Accelerated aging and cancer in ERCC1-XPF-deficient mouse models

Laura Niedernhofer, M.D., Ph.D.

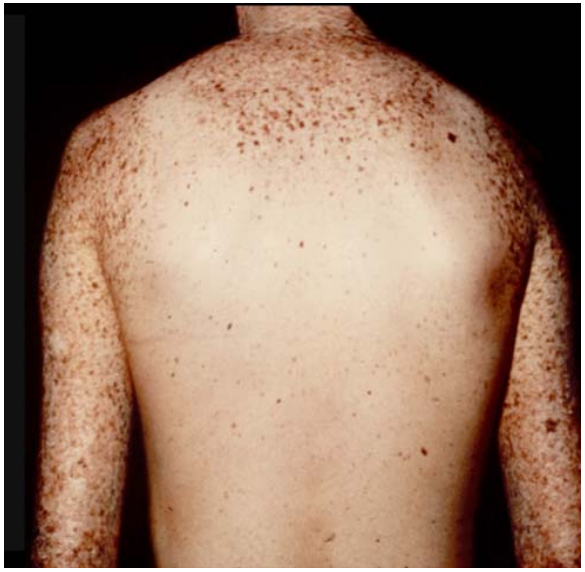
Department of Molecular Genetics and Biochemistry
University of Pittsburgh Cancer Institute

Outline

- Deficiency of ERCC1-XPF DNA repair endonuclease causes accelerated aging.
- New mouse models of ERCC1-XPF deficiency.
- Strategies to identify types of DNA damage that promote cancer and aging, and their sources.

Nucleotide **E**xcision **R**epair

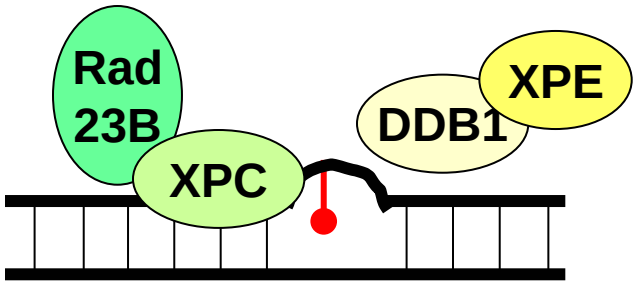
xeroderma pigmentosum



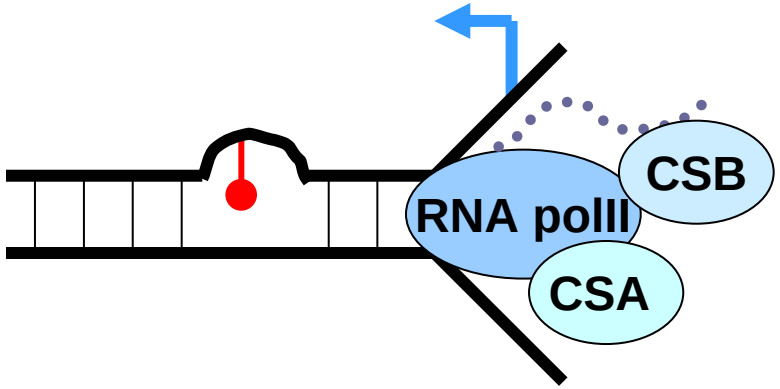
- photosensitivity
- pigmentation abnormalities
- atrophic skin
- skin cancer (>2000x↑)
- neurodegeneration
- 7 complementation groups

  XPA - XPG

NER: Damage recognition

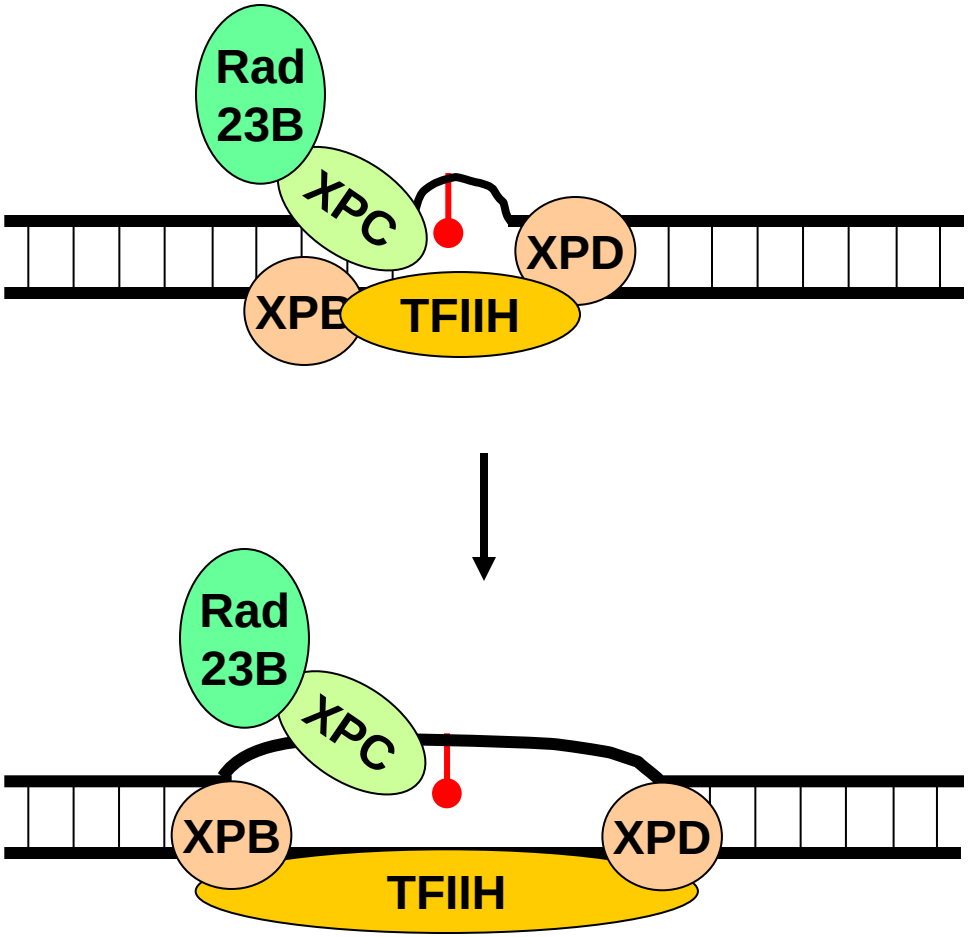


Global:
genome wide

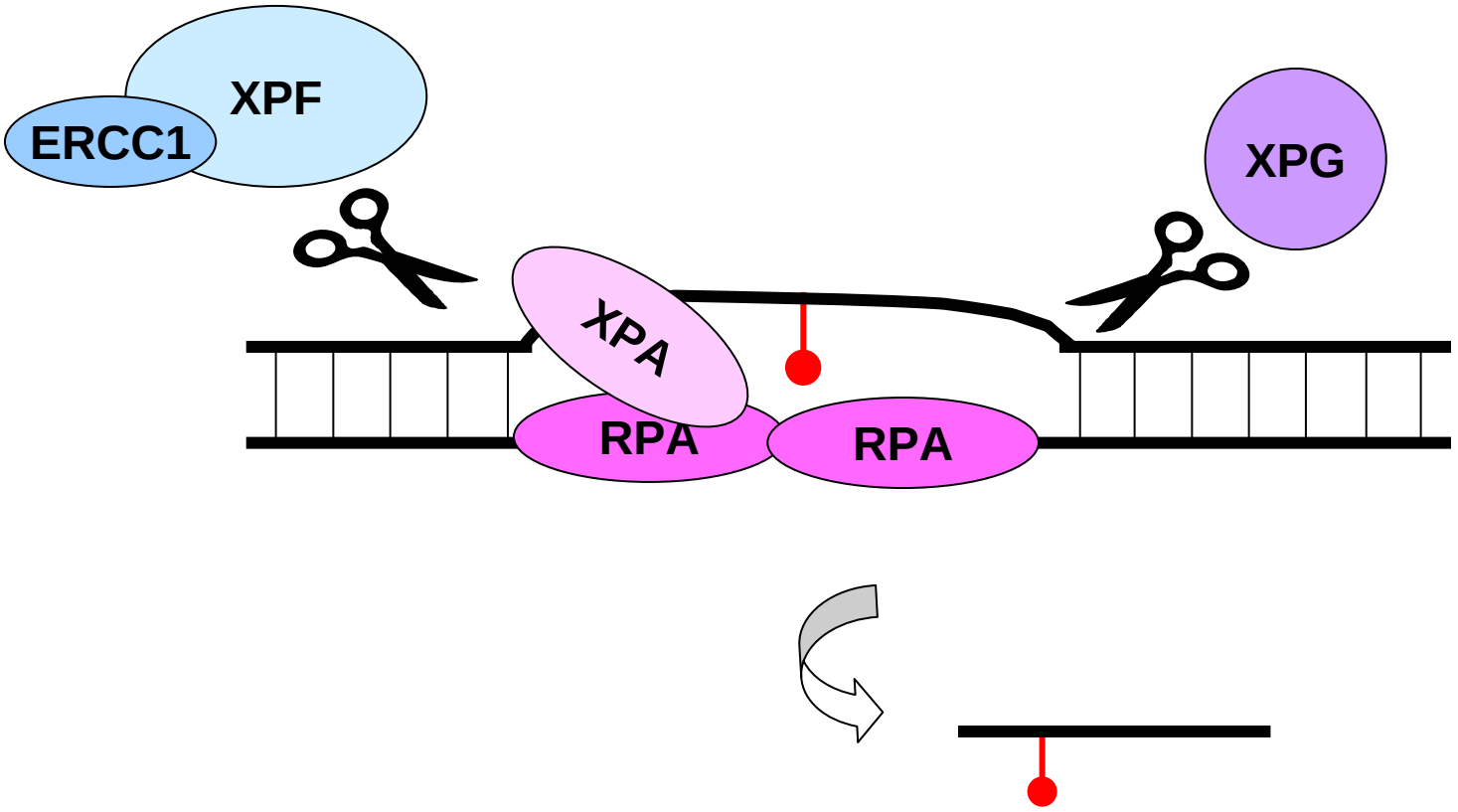


Transcription-coupled:
transcribed strand

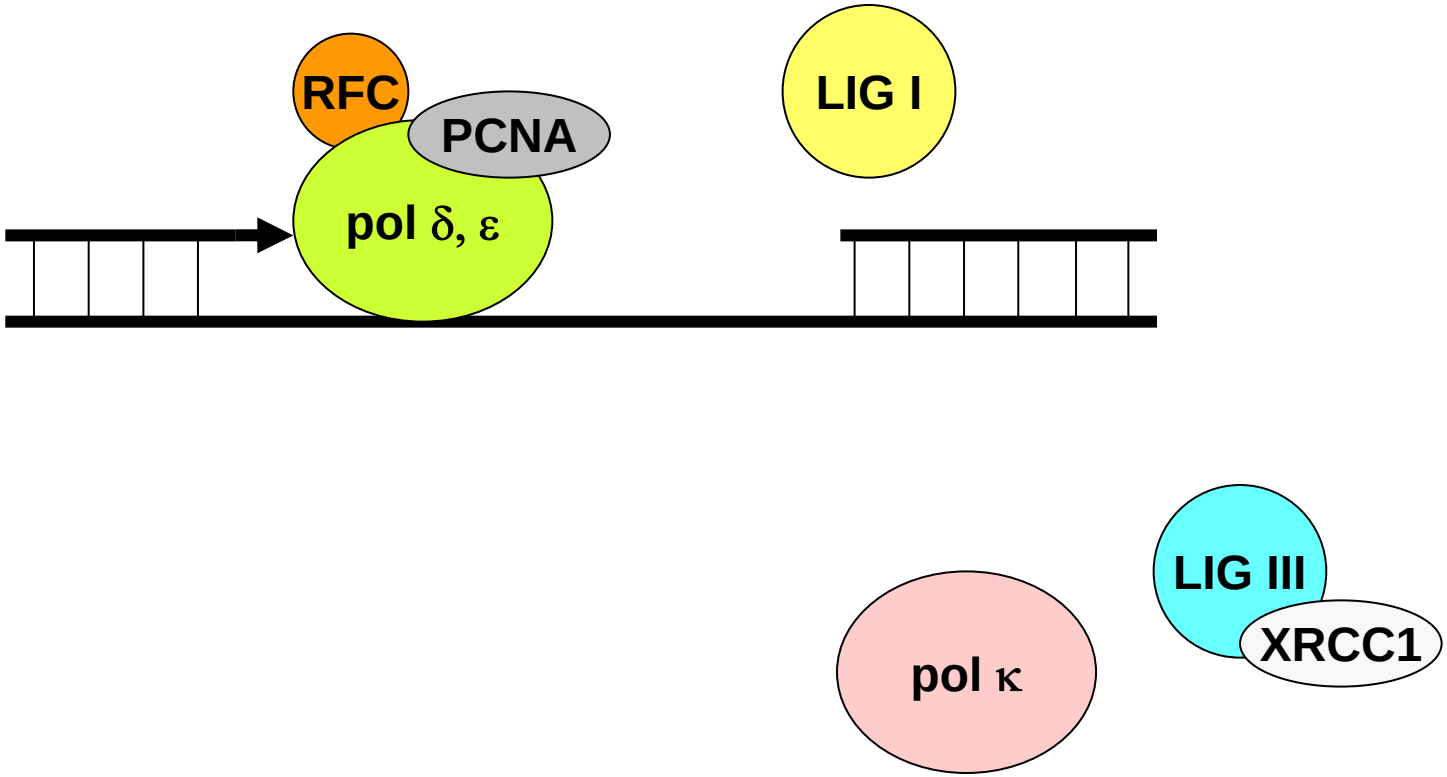
NER: Open complex formation



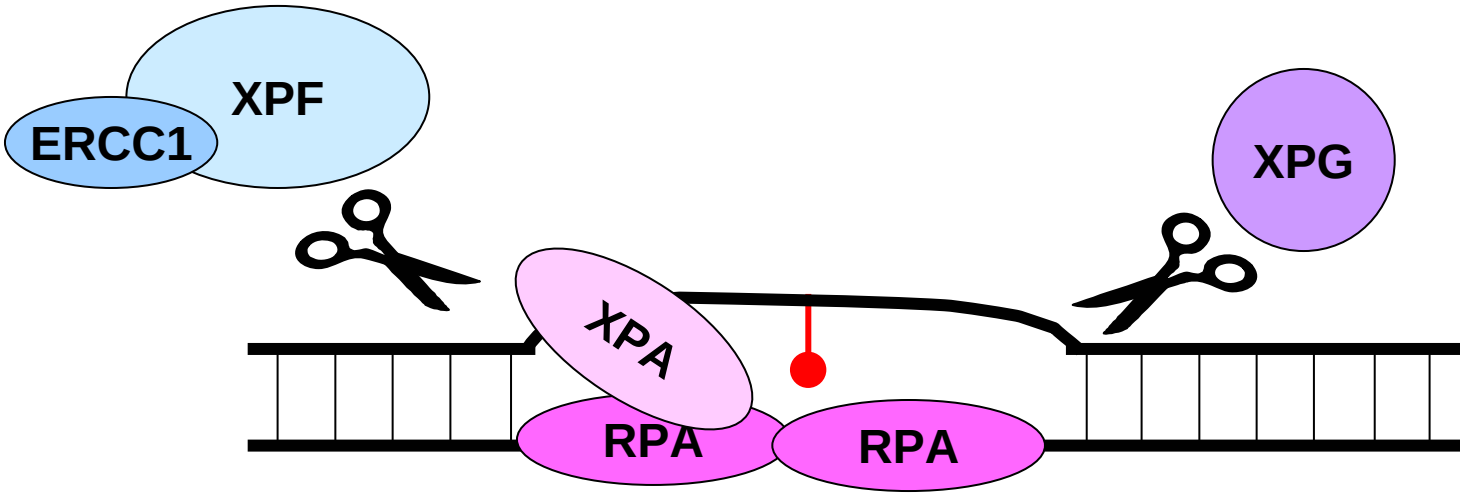
NER: Damage excision



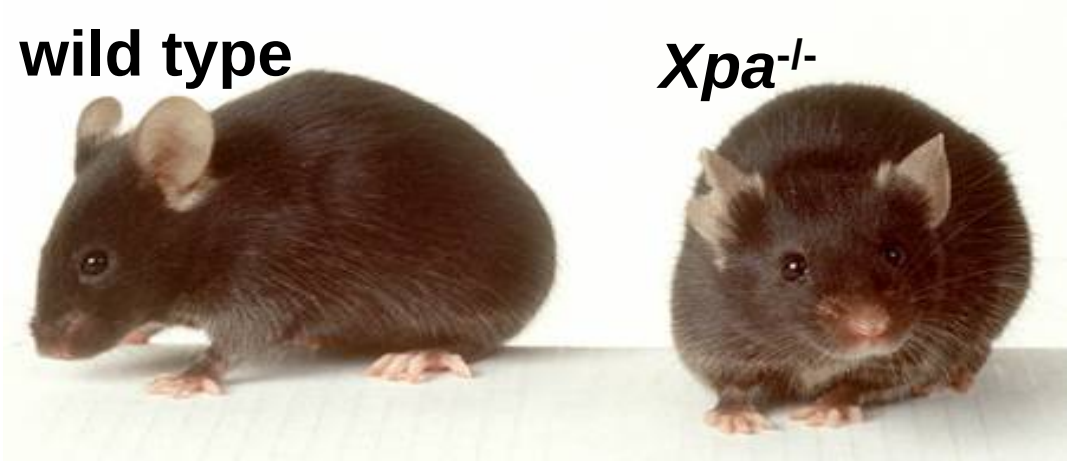
NER: Gap filling DNA synthesis



ERCC1 ?



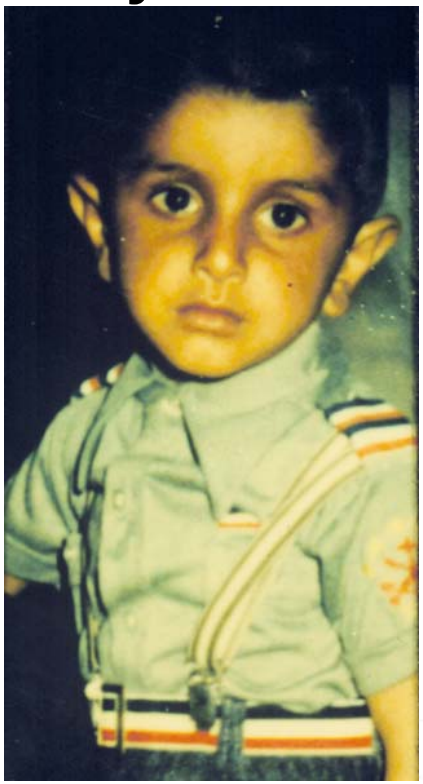
Ercc1$^{-/-}$ phenotype



ERCC1 has function(s) distinct from NER

Progeroid syndrome due to a mutation in *XPF*

3 yrs old



16 yrs old

Nature (2006) **444**:1038-43

ERCC1 and XPF function exclusively as a heterodimer

Mutations in *XPF* lead to two diseases

Genome-wide expression profiling

1) *Ercc1*$^{-/-}$ mice vs. wild type littermates

2) Old wild type mice vs. young wild type mice

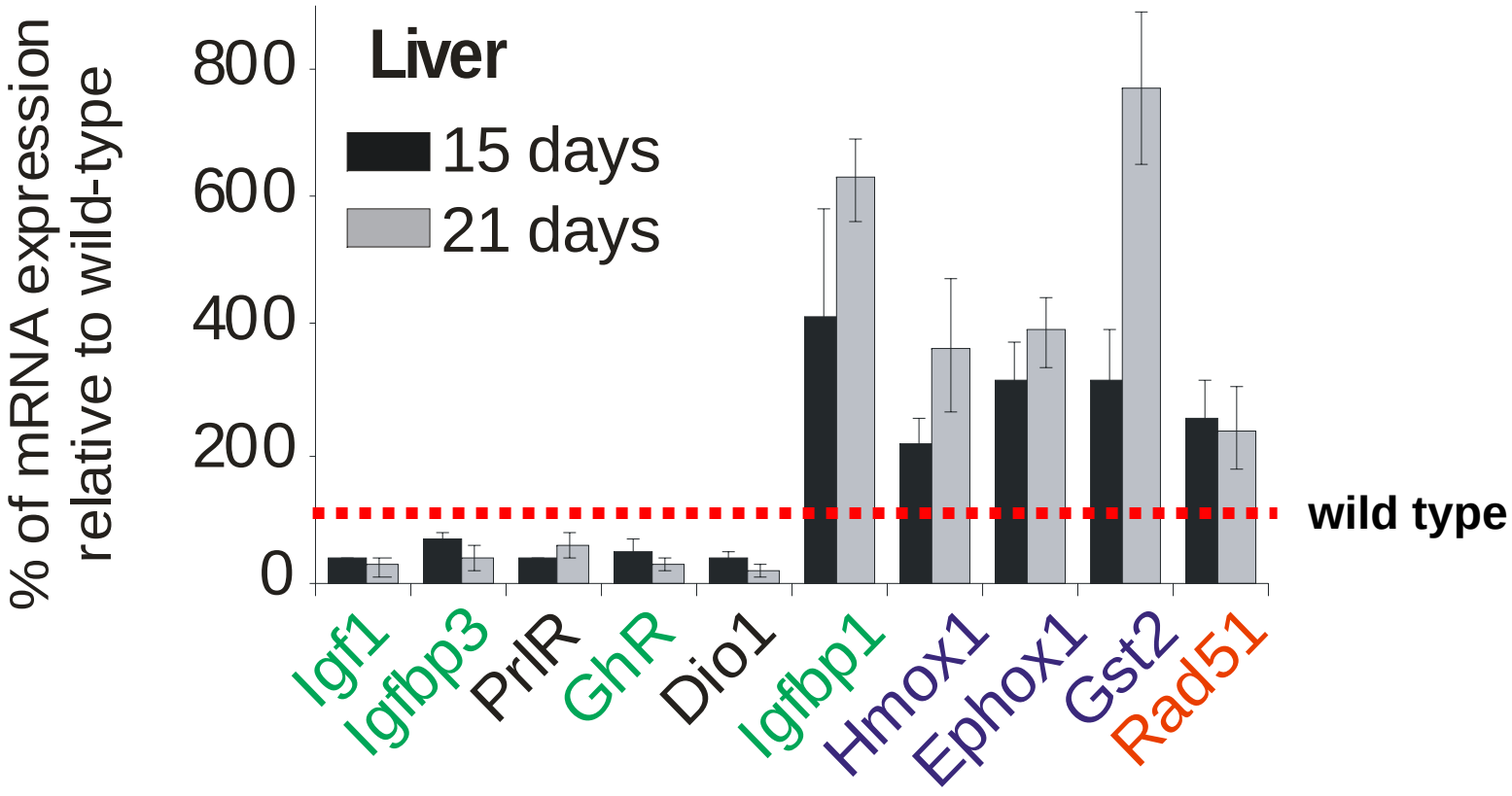
Liver:

1) life limiting
2) age-associated changes
3) p53 stabilization

Pathways significantly altered in *Ercc1*$^{-/-}$ mice

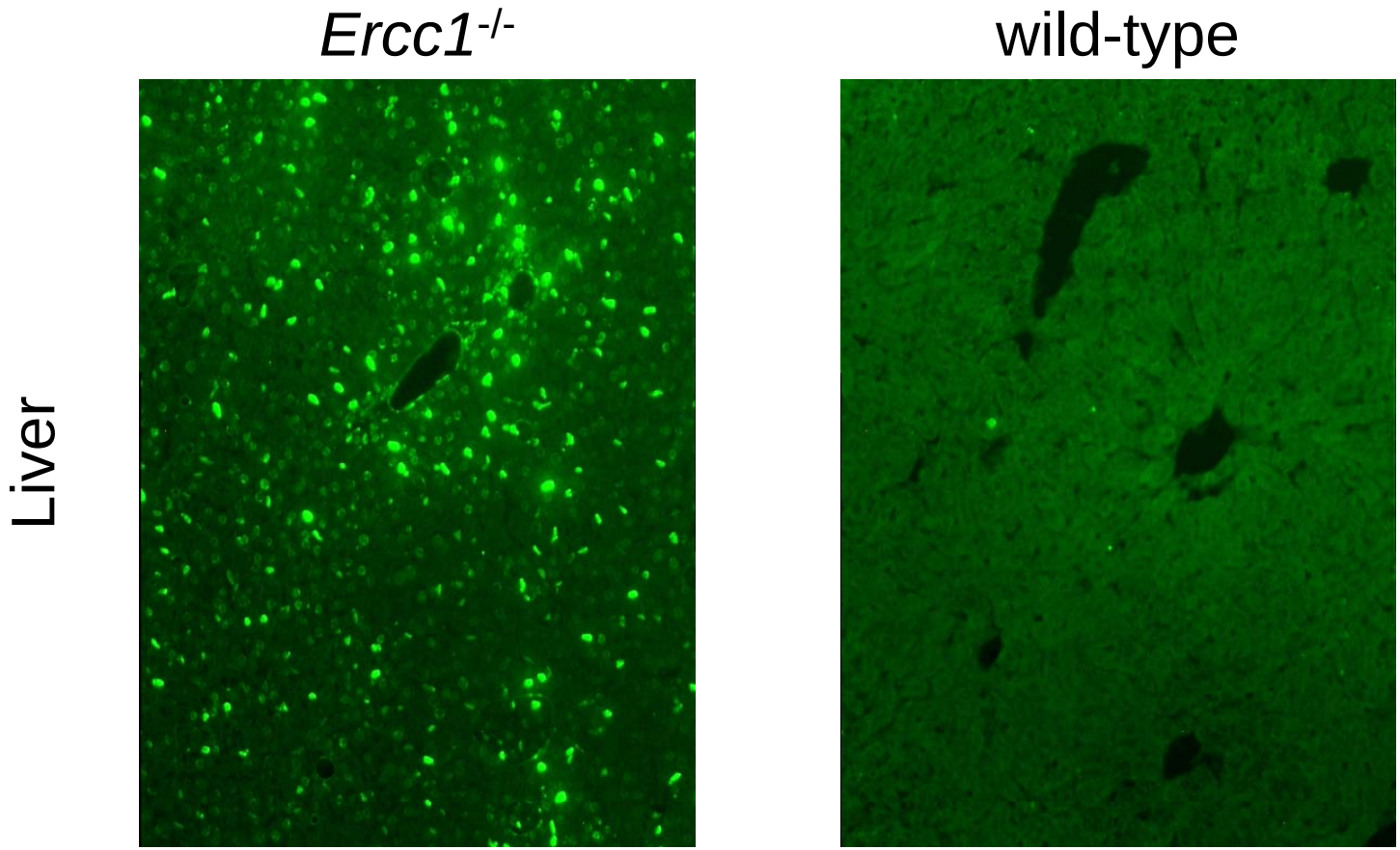
DNA repair	↑
apoptosis	↑
GH / IGF1 hormonal axis	↓
oxidative metabolism	↓
glycogen synthesis	↑
fatty acid synthesis	↑
anti-oxidant defenses	↑

Confirmation by qRT-PCR



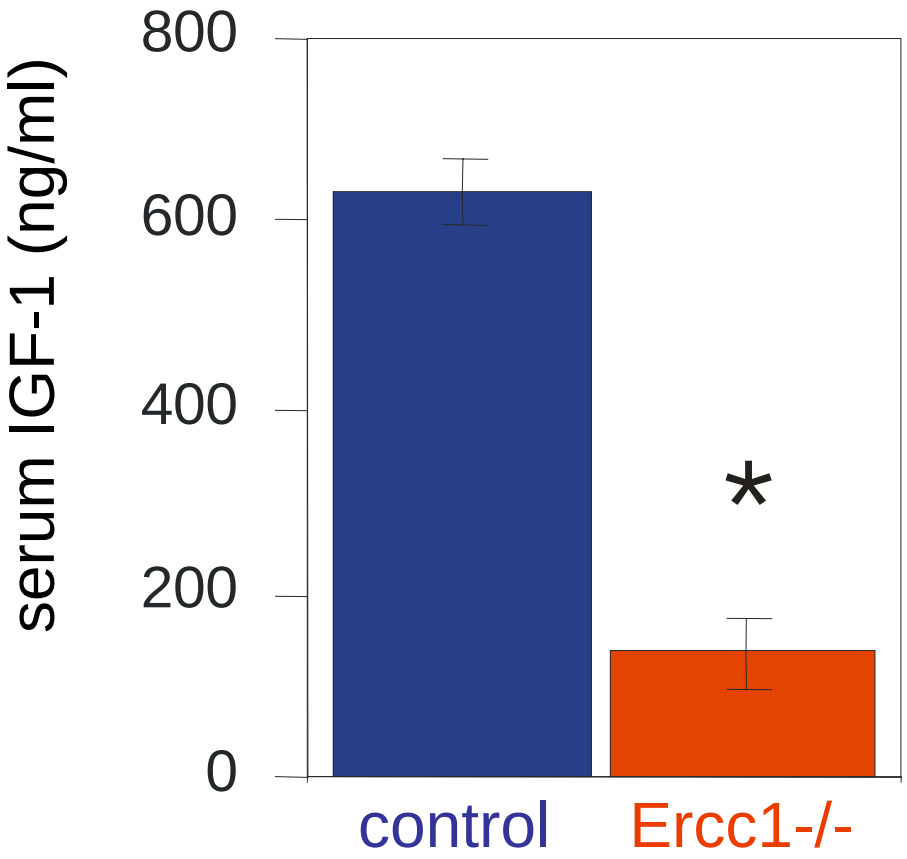
Gene expression changes in *Ercc1*$^{-/-}$ mice are progressive and systemic

Confirmation of biological endpoints



TUNEL assay to measure apoptosis

Confirmation of biological endpoints



Similarity between progeria due to ERCC1-deficiency and aging:

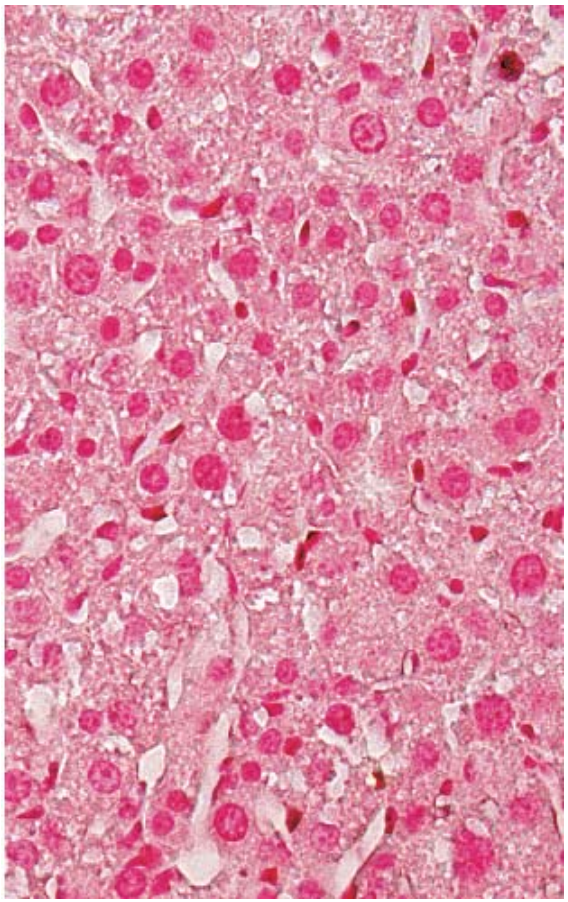
all genes: **32% ($p<0.05$)**

all pathways: **86%**

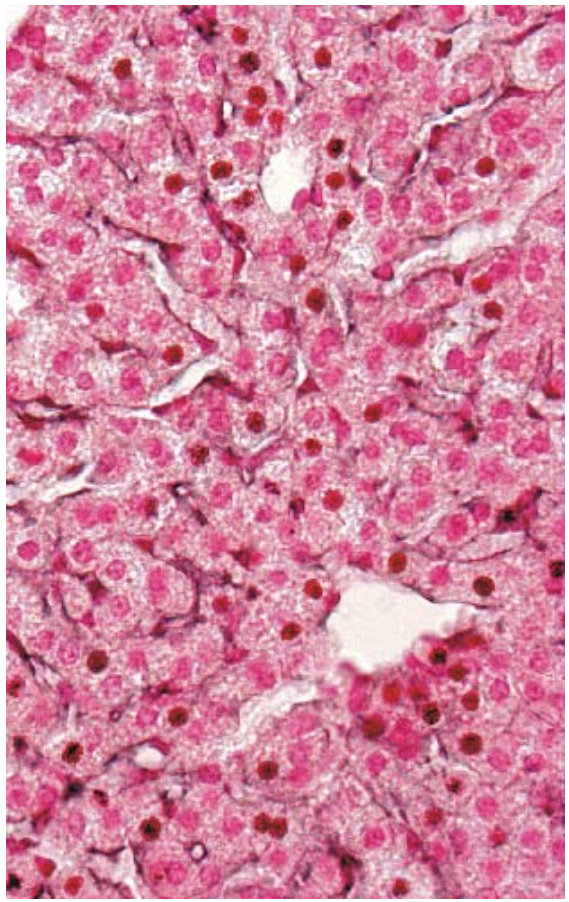
growth hormone axis: **>95%**

Histologic comparison of *Ercc1*$^{-/-}$ mice and aged mice

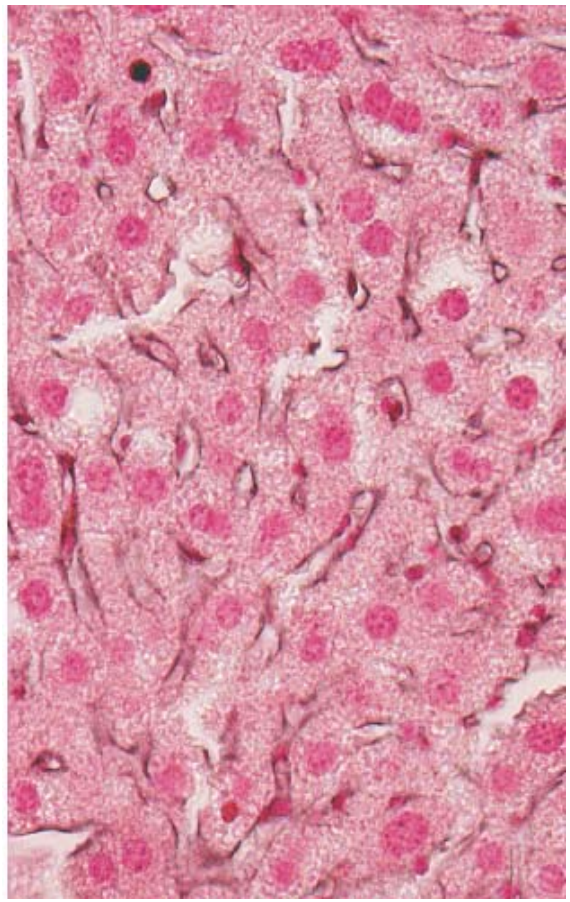
Ercc1$^{-/-}$



wt littermate



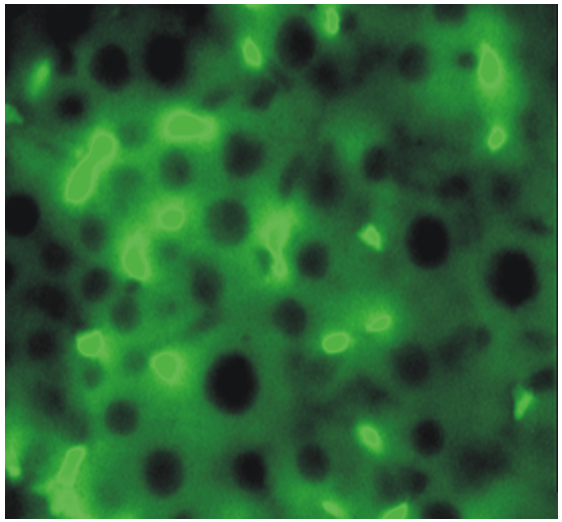
wt 24 mths



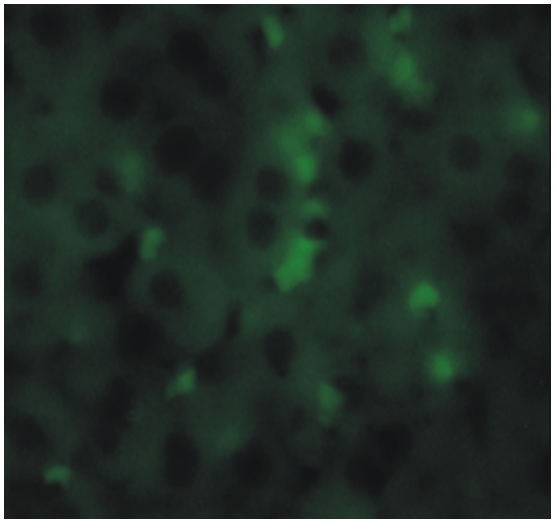
anti-BrdU to identify proliferating nuclei

Histologic comparison of *Ercc1-/-* mice and aged mice

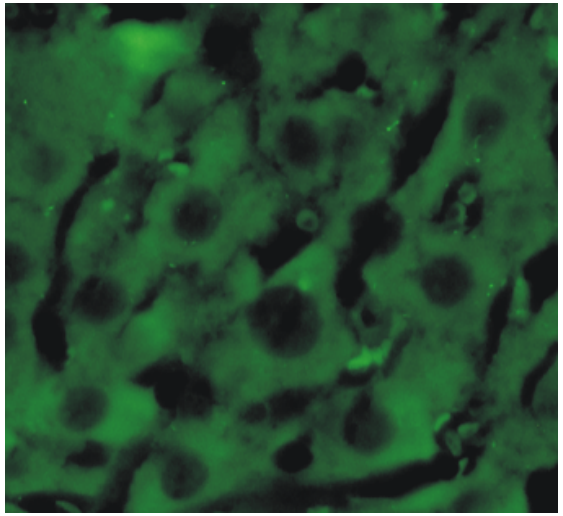
Ercc1 $^{-/-}$



wt littermate



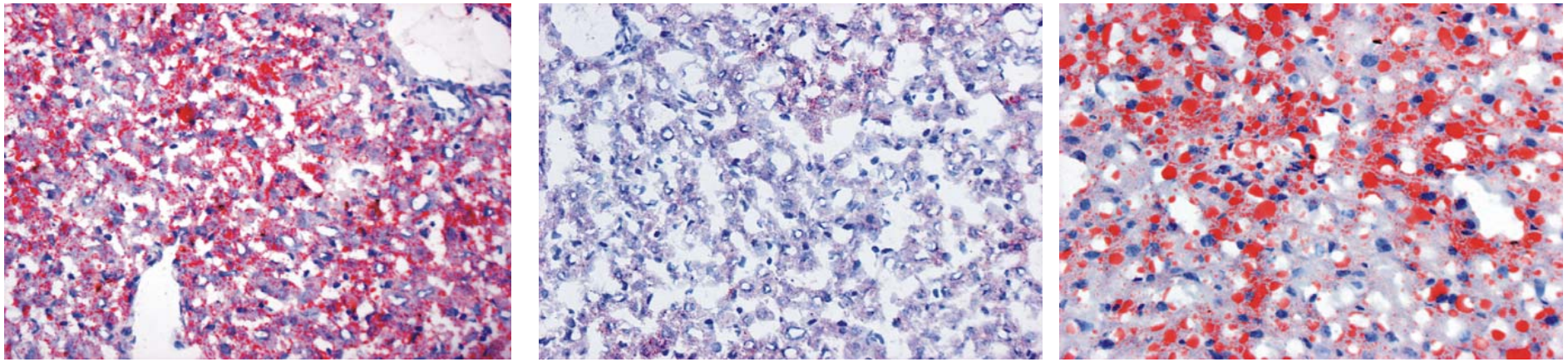
wt 24 mths



IGFBP-1 expression

Histologic comparison of *Ercc1*$^{-/-}$ mice and aged mice

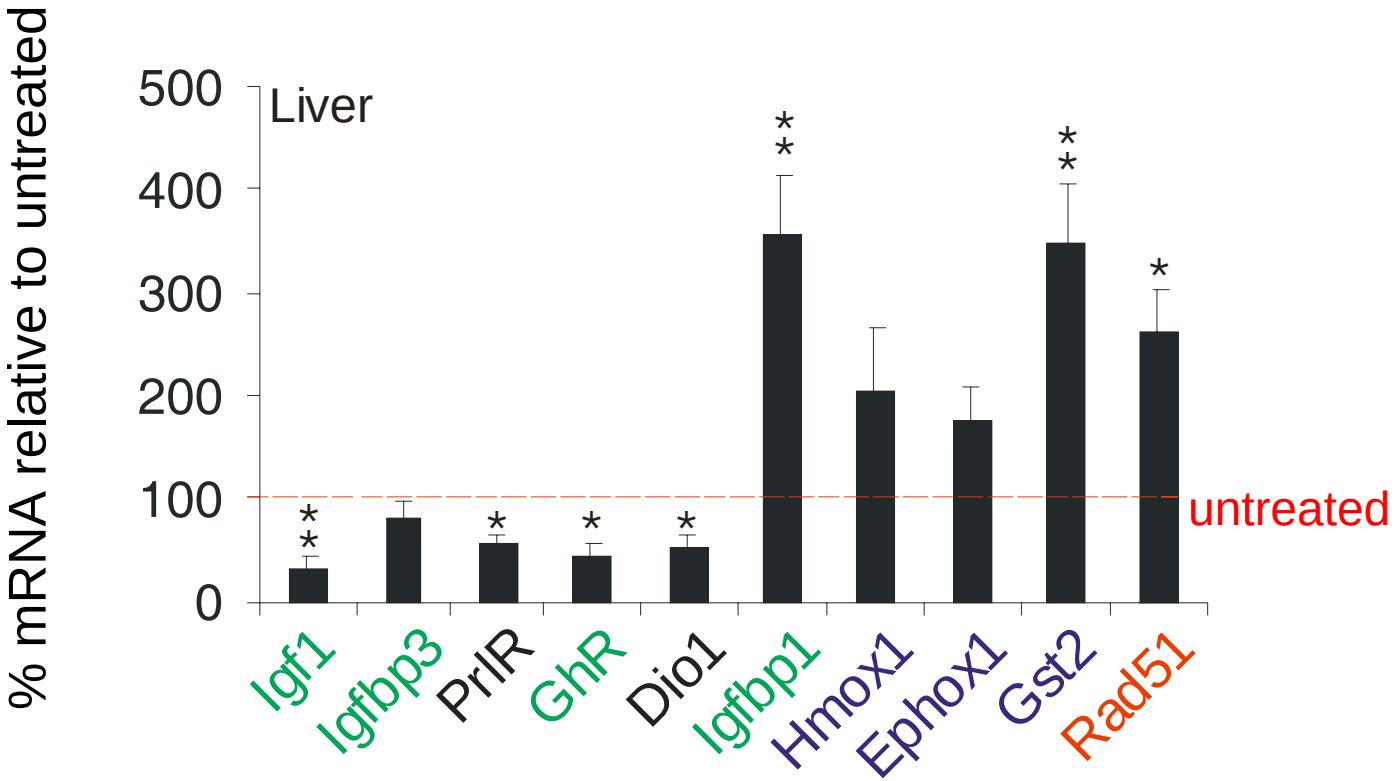
Ercc1 $^{-/-}$ wt littermate wt 24 months

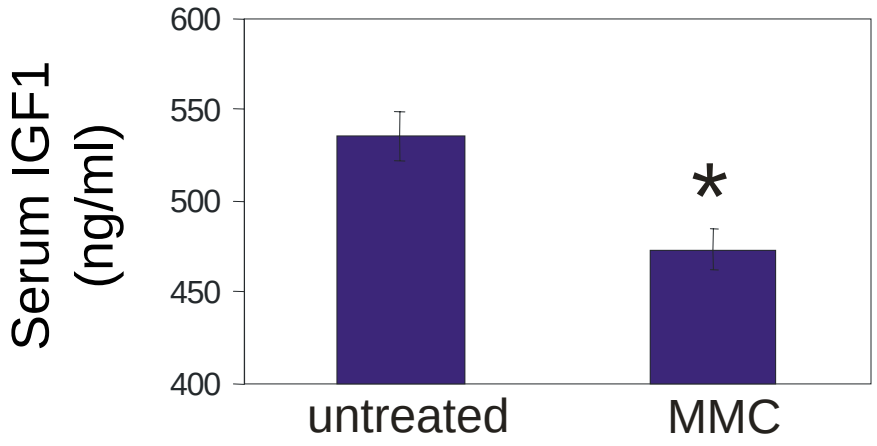


Oil Red O stain for liver triglycerides

Does genotoxic stress induce a similar response in a normal host?

0.1 mg/kg MMC
(100X below LD)
intraperitoneal
weekly x 5 wks


% mRNA relative to untreated
Liver
500
400
300
200
100
0
untreated
**
*
*
*
**
**
*
Igf1
Igfbp3
PrlR
GhR
Dio1
Igfbp1
Hmox1
Ephox1
Gst2
Rad51

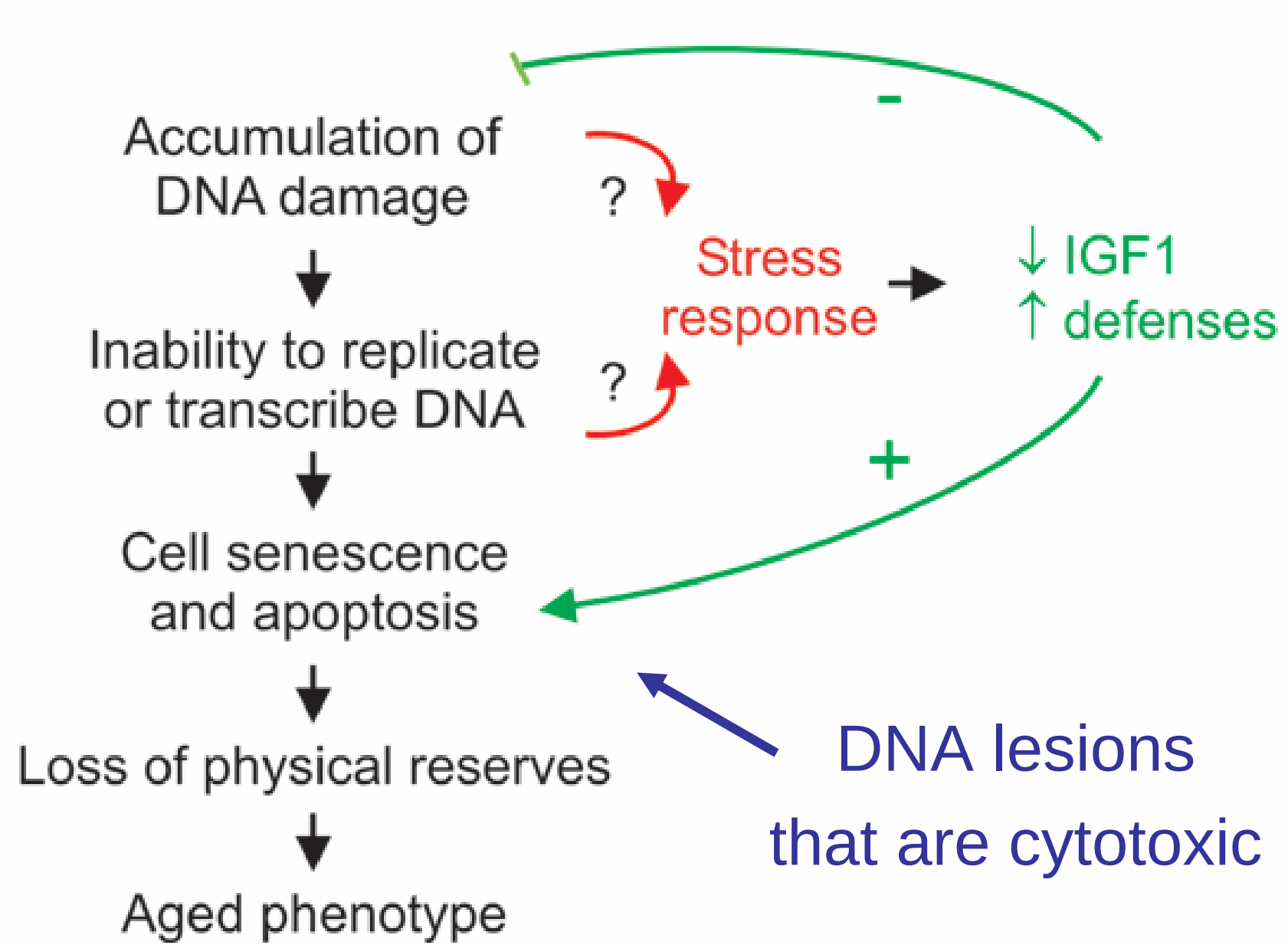

Serum IGF1
(ng/ml)
600
550
500
450
400
*
untreated
MMC

A common response to stress mediated by the somatotroph axis

Biological process:	*Ercc1* $^{-/-}$	old age	*Ghr*$^{-/-}$; *Igf1*$^{+/-}$	CR
GH / IGF1 hormonal axis	↓	↓	↓	↓
oxidative metabolism	↓	↓	↓	↓
glycogen synthesis	↑	↑	↑	↑
fatty acid synthesis	↑	↑	↑	↑
peroxisome biogenesis	↑	↑	↑	↑
anti-oxidant defenses	↑	-	↑	↑

A. Bartke R. Miller

Model:


Accumulation of DNA damage
?
Stress response
↓ IGF1
↑ defenses
-
Inability to replicate or transcribe DNA
?
+
Cell senescence and apoptosis
Loss of physical reserves
Aged phenotype
DNA lesions that are cytotoxic

Implications:

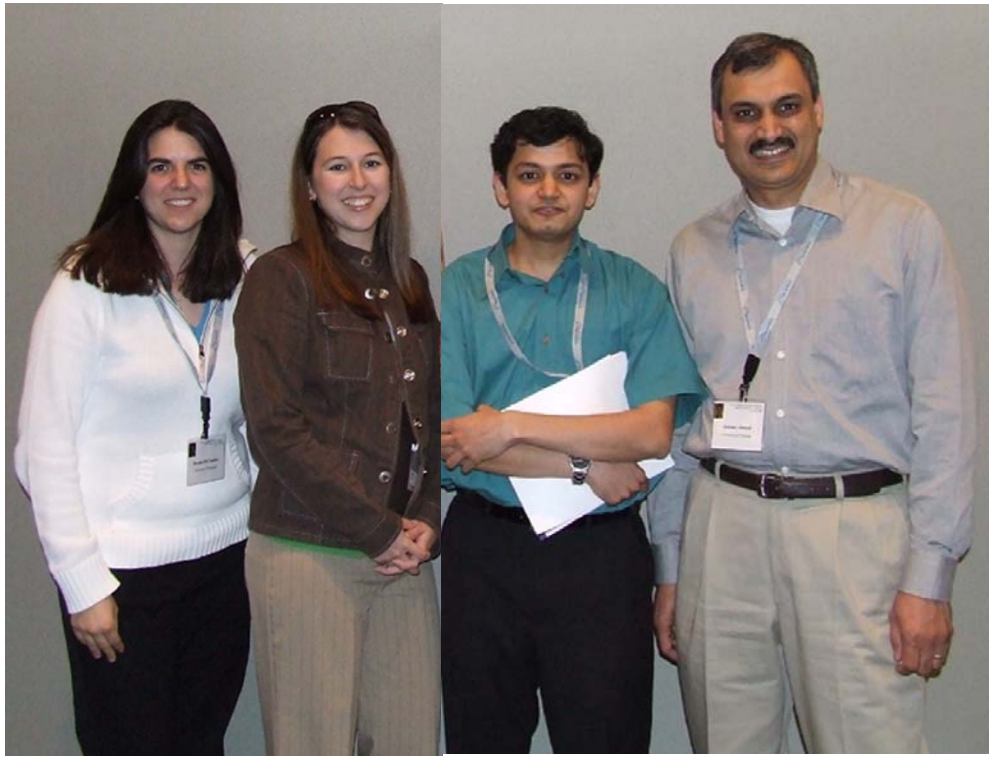
1. Prevention of DNA damage (or improving DNA repair) may delay aging.

2. Cancer therapy with genotoxins may cause accelerated aging in cancer survivors.

3. Progeria caused by defects in the DNA damage response is accelerated aging.

4. Mouse models of human progerias are a valid and rapid system for studying aging.

Acknowledgments



Dr. Anwaar Ahmad
Andria Robinson
Nikhil Bhagwat
Brooke McClendon
Hillary Shane

Jan Hoeijmakers:
George Garinis
Ellen van Drunen

University of Pittsburgh Cancer Institute:
Rick Wood, Rob Sobol, Chris Bakkenist, Yong Wan, Vesna Rapic-Otrin