Generation Mechanism and Cause of Wrinkle

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피부주름살의 발생기전 및 원인

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Abstract

새 천년으로 들어선 2000년도부터 우리나라의 65세 이상 노령인구는 7.1%를 차지하게 되어 본격적인 노령화사회 (UN에서 65세 이상인구가 총 인구의 7% 이상일 경우 노령화 사회로 정의)로 진입하였다. 평균수명의 계속적인 증가에 따라 노인 인구는 급격히 늘어날 전망이며, 따라서 노인성 질환의 발생도 늘어나게 되어 가정 또는 사회가 떠 맡아야할 경제적, 정신적 부담은 더욱 증가하게 된다. 건강하고 행복한 인생의 황혼기를 보내는 것은 인간의 권리이며 누구나 바라는 소망이다. 피부의 노화현상은 심장질환, 암 등에 못지 않게 중요하며, 노인의 경제적, 사회적 활동을 심각하게 위축시키고 있다. 피부노화를 예방하고 노인성 피부질환을 치료할 수 있는 방법을 개발함으로써 노인의 경제, 사회활동을 활동적으로 유지시킬 수 있다.

피부노화는 크게 두 종류로 나눌 수 있다. 그 한가지는 내인성노화 (intrinsic aging)로서 세월이 흘러감에 따라 피할 수 없는 노화 현상을 말한다. 두 번째는 광노화 (photoaging)로서 오랫동안 햇빛에 노출된 얼굴, 손등, 목뒤 등의 피부에서 관찰되는 노화현상을 말하는 것으로 내인성노화 현상과 자외선에 의한 영향이 합쳐진 결과로 발생한다. 광노화 현상은 자외선의 노출을 피하면 예방할 수 있는 피부노화 현상이다. 내인성 노화는 햇빛에 노출되지 않은 피부에서 주로 관찰된다. 임상적 특징은 비교적 경미하며, 잔주름, 피부건조증, 탄력감소 등을 들 수 있다. 그러나 광노화의 임상적 특징은 내인성 노화에 비하여 심하고, 일찍부터 관찰된다. 내인성 노화에 비하여 굵고 깊은 주름이 발생하며, 잔주름도 많이 발생한다. 햇빛에 노출된 피부에 불규칙한 색소침착이 발생하며 일광흑자 (solar lentigo) 등의 색소질환이 증가한다. 피부가 매우 거칠고, 건조해지며, 탄력성이 감소하여 심한 경우 피부가 처지게 된다

피부노화의 대표적인 증상은 주름살이며, 아직까지 그 발생기전에 대하여는 여러 가지 학설이 있으나 정확히 알려져 있지 않다. 피부에 존재하는 교원질, 탄력섬유등 기질단백질의 손상이 피부 주름살의 주 원인으로 알려져 있다. 또한 얼굴에 존재하는 근육의 분포와 움직임, 유전적 소인, 자외선, 흡연, 폐경, 산화적 손상, 열 등 여러 원인이 복합적으로 작용할 것으로 생각된다. 피부주름살의 원인을 밝히고, 원인인자가 피부주름살을 초래하는 분자생물학적 기전을 이해함으로써 주름살을 예방하고 치료할 수 있는 새로운 방법을 개발할 수 있다.

EDUCATION

1984 B.A. & M.D., Seoul National University, College of Medicine, Seoul, Korea

1988 Master degree(Dermatology), Postgraduate school, SeoulNationalUniversity

1993 Ph.D. degree (Dermatology), Postgraduate school, Seoul NationalUniversity

PROFESSIONAL AND RESEARCH EXPERIENCE

1988 A staff doctor Department of Dermatology, Capital Armed Forces General Hospital Seoul, Korea

1991 Research Fellowship Department of Dermatology, Seoul National University College of Medicine

1997 Research Fellow Department of Dermatology, University of Michigan

1993 Instructor, Assistant Prof. and Associate Prof. Department of Dermatology, Seoul National University , College of Medicine

MEMBERSHIP

Korean Dermatological Association

Korean Society of Investigative Dermatology

Society of Investigative Dermatology

American Academy of Dermatology

American Society for Photobiology

General mechanism and cause of wrinkle

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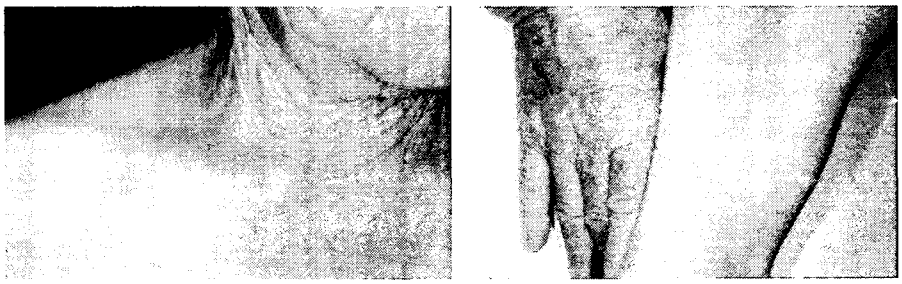
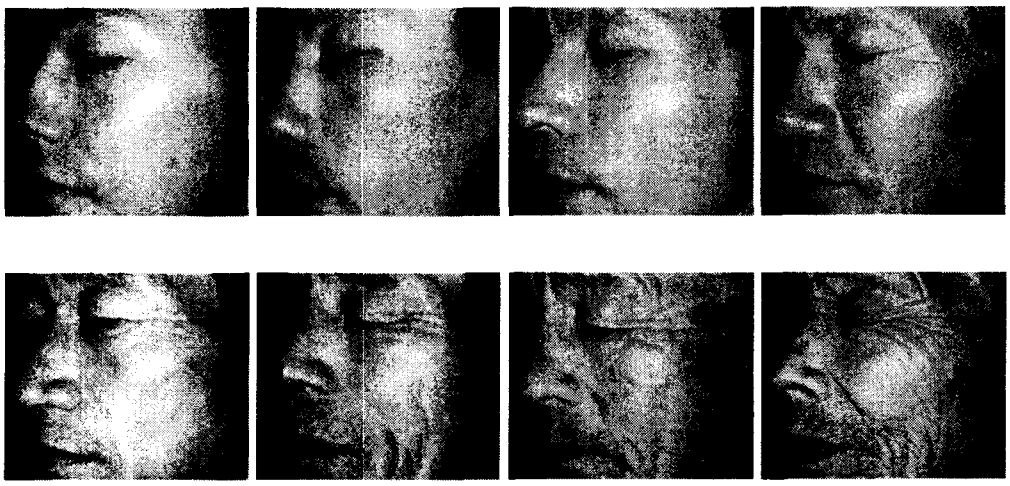
Intrinsic aging *versus* photoaging



Photographic wrinkle grade in Asian skin (Korean women)

Photographic wrinkle grade in Asian skin (Korean men)



이마 주름살:
- 유전적 요인
- 표정근의 움직임
- 자외선 (?)

눈가 (Crow's feet) 주름살:
- 표정 (많이 웃는 경우)
- 자외선

뺨의 주름살:
- 유전적 요인 (광대뼈)
- 자외선

입주위의 주름살:
- 유전적 원인
- 자외선 (?)

Risk factors of wrinkles in Asian skin

1. Age
2. Sun-exposure (UV, Heat)
3. Female :
   - menopause
   - pregnancy
   - Hormone replacement therapy (HRT))
4. Smoking
5. Skin color

Prevalence odds ratios for severe wrinkling adjusted for age, sex, smoking and sun exposure

Characteristics	Wrinkled subjects N(%)	Prevalence odds ratio	95% C.I	P-value for trend
Age				
30-59y	125 (16.80)	1.00		
60-69y	81 (81.48)	12.45	4.65 - 33.28	
70y<	201 (90.54)	56.16	21.35 -147.71	0.0001
Sun exposure, h/day				
1-2	99 (19.19)	1.00		
3-4	62 (20.97)	0.84	0.31 - 2.24	
5<	246 (64.63)	4.85	2.35 -10.17	0.0001
Sex				
male	236 (43.22)	1.00		
female	171 (52.05)	3.69	1.74 - 7.84	0.0001

Chung et al. Arch Dermatol 2001;137:1043-1051

Why do women have more wrinkles ?

- **Skin wrinkles result from a reduction of collagen content in the dermis.**
- **There is a decline in collagen content in skin and bone by hypo-estrogenism after menopause.**
- **Decrease of skin collagen due to estrogen deficiency in postmenopausal women may aggravate the severity of wrinkles.**

Facial wrinkling was increased with menopausal age in Korean women

Menopausal age	Wrinkled subjects No.(%)	POR	95%C.I
-5	10(40.0)	1.0	
6-10	13(76.4)	5.070	0.985-26.064
11+	36(80.0)	3.909	1.071-14.275

Table 1. Prevalence odds ration of menstrual, lactational, and reproductive factors related to wrinkle risk in Korean women

Characteristics	wrinkled(%)	POR	95% CI
Age at menarche			
-14	7(35.0)	1.0	
15-18	74(64.9)	3.389	0.593-19.365
19 +	19(78.0)	4.727	0.547-40.882
Age at menopause			
- 44	24(38.1)	1.0	
45-49	24(85.7)	3.557	0.565 - 22.398
50+	52(75.3)	1.162	0.324 - 4.170
Age at first full term pregnancy			
-21	38(77.5)	1.0	
22-26	51(68.9)	3.442	0.823-14.391
27+	11(29.7)	0.577	0.090-3.712
History of HRT			
No	92(65.7)	1.0	
Yes	8(44.4)	0.211	0.047-0.949
Menstrual regularity			
Irregular	34(55.7)	1.0	
Regular	67(53.6)	0.716	0.224-2.288
Menopausal status			
Premenopausal	1(1.8)	1.0	
Postmenopausal	100(75.7)	5.001	0.370-67.662
History of full term pregnancy			
No	1(6.2)	1.0	
Yes	100(62.5)	2.364	0.018-310.874
Number of full term pregnancy /unit		1.835	1.017-3.314
History of breast feeding			
No	3(23.0)	1.0	
Yes	96(66.2)	0.090	0.003-2.649

Increased number of full term pregnancies may result in lowered estrogen levels in multiparous women.

1. **Parous women develop higher levels of sex hormone-binding globulin and lower levels of free (non-protein-bound) estradiol.**
2. **Progesterone, which is also produced excessively during pregnancy, may antagonize the estrogen effects on the skin.**
3. **Lactation delays the return of ovulation after pregnancy, which result in lowered estrogen production.**

Smoking and Photoaging in Asian

- **SMOKER'S FACE**
  - Prominent wrinkles
  - Gauntness
  - An atrophic, pigmented skin
  - Slightly red complexion
- Smoking causes premature aging and wrinkling in Caucasians.
- Smoking plays no role in wrinkling in Blacks.

- Asian skin : ?

Prevalence odds ratios for severe wrinkling adjusted for age, sex, and sun exposure

Characteristics	Wrinkled subjects N(%)	Prevalence odds ratio	95% C.I	P-value for trend
Cigarette(pack-year)				
0-0.9	194(40.72)	1.00		
1-29.9	99(40.40)	1.50	0.69-3.27	
30+	114(63.16)	2.83	1.25-6.44	0.0085
50+	53(79.63)	5.53	1.96-15.60	0.0020

Chung et al. Arch Dermatol 2001;137:1043-1051

Combined Effects of Cigarette Smoking and Sun-exposure on Wrinkles

	Wrinkled Subjets n (%)	Odd Ratio	95% CI
Neither	66 (27.27)	1	
Smoking only	65 (21.54)	1.820	0.608-5.449
Sun exposure	106 (57.55)	5.514	2.366-12.850
Both	140 (70.00)	11.054	4.184-29.207

Chung et al. Arch Dermatol 2001;137:1043-1051

Skin color and wrinkles in Asians

Skin color: Risk factors for skin cancer and photoaging

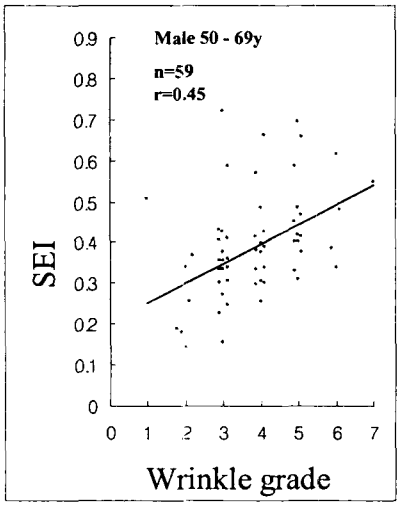
Constitutive pigmentation

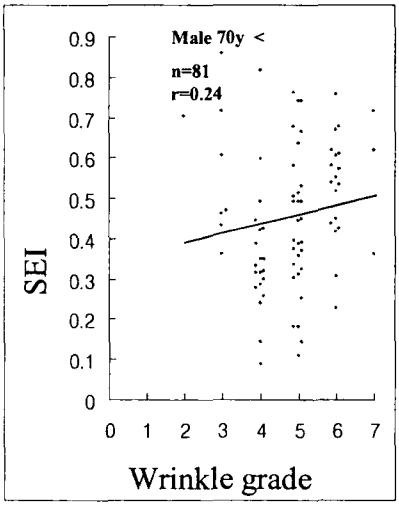
Facultative pigmentation

Sun Exposure Index (SEI):

$$SEI = \frac{\text{Facultative pigmentation-constitutive pigmentation}}{\text{Constitutive pigmentation}}$$

Relationship between wrinkle grade and SEI_{face}

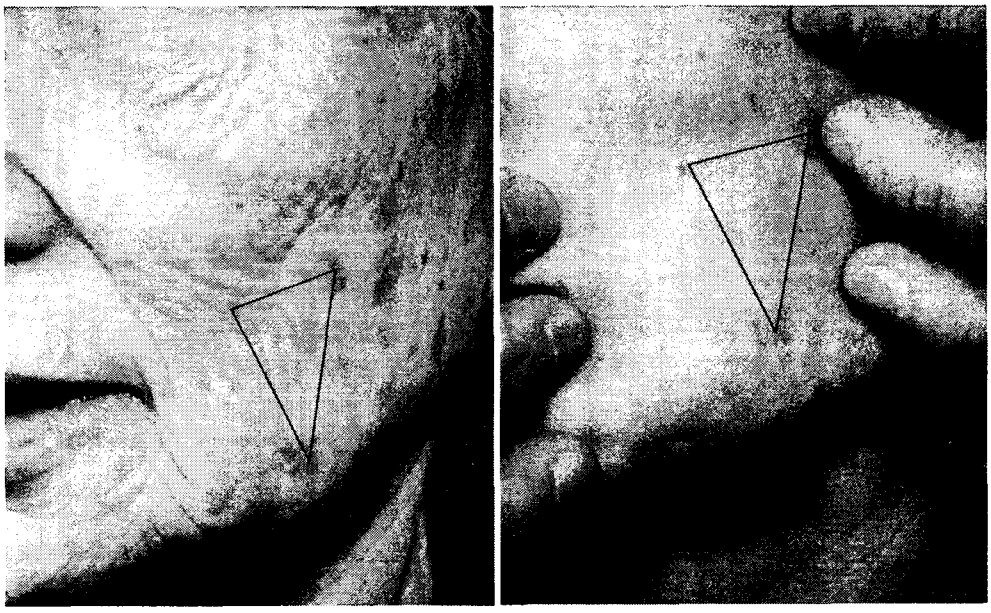




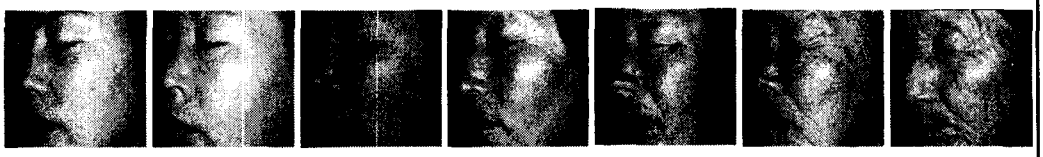
Risk factors of wrinkles in Asian skin

1. Age
2. Sun-exposure (UV, Heat)
3. Female :
   - Menopause
   - Pregnancy
   - Hormone replacement trapy (HRT)
4. Smoking
5. Skin color

노인 노출부에서의 주름살의 원인은?: 교원질 결핍, 탄력성 감소



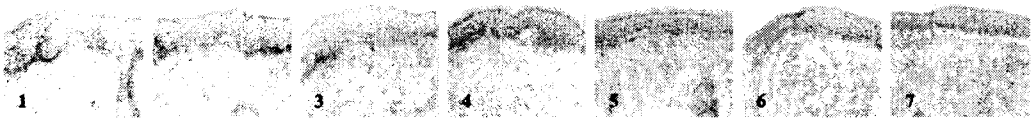
광노화된 피부: 교원질의 결핍이 주름살의 원인?



Procollagen type I (SP1.D8)

A. Sun-protected skin (Buttock)

B. Sun-exposed skin (Face)



Skin Wrinkling

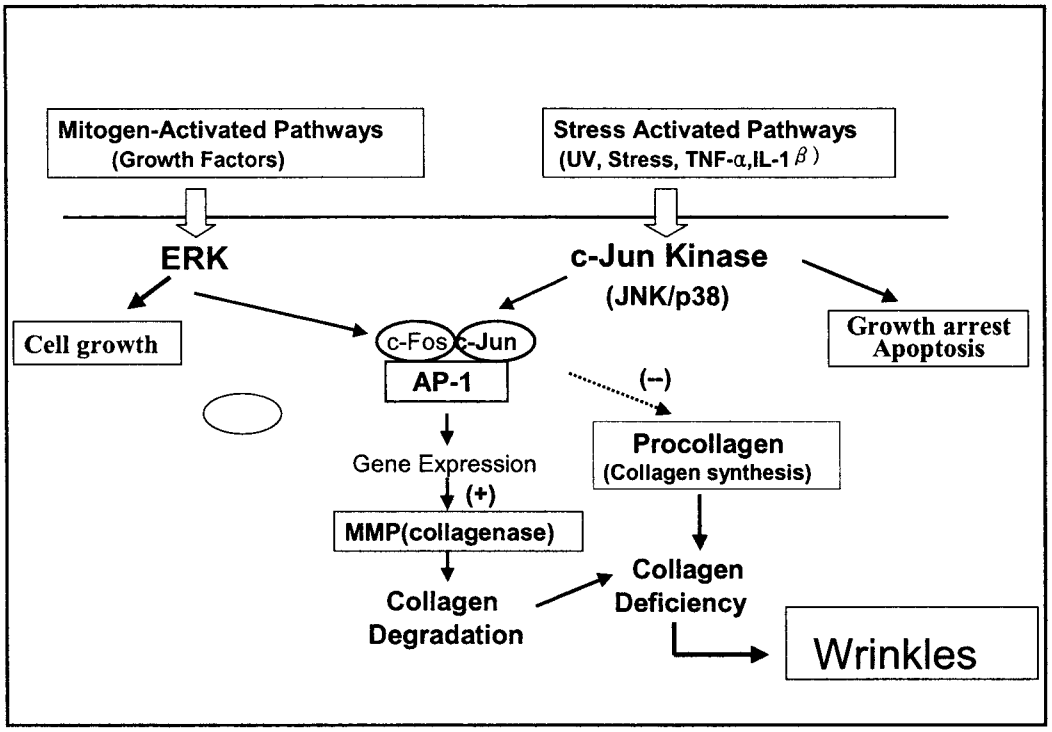
UV/ Aging

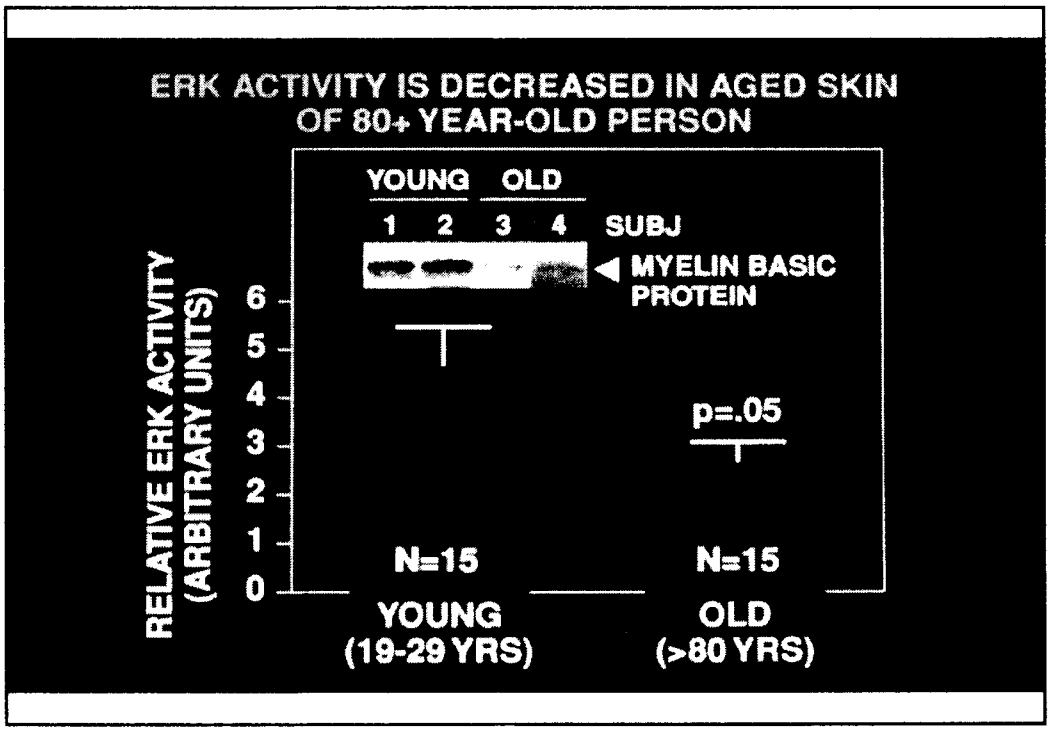
MMP (degradation) ⇧

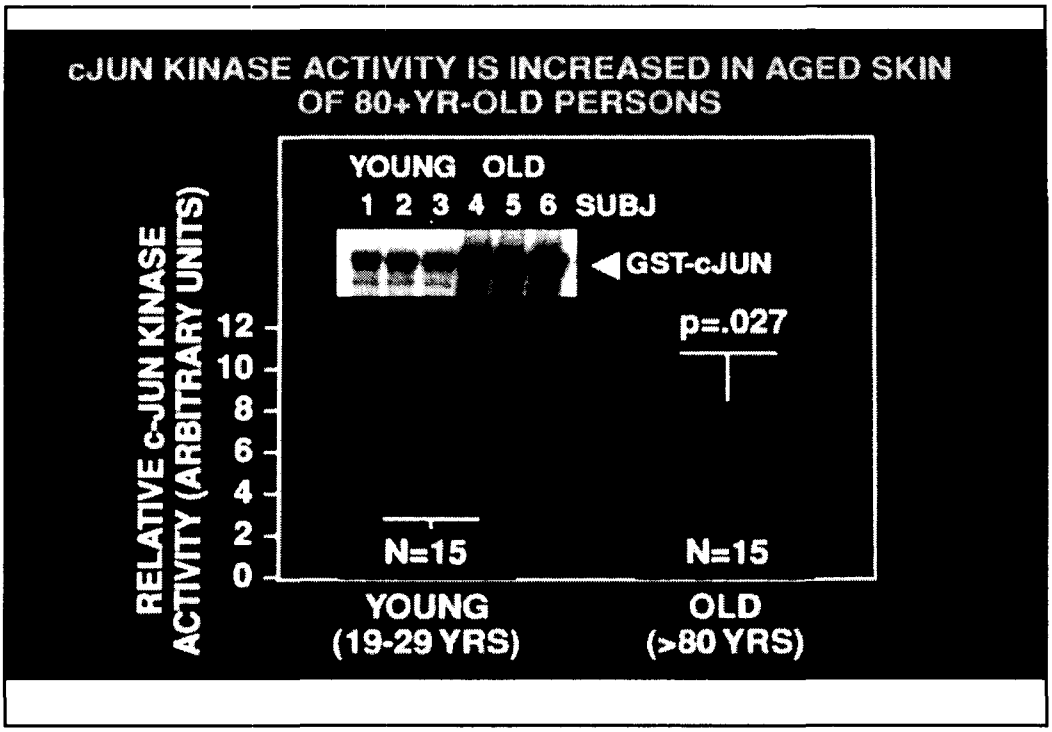
Procollagen (synthesis) ⇩

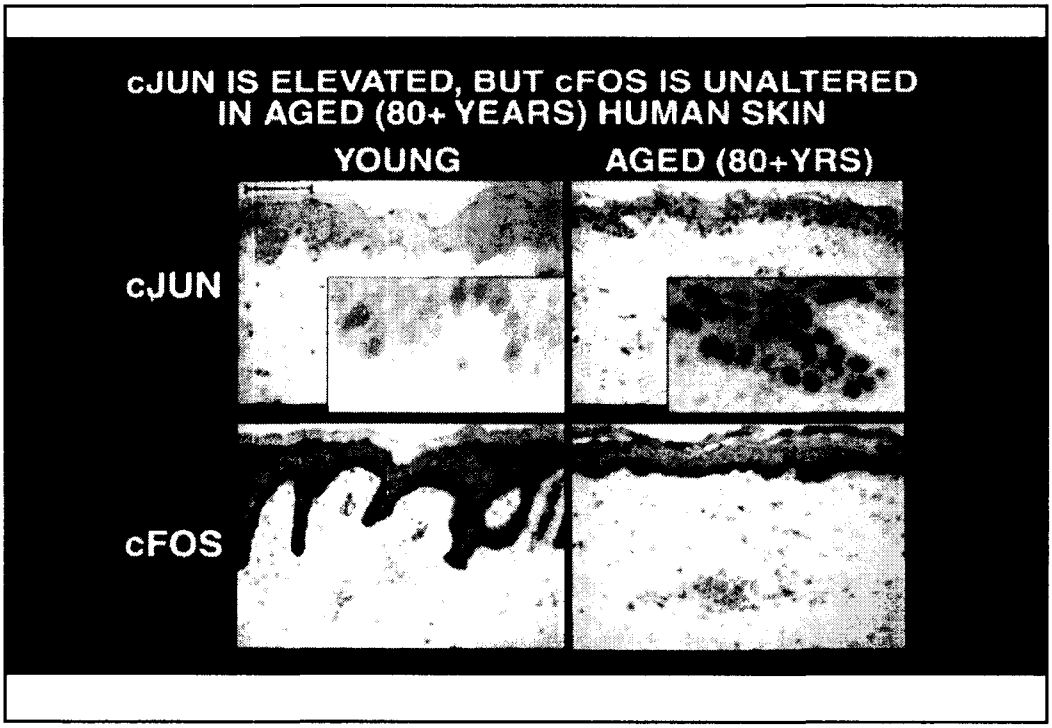
UV

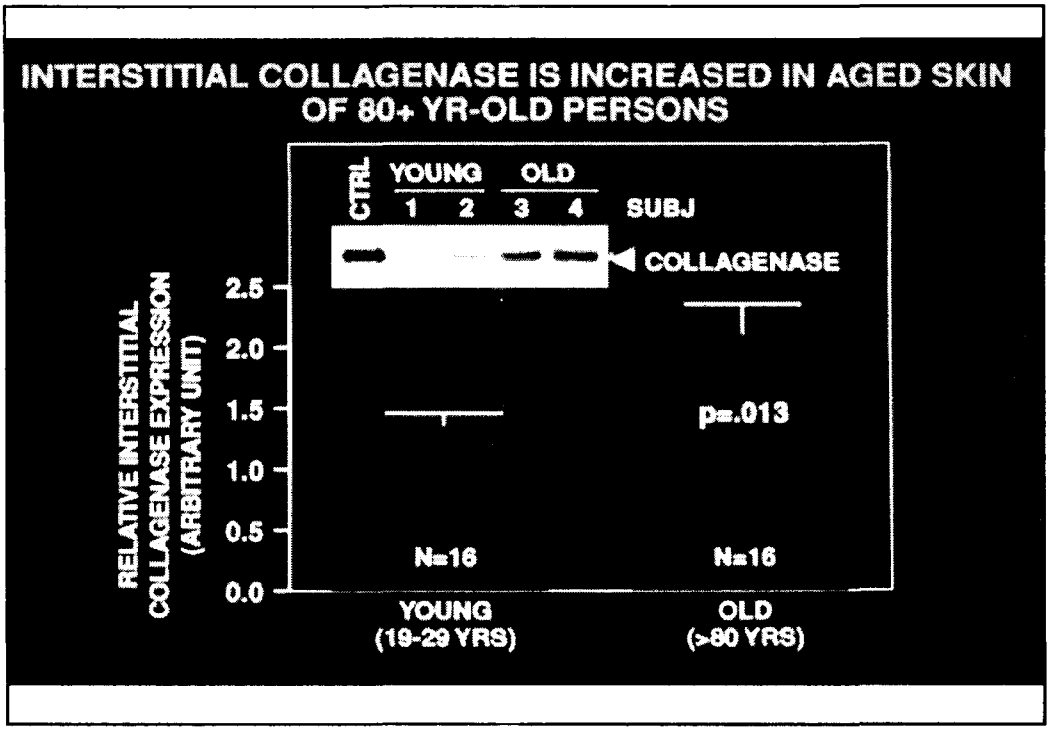
Intrinsic aging ⇨ **Collagen Deficiency** ⇨ **Wrinkles**

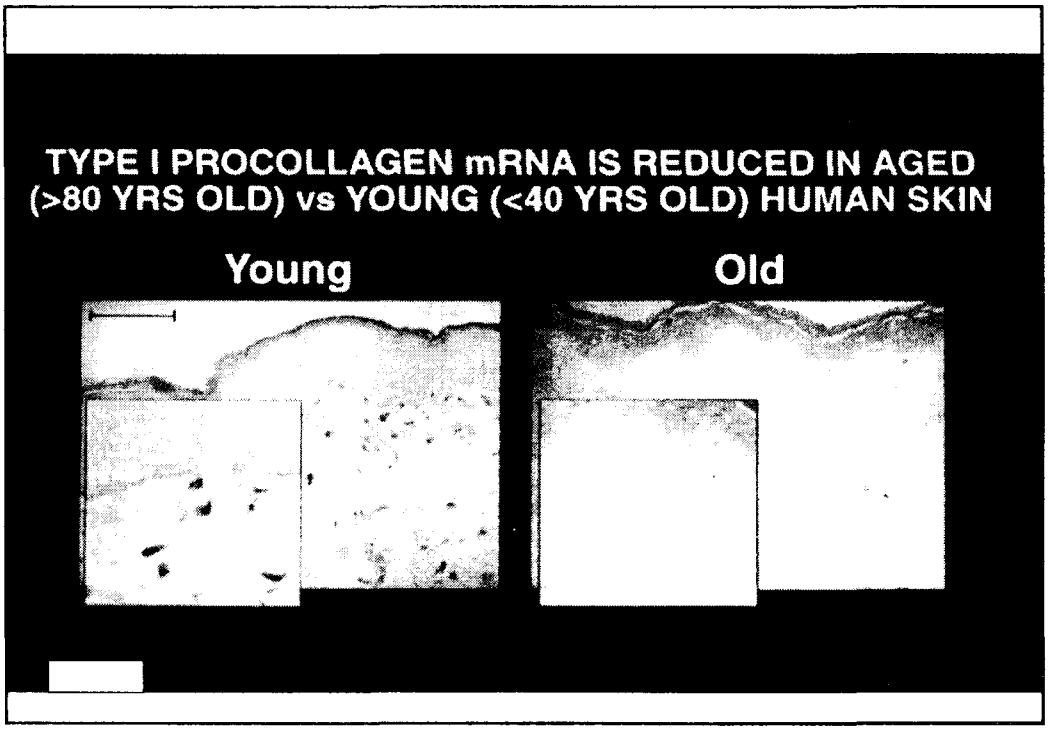

Mitogen-Activated Pathways
(Growth Factors)
Stress Activated Pathways
(UV, Stress, TNF-α,IL-1β)
ERK
c-Jun Kinase
(JNK/p38)
Cell growth
c-Fos
c-Jun
AP-1
Growth arrest
Apoptosis
(--)
Procollagen
(Collagen synthesis)
Gene Expression
(+)
MMP(collagenase)
Collagen
Degradation
Collagen
Deficiency
Wrinkles


ERK ACTIVITY IS DECREASED IN AGED SKIN
OF 80+ YEAR-OLD PERSON
YOUNG
OLD
1 2 3 4
SUBJ
MYELIN BASIC
PROTEIN
RELATIVE ERK ACTIVITY
(ARBITRARY UNITS)
6
5
4
3
2
1
0
p=.05
N=15
N=15
YOUNG
(19-29 YRS)
OLD
(>80 YRS)

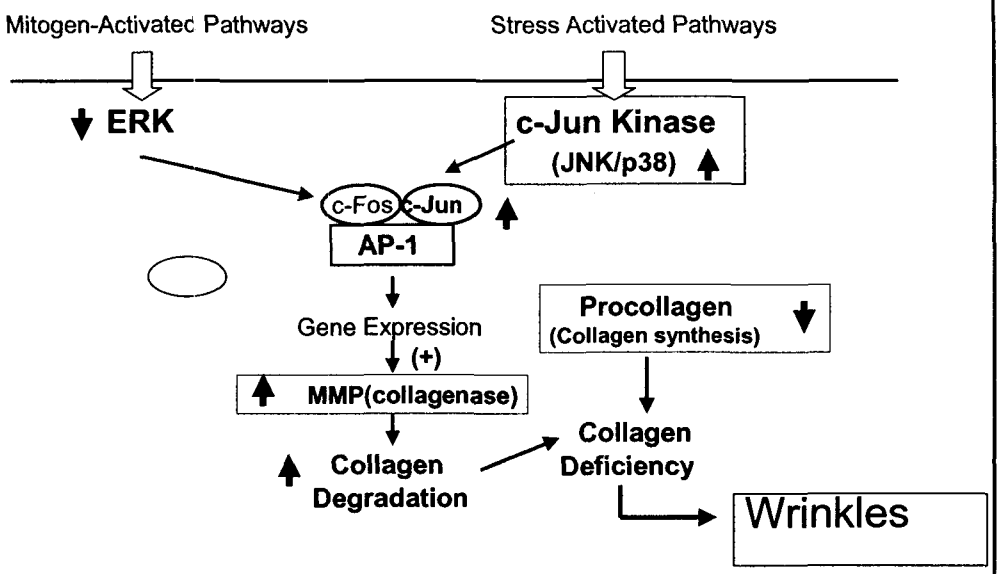

cJUN KINASE ACTIVITY IS INCREASED IN AGED SKIN
OF 80+YR-OLD PERSONS
YOUNG OLD
1 2 3 4 5 6 SUBJ
GST-cJUN
p=.027
RELATIVE c-JUN KINASE
ACTIVITY (ARBITRARY UNITS)
12
10
8
6
4
2
0
N=15
N=15
YOUNG
(19-29 YRS)
OLD
(>80 YRS)


cJUN IS ELEVATED, BUT cFOS IS UNALTERED
IN AGED (80+ YEARS) HUMAN SKIN
YOUNG
AGED (80+YRS)
cJUN
cFOS


INTERSTITIAL COLLAGENASE IS INCREASED IN AGED SKIN OF 80+ YR-OLD PERSONS
CTRL
YOUNG
OLD
1
2
3
4
SUBJ
COLLAGENASE
RELATIVE INTERSTITIAL COLLAGENASE EXPRESSION (ARBITRARY UNIT)
2.5
2.0
1.5
1.0
0.5
0.0
p=.013
N=16
N=16
YOUNG (19-29 YRS)
OLD (>80 YRS)


TYPE I PROCOLLAGEN mRNA IS REDUCED IN AGED (>80 YRS OLD) vs YOUNG (<40 YRS OLD) HUMAN SKIN
Young
Old

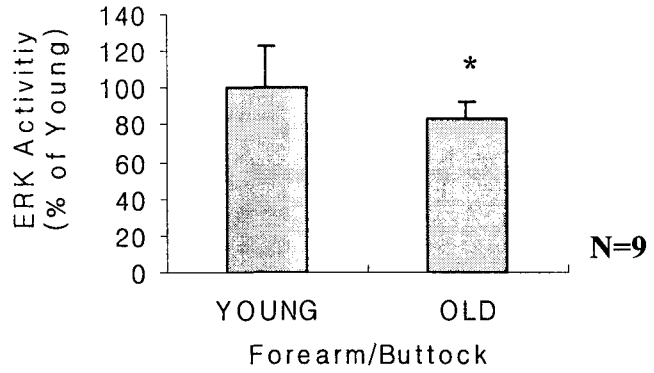
Intrinsic Skin Aging



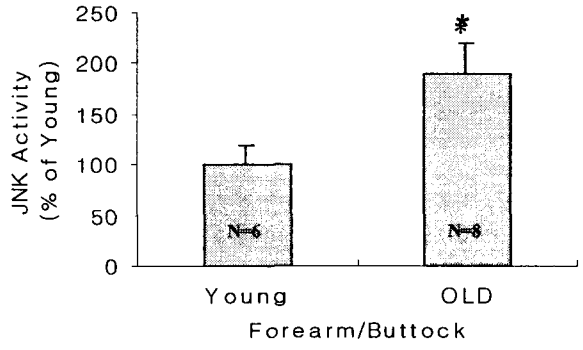
JH Chung et al: J Invest Dermatol 114;117-182, 2000

Why does the photoaged skin have more wrinkles?

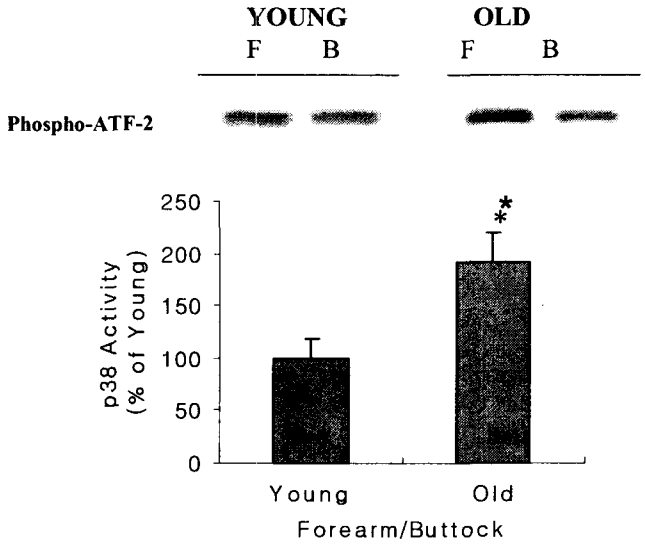
ERK Activity was lower in photoaged skin than intrinsically aged skin of same individual



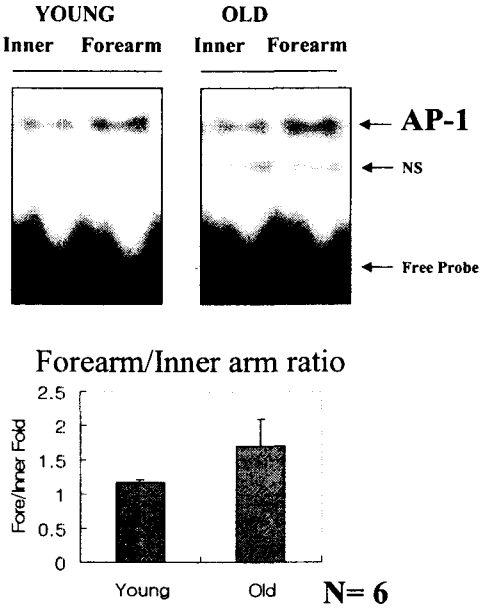
JNK Activity was higher in photoaged skin than intrinsically aged skin of same individual



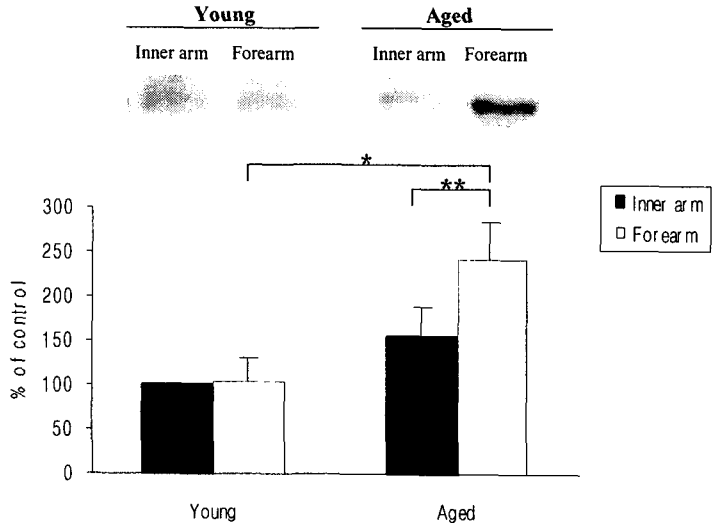
p38 activity was higher in photoaged skin than intrinsically aged skin of same individual



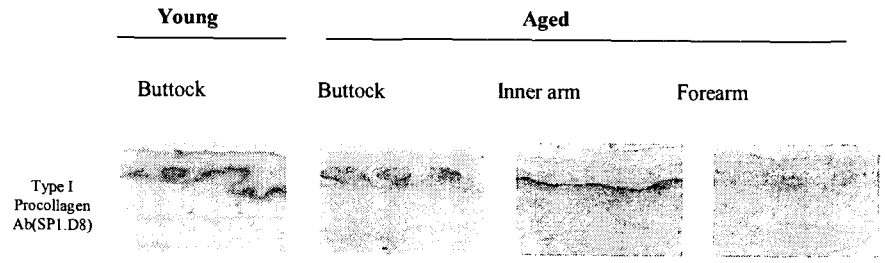
AP-1 DNA binding activity was increased in photoaged skin



MMP-1 Expression was higher in photoaged skin

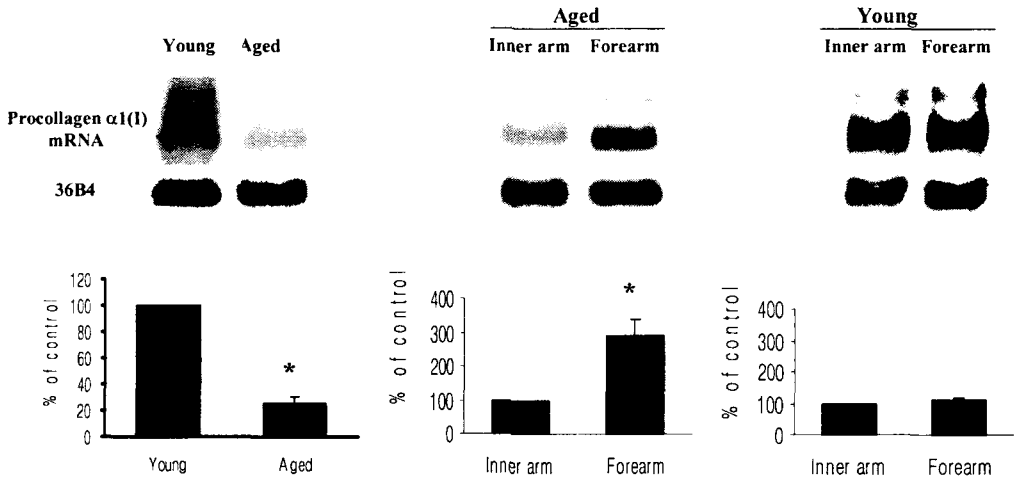


Chung JH; J Invest Dermatol 117;1218, 2001



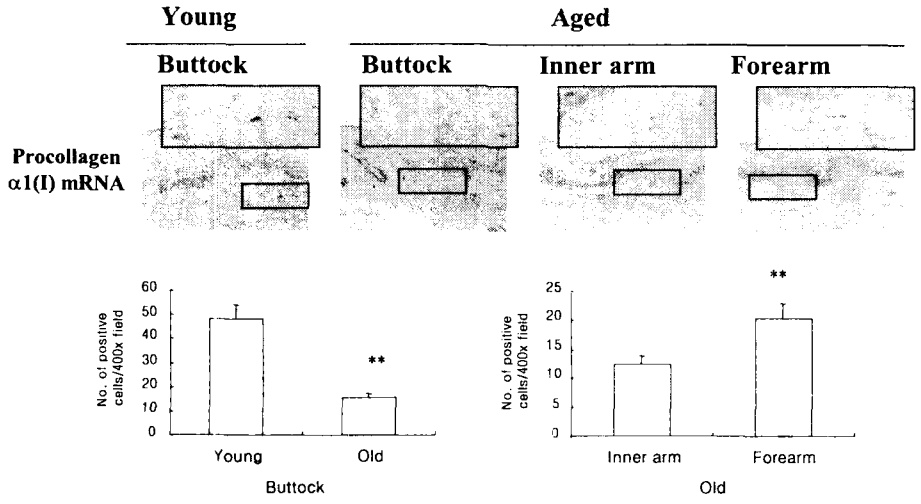
Chung JH; J Invest Dermatol 117;1218, 2001

The expressions of type I procollagen mRNA were higher in the photoaged skin than in the chronologically aged skin.

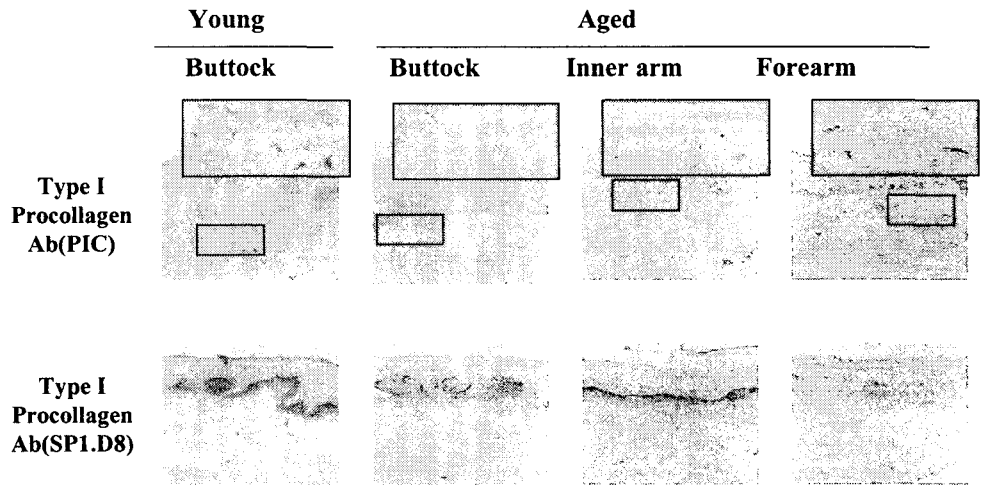


Chung et al: J Invest Dermatol 2001;117:1218-1224

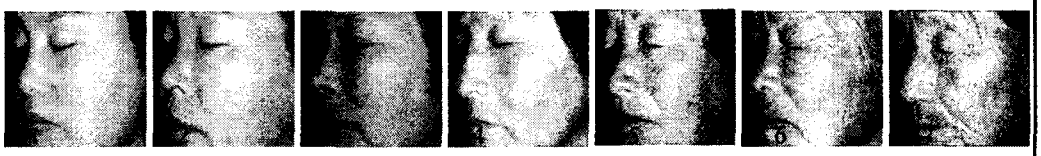
Procollagen α1(I) mRNA synthesis was increased in photoaged skin compared with naturally aged skin.



Type I procollagen protein synthesis was increased in photoaged skin compared with naturally aged skin.



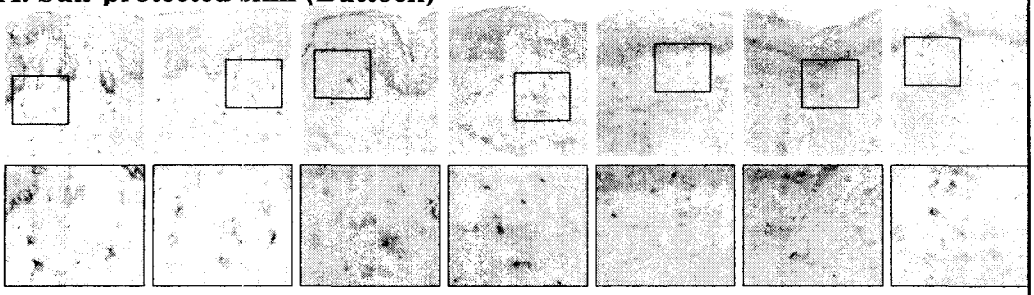
Photographic wrinkle grades



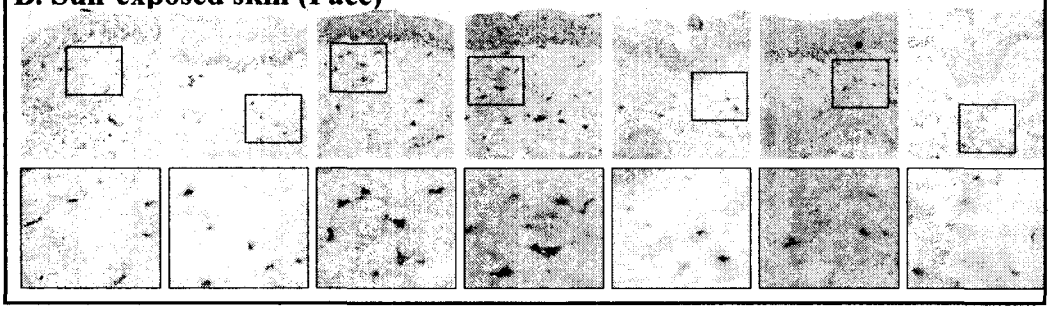
20y 30y 40y 50y 60y 70y 80y

Procollagen α1(I) mRNA

A. Sun-protected skin (Buttock)

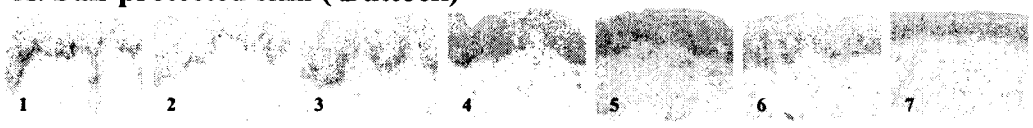


B. Sun-exposed skin (Face)

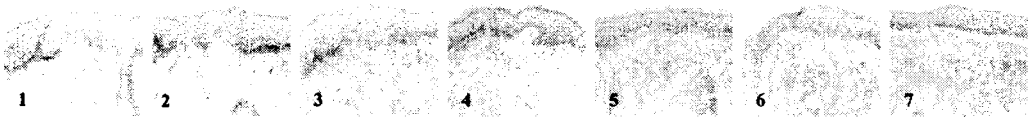


Type I Procollagen protein

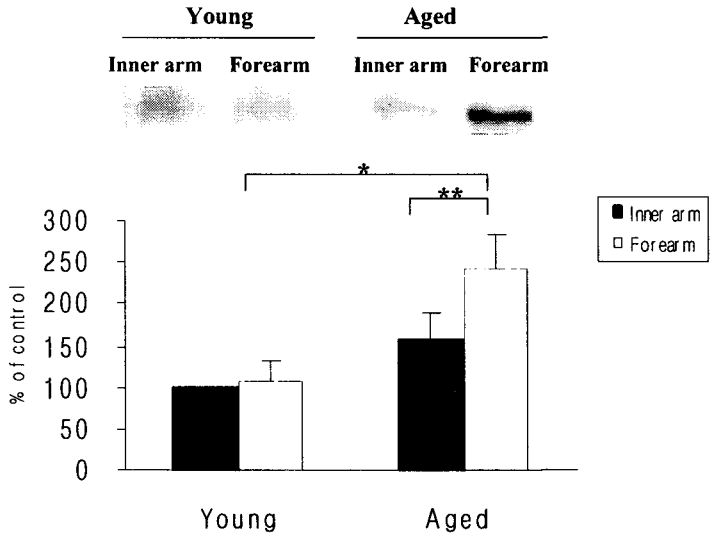
A. Sun-protected skin (Buttock)



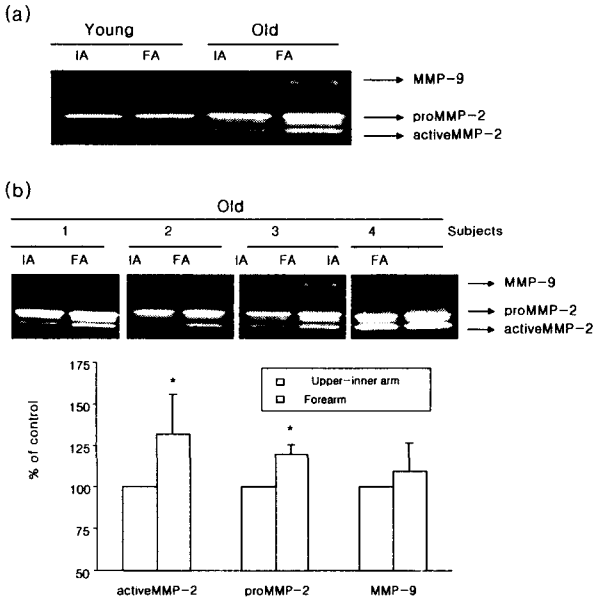
B. Sun-exposed skin (Face)



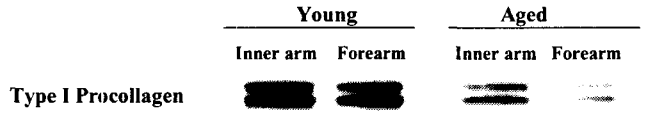
The level of MMP-1 protein was higher in the dermis of photoaged human skin in vivo.

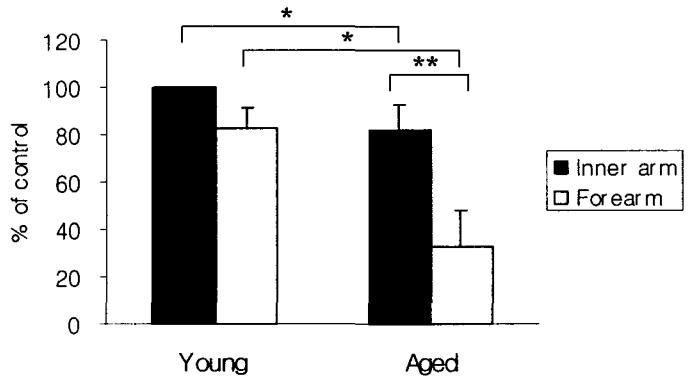


Gelatinase activity was increased in the dermis of photoaged human skin in vivo.



Type I procollagen protein
in photoaged skin was lower than in the naturally aged skin.





Natural aging

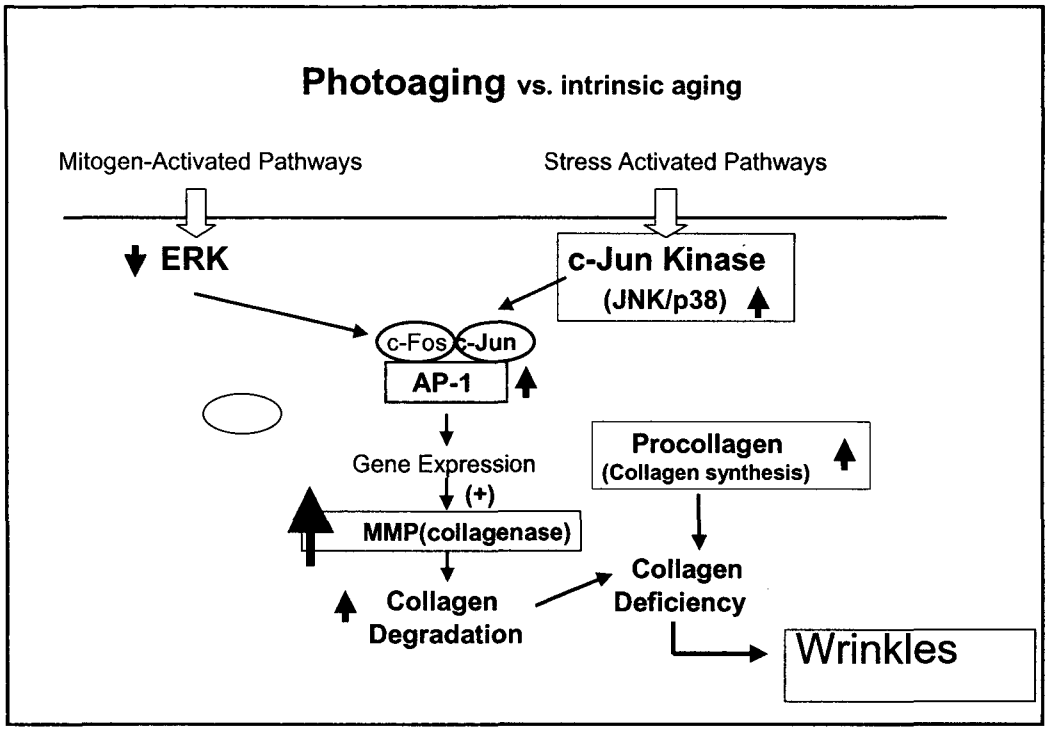
Procollagen synthesis: ⇩

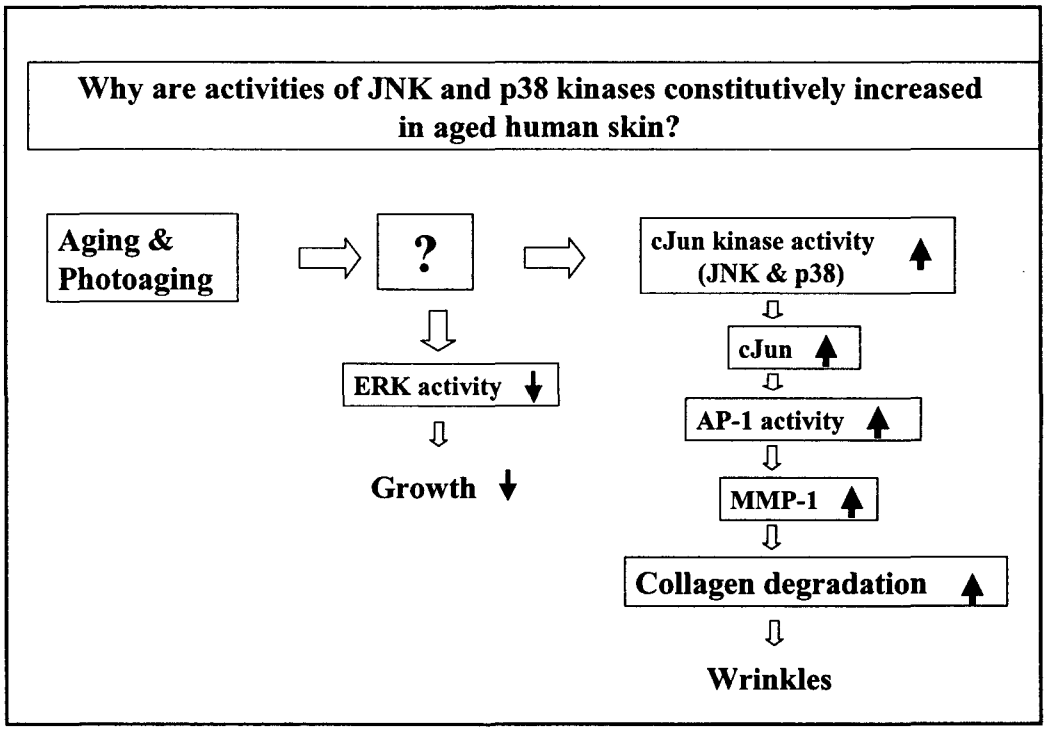
MMP: ⇧

Photoaging

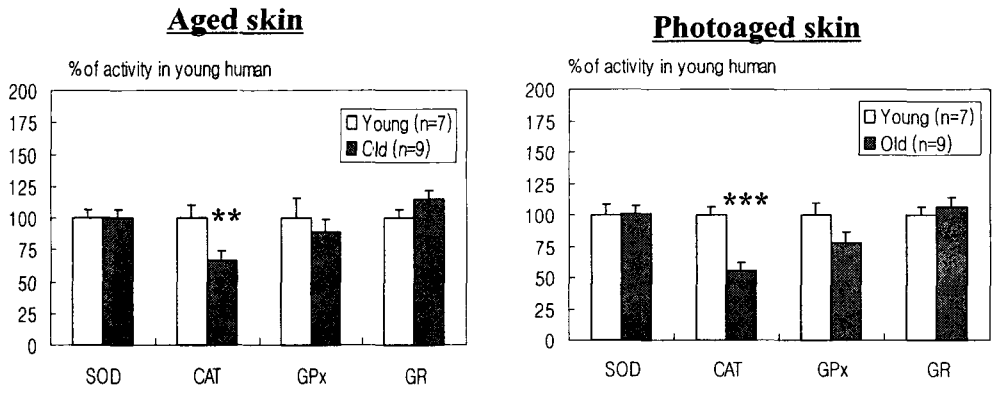
Procollagen synthesis: ⇧

MMP : ⇧

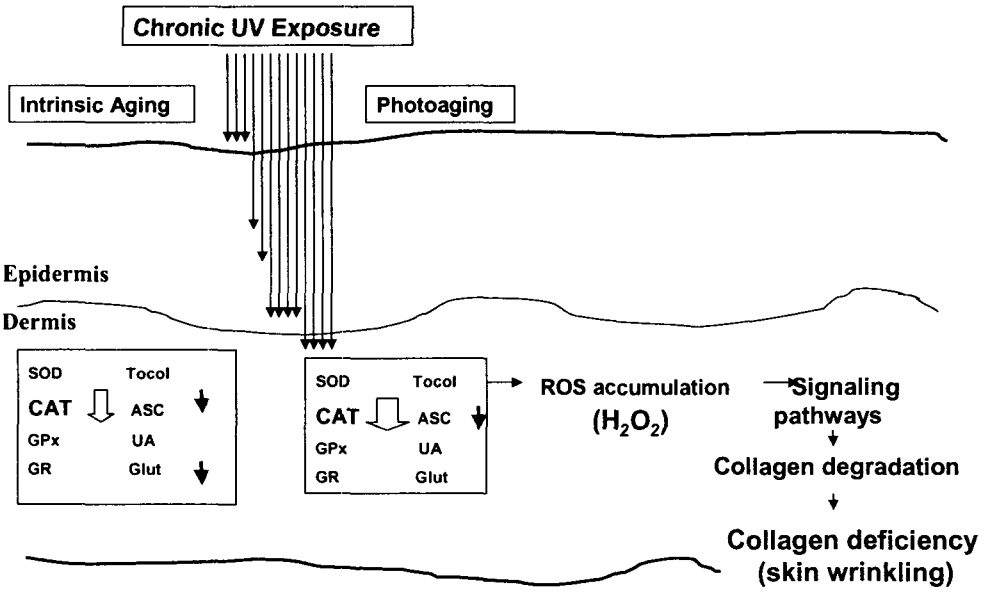

Photoaging vs. intrinsic aging
Mitogen-Activated Pathways
Stress Activated Pathways
ERK
c-Jun Kinase
(JNK/p38)
c-Fos
c-Jun
AP-1
Gene Expression
(+)
Procollagen
(Collagen synthesis)
MMP(collagenase)
Collagen
Degradation
Collagen
Deficiency
Wrinkles


Why are activities of JNK and p38 kinases constitutively increased in aged human skin?
Aging & Photoaging
?
ERK activity
Growth
cJun kinase activity (JNK & p38)
cJun
AP-1 activity
MMP-1
Collagen degradation
Wrinkles

Catalase is decreased in the dermis of aged and photoaged human skin

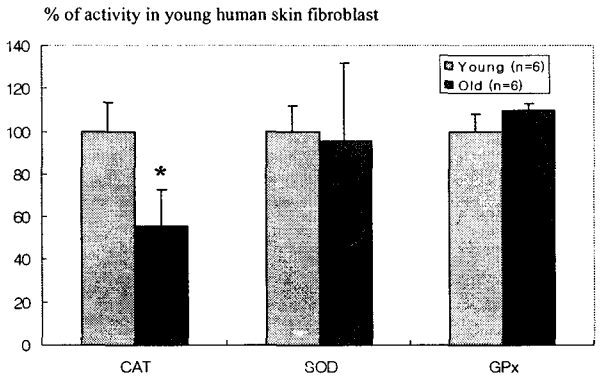


Rhie G, Chung JH: J Invest Dermatol 117:1212, 2001



Rhie G, Chung JH: J Invest Dermatol 117:1212, 2001

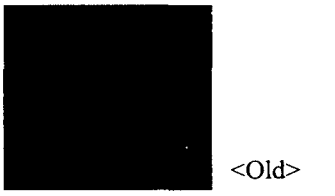
Major Antioxidant Enzyme Activities in Young and Old Human Skin Fibroblast



* P < 0.05

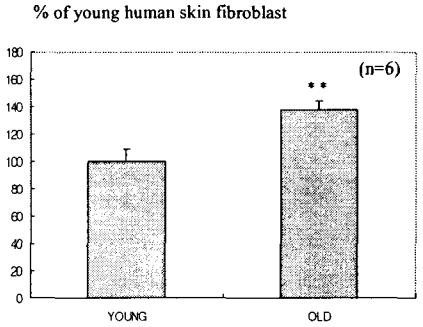
H_2O_2 Accumulation in Human Skin Fibroblasts

<Young>



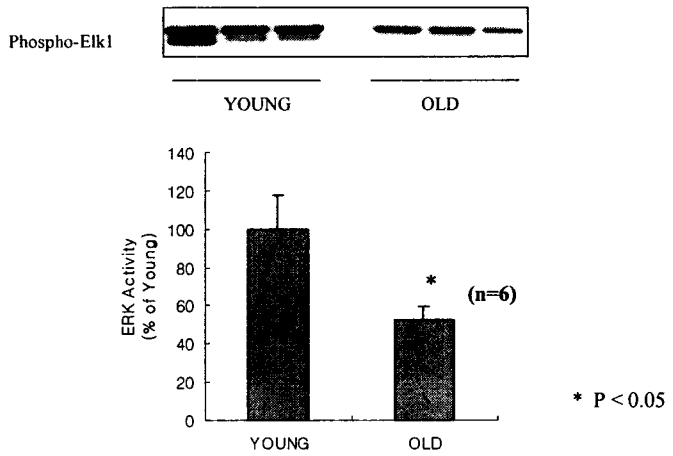
<Old>

DCF Staining

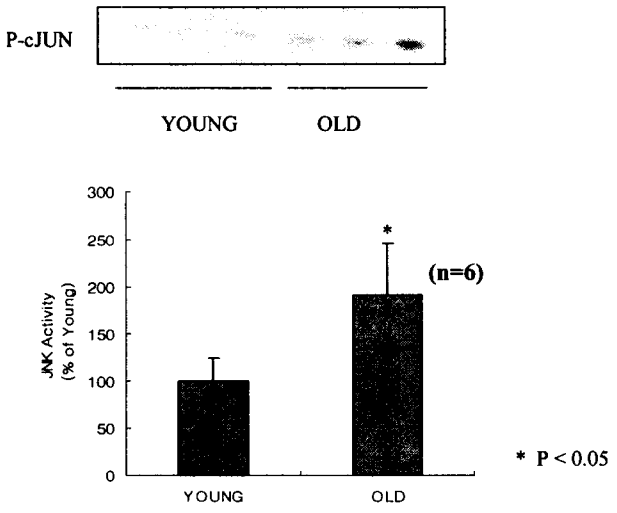


** P < 0.01

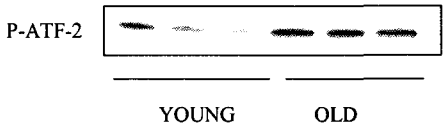
ERK Activity was decreased in old human skin fibroblasts



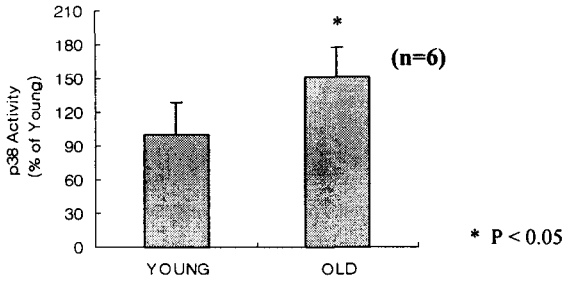
JNK Activity was Increased in Old Human Skin Fibroblast



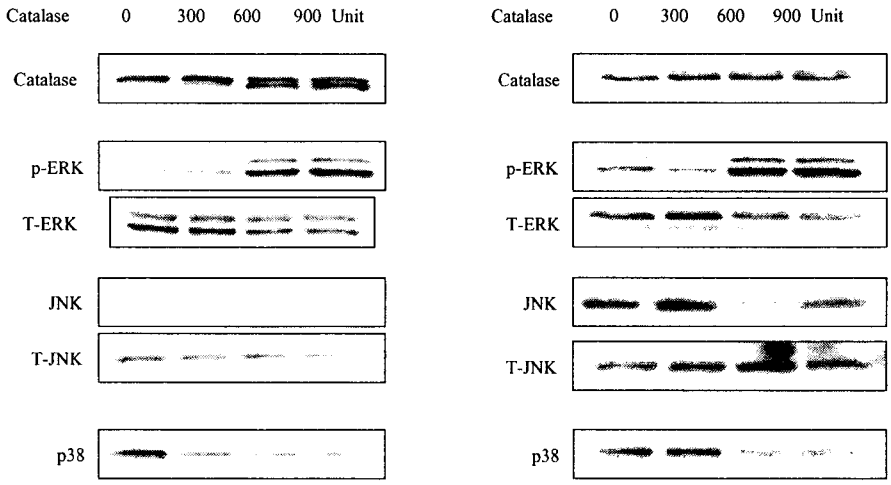
p38 Activity was Increased in Old Human Skin Fibroblast



YOUNG OLD

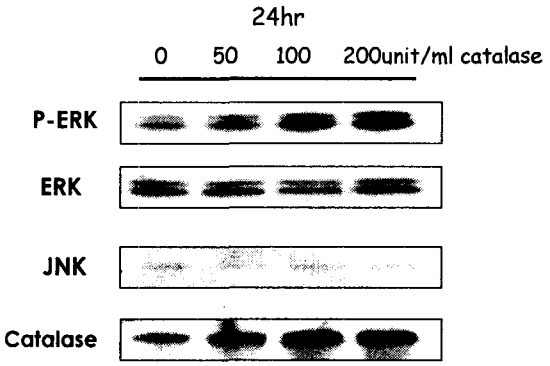


Catalase increased ERK activity, and decreased JNK/p38 kinase activities in aged fibroblasts

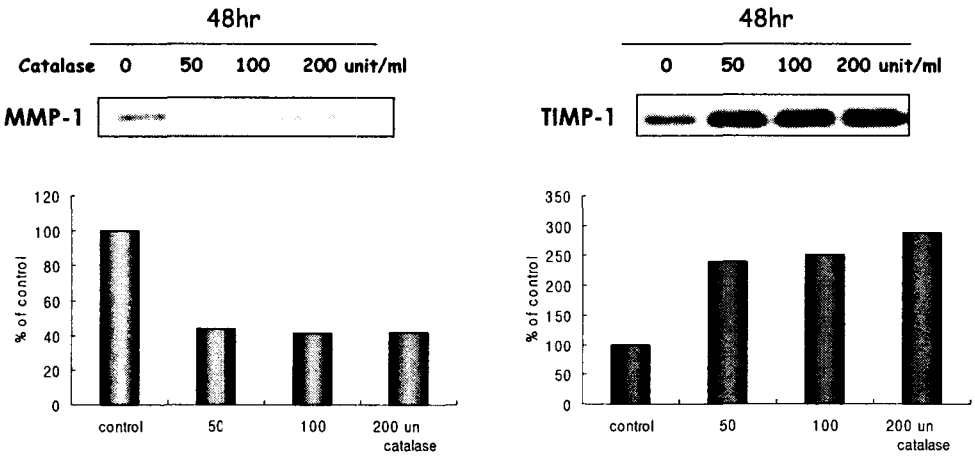


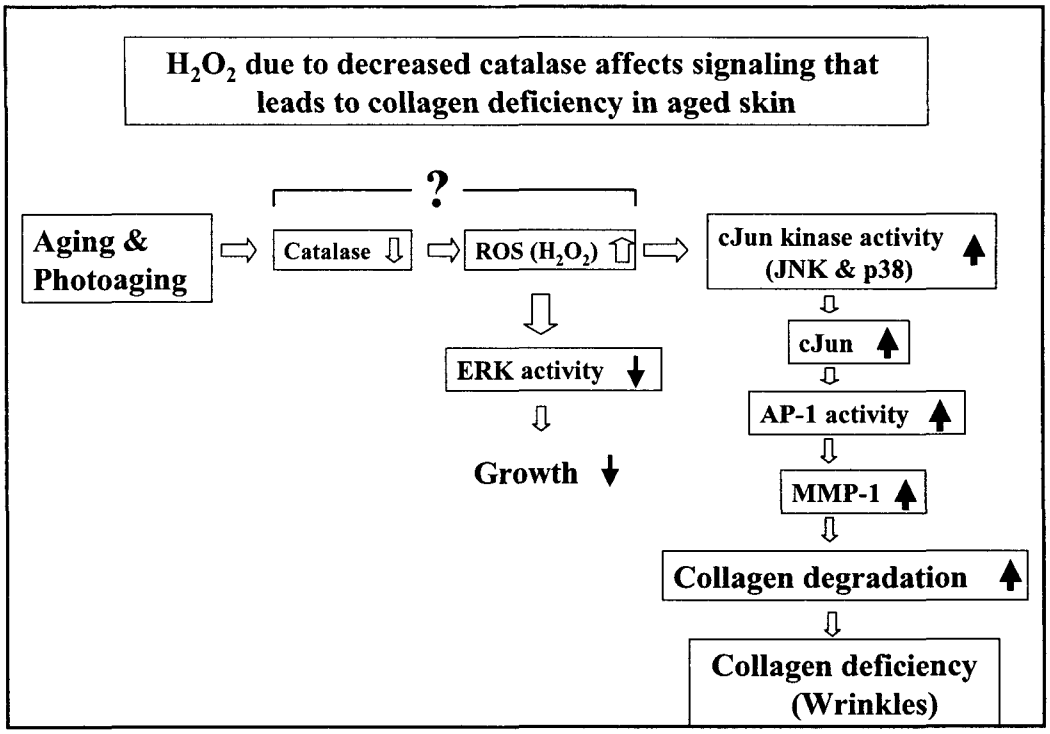
Subject 1 **Subject 2**

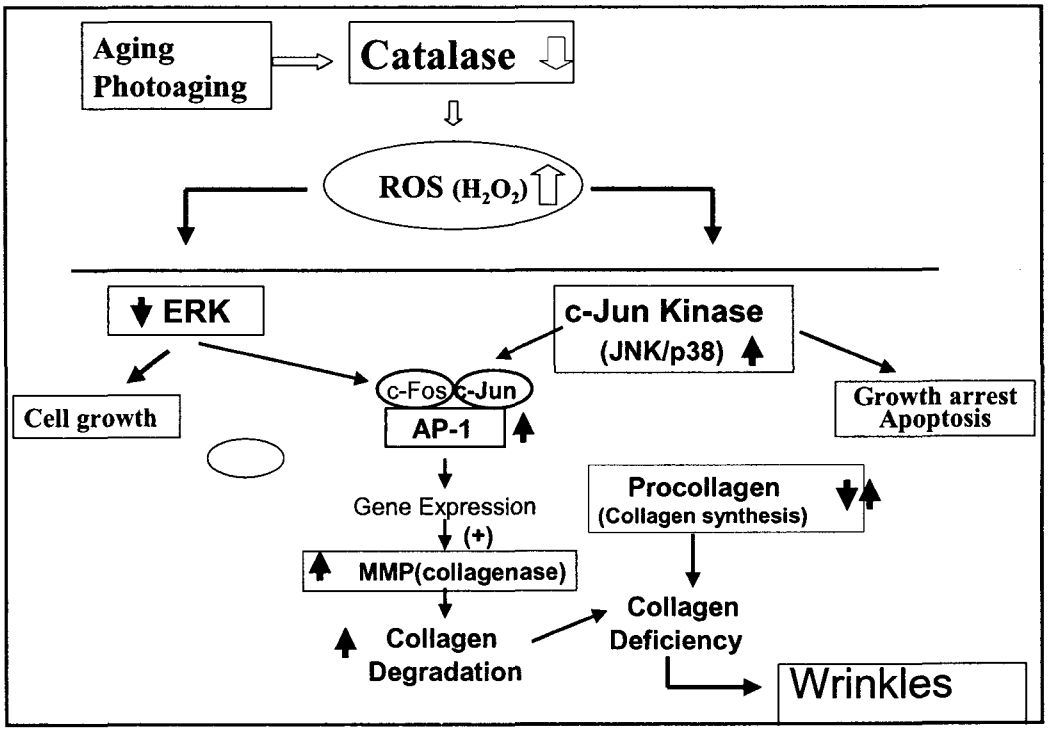
Catalase increased ERK activity, and decreased JNK kinase activities in aged fibroblasts



Catalase decreased MMP-1 expression and increased TIMP-1 expression in aged fibroblasts




H_2O_2 due to decreased catalase affects signaling that leads to collagen deficiency in aged skin
?
Aging & Photoaging
Catalase
ROS (H_2O_2)
cJun kinase activity (JNK & p38)
ERK activity
Growth
cJun
AP-1 activity
MMP-1
Collagen degradation
Collagen deficiency (Wrinkles)


Aging Photoaging
Catalase
ROS (H_2O_2)
ERK
c-Jun Kinase (JNK/p38)
Cell growth
c-Fos
c-Jun
AP-1
Growth arrest Apoptosis
Gene Expression
(+)
Procollagen (Collagen synthesis)
MMP(collagenase)
Collagen Degradation
Collagen Deficiency
Wrinkles

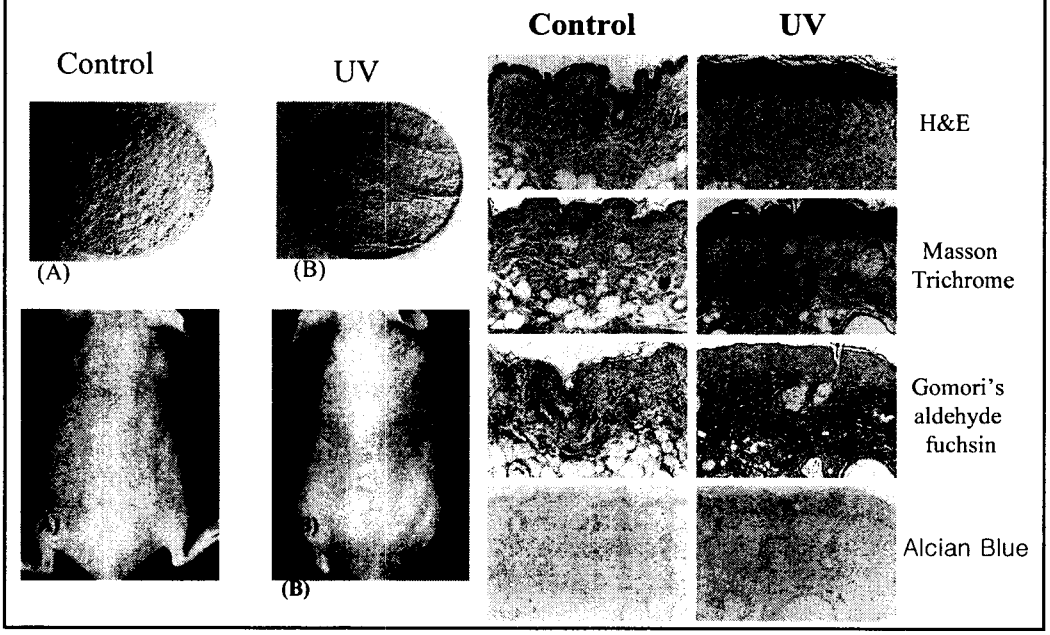
주름살이란 무엇인가?

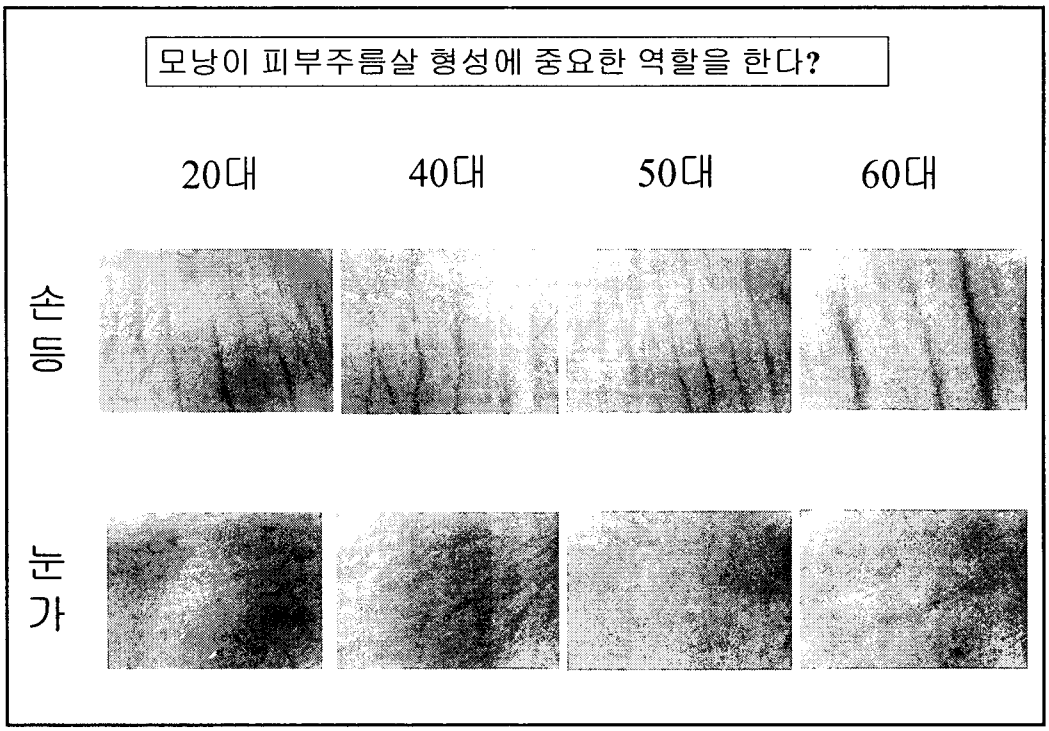
- 주름살은 교원질 결핍에 의한 결과인가?
- 주름살은 피부 탄력성이 없어져 생기는 것인가?

주름살의 조직학적 변화

- 주름살의 조직학적 변화는 무엇인가?
  *근육운동에 의한 주름살
  * 자외선에 의한 주름살

생쥐모델에서의 주름살의 원인은?: 교원섬유 증가, 탄력섬유이상?




모낭이 피부주름살 형성에 중요한 역할을 한다?
20대
40대
50대
60대
손등
눈가