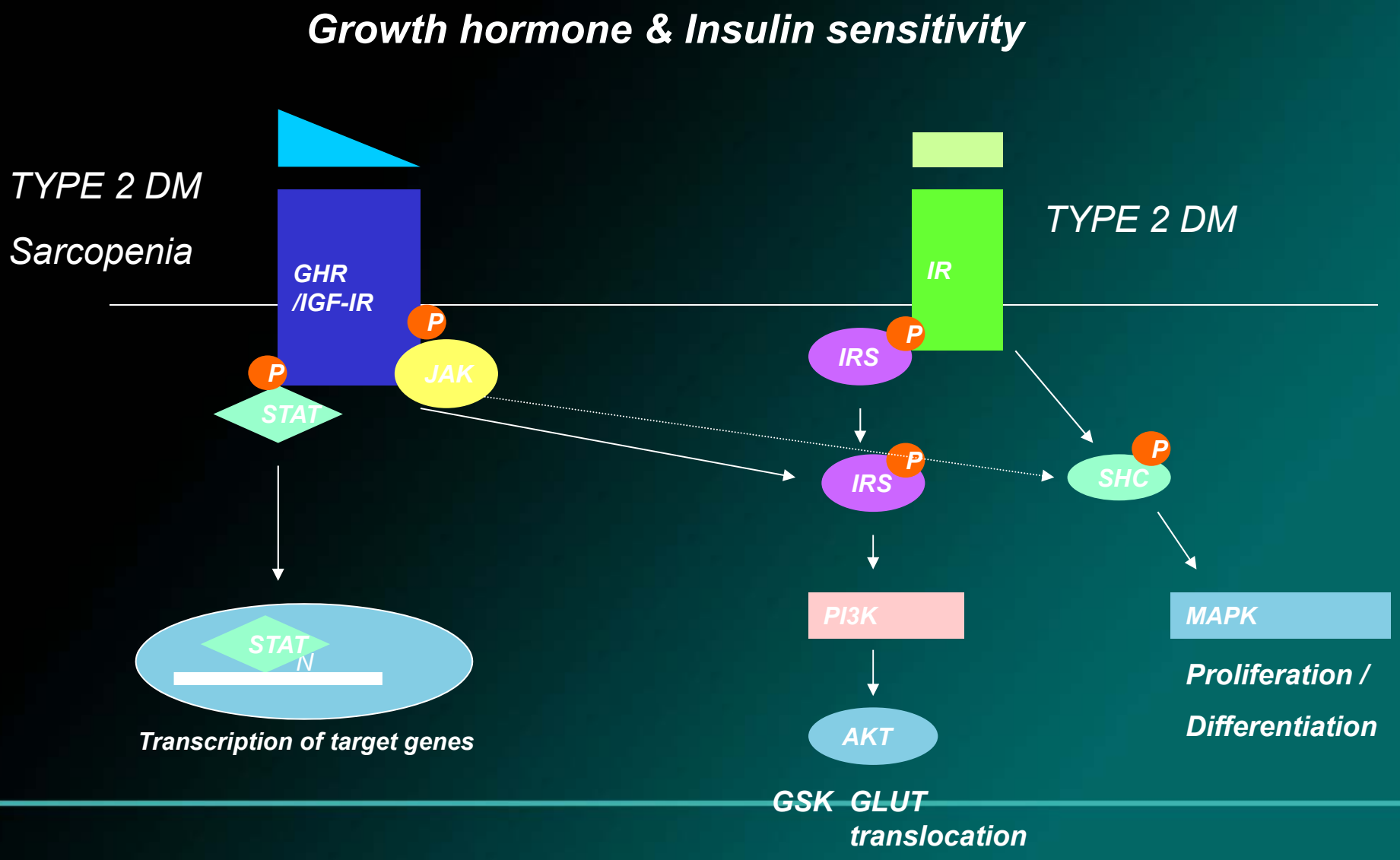


Oh et al (2011) Modulation of Insulin Sensitivity and Caveolin-1 Expression by Orchidectomy. Molecular Medicine. 17(1-2):4-11.

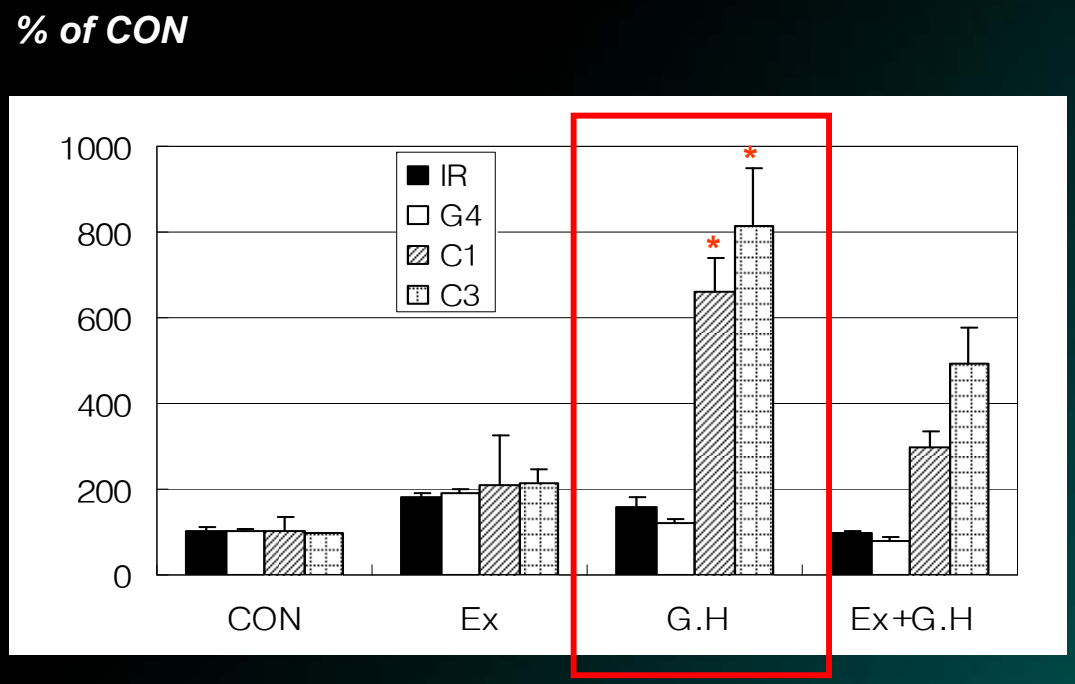
Caveolin-1 and Hormone Sensitivity ?

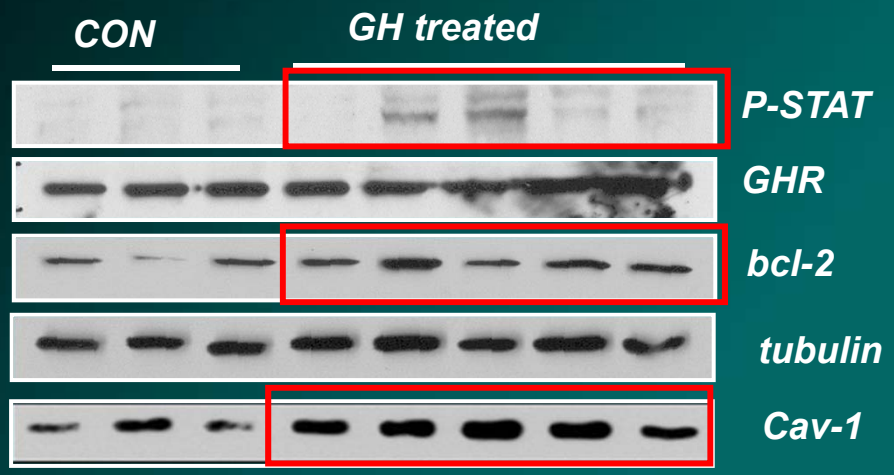
2. Growth Hormone Effects

Aging dependent growth hormone sensitivity



Growth hormone responses in skeletal muscle

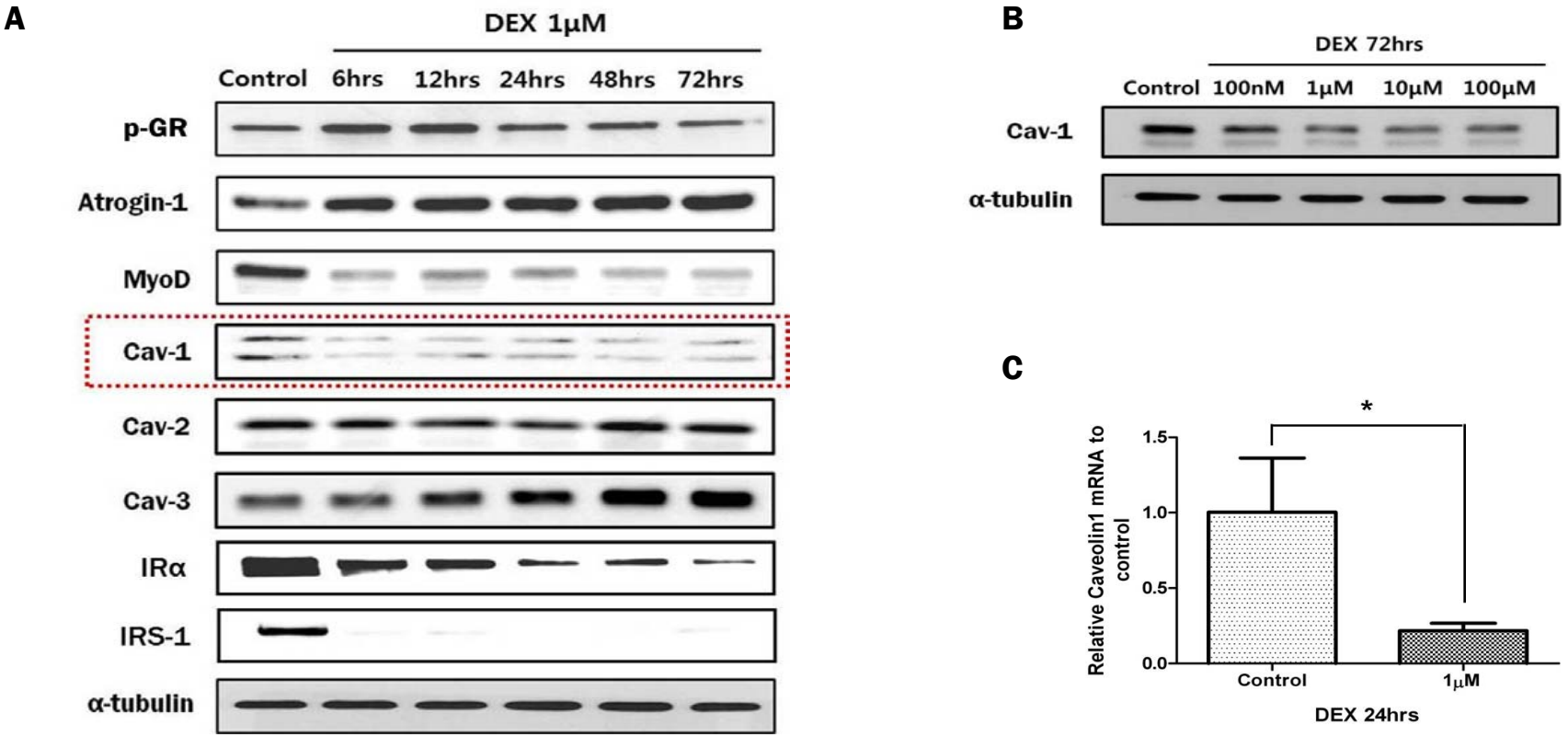




Caveolin-1 and Hormone Sensitivity ?

3. Glucocorticoid hormone effects

Dexamethasone inhibits caveolin-1 in C2C12 myotubes



Caveolin-1 status in muscle tissues is
sensitive to hormonal status
and
might be responsible for
muscle differentiation
and
age dependent muscle loss

Summary

A1. Regulation of insulin response in skeletal muscle cell by caveolin status

A2. Development and Characterization of ageing dependent type 2 diabetic JYD animal model

A3. Potential role for skeletal muscle caveolin-1 in ageing dependent type 2 diabetic JYD model

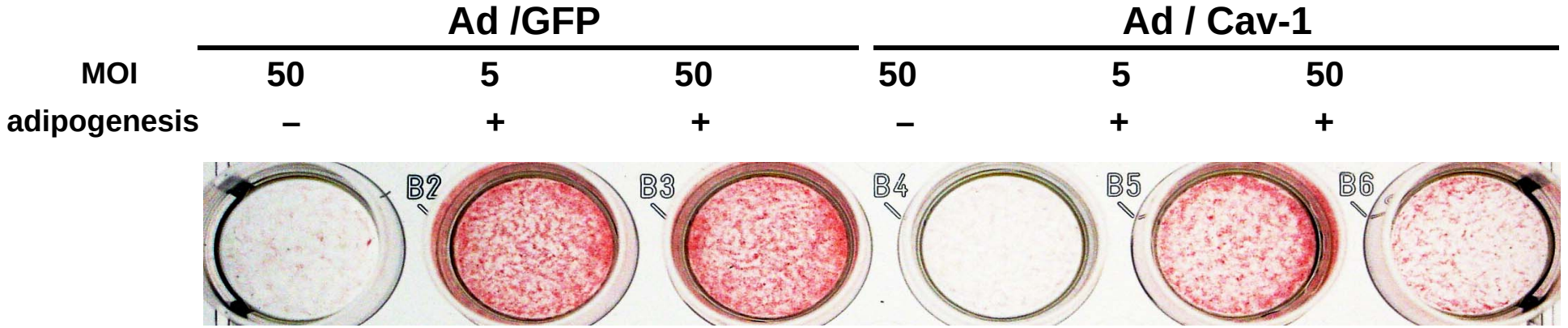
A4. Exercise type and muscle fiber specific induction of caveolin-1 expression for insulin sensitivity

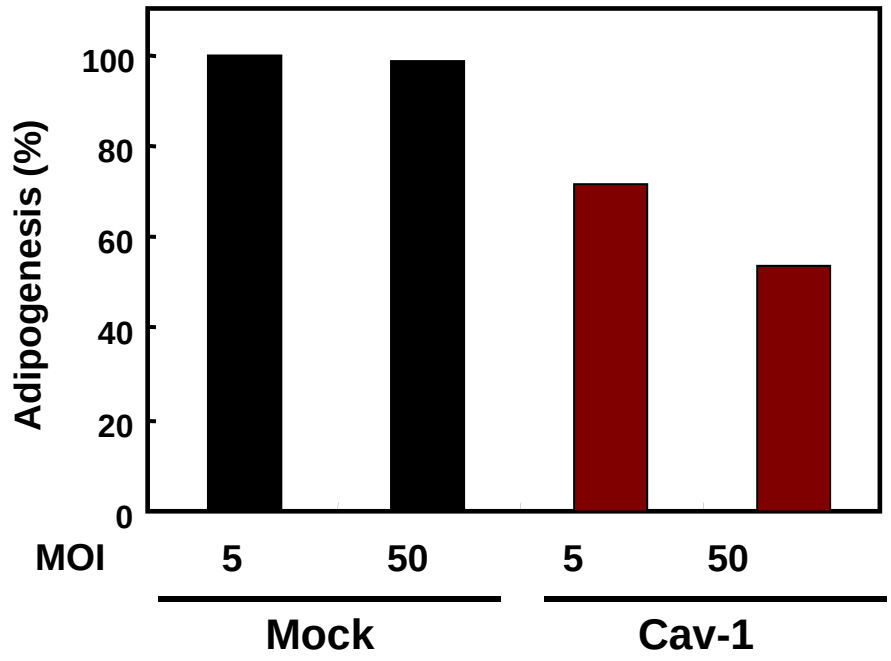
A5. Modulation of Insulin Sensitivity and Caveolin-1 Expression by Gonadectomy in Non-Obese Type 2 Diabetes

Further Questions

Caveolin-1
in
Stem Cell Differentiation
Cancer Development
Longevity

Inhibitory effect of caveolin-1 on adipogenic differentiation in young hMSC





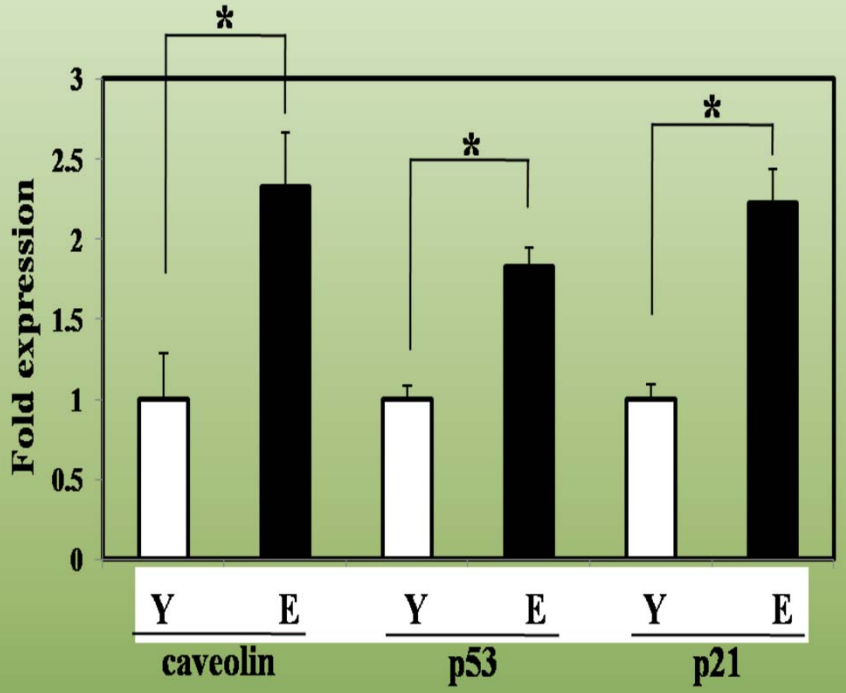
Park et al (2005)
Mechanism of Aging and Development

Caveolin-1 as an index of wound healing

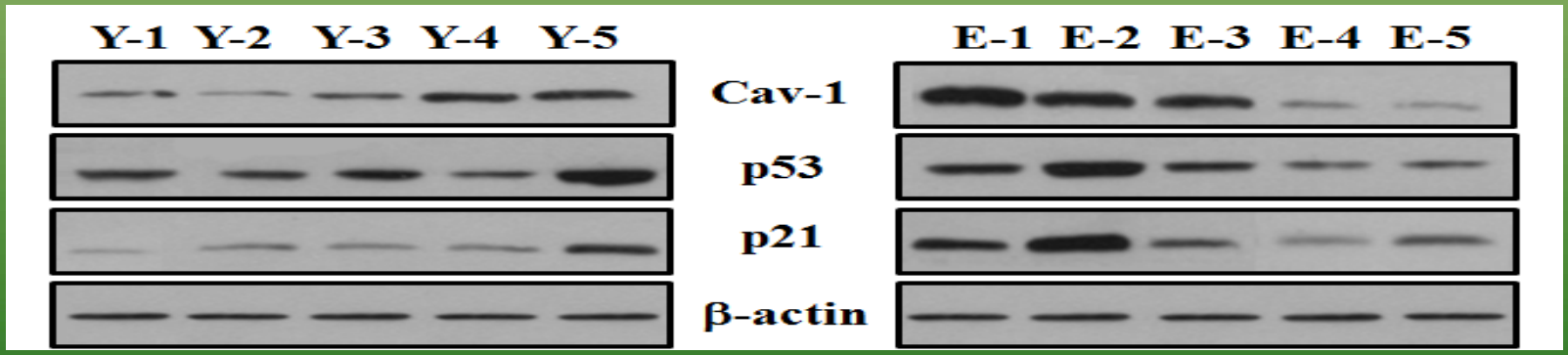
Rhim et al (2010). Molecular Medicine 16:527-534

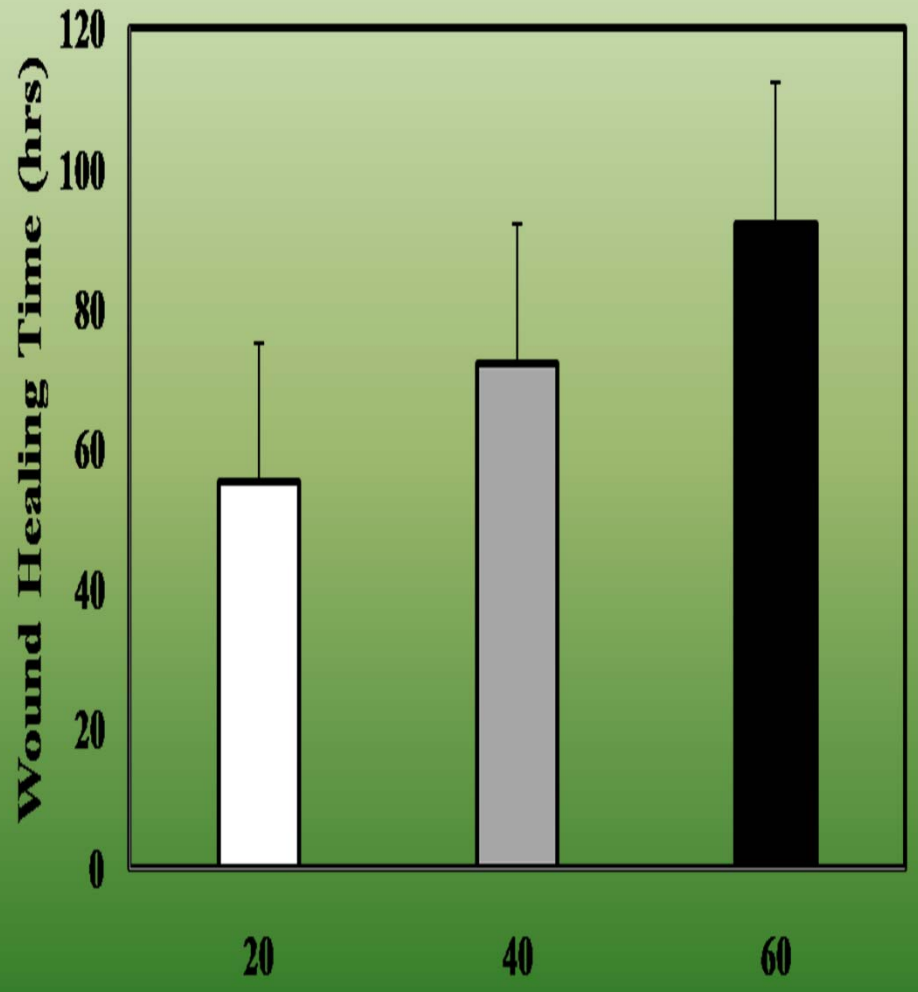
Modulation of wound healing by caveolin-1 status in human corneal epithelium after excimer laser photoablation surgery

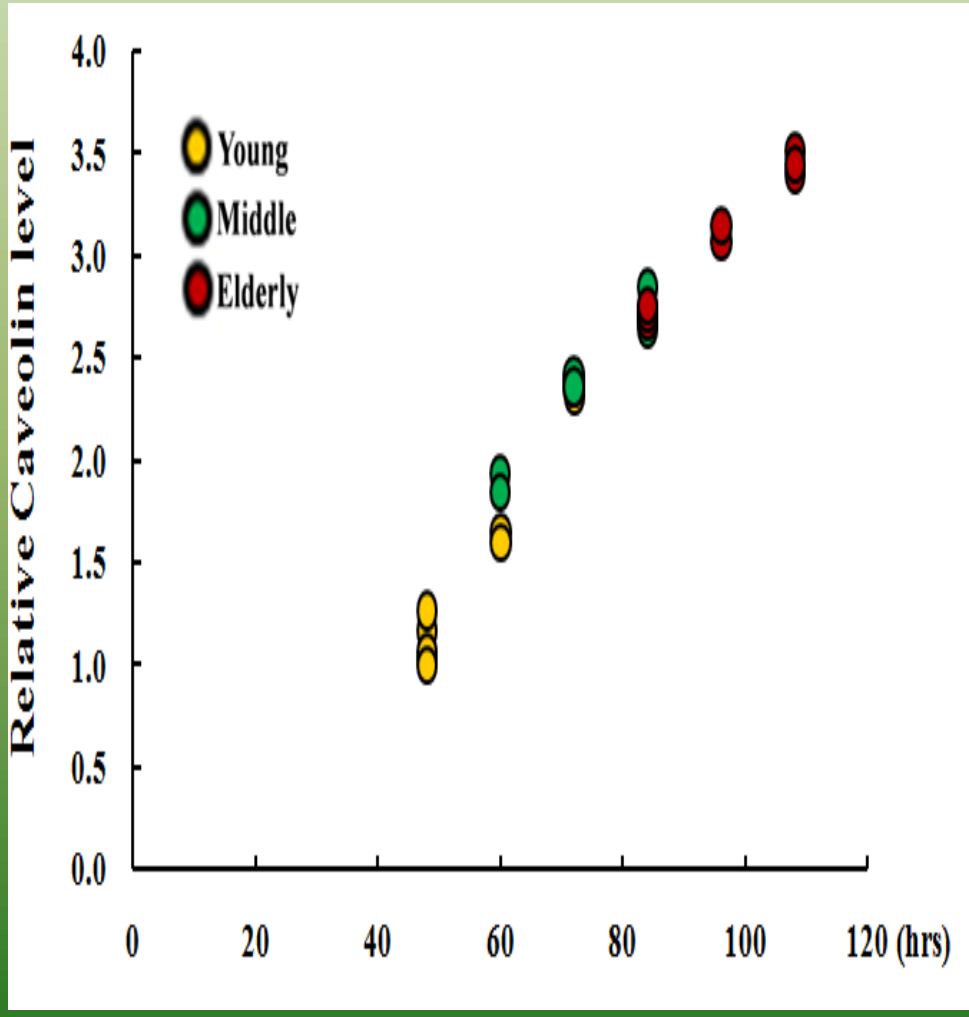
Ji-Heon Rhim[1], Jae Hoon Kim[2], Jae Chan Kim[2] and Sang Chul Park[1]*



Case No.	Sex/Age	Case No.	Sex/Age
Y-1	M/20	E-1	M/50
Y-2	M/21	E-2	F/52
Y-3	M/22	E-3	F/53
Y-4	F/23	E-4	F/56
Y-5	F/24	E-5	M/59




Wound Healing Time (hrs)
120
100
80
60
40
20
0
20
40
60


Relative Caveolin level
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
Young
Middle
Elderly
0
20
40
60
80
100
120 (hrs)

Summary of Variations detected in caveolin -1

Exon	Locus	Amino acid change	Frequency	
			Normal(=62)	Centenarian(=65)
3	intron	-	3.22%	0.00%
3	exon	-	4.84%	0.00%
3	exon	Val->Ile	1.61%	0.00%

Caveolin and aging

Cellular aging mechanism

1. Mitogenic response
2. Intracellular trafficking
3. Polarity
4. Metabolic response by hormone sensitivity
5. Microbial infection
6. Structural determination

Age related diseases

1. Stem cell differentiation
2. Cancer cell differentiation
3. Wound healing
4. Diabetes
5. Dementia
6. Vascular tone
7. Infectious diseases
8. Muscle aging

Collaborators

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Sung Jin Ryu (NIH)
Yoon Sin Oh (Gachon Univ)
Jeong Soo Park (Dangook Univ)
Kyung A Cho (Chonnam Univ)
Young Hoon Son (SNU)

Hee Sook Jun (Gachon Univ)
Ji Won Yoon (Chicago Univ *)

Chang Geun Kim (SSU)