



Aziz Sancar

Bilimsel Katkıları

Prof. Dr. Şevket Ruacan
Koç Üniversitesi Tıp Fakültesi



Aziz Sancar

- 8 Eylül 1946 Savur, Mardin doğumlu.
- İstanbul Tıp Fakültesi 1969 mezunu
- Texas Üniversitesi (Dallas) moleküler biyoloji doktorası (1977)
- Yale Üniversitesi doktora sonrası çalışma
- North Carolina Üniversitesi
- TÜBİTAK Bilim Ödülü (2006)
- Vehbi Koç Ödülü (2007)
- Nobel Kimya Ödülü (2015)

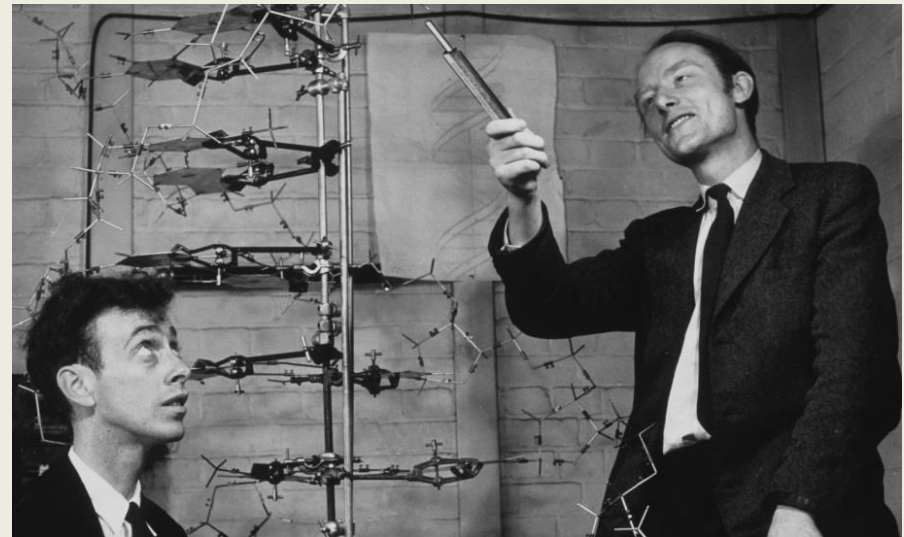
Aziz Sançar

- North Carolina Üniversitesi Biyokimya ve Biyofizik Bölümü
- Araştırma alanları: Biyokimya
Moleküler Biyoloji
DNA onarımı
Kanser
Biyolojik Saat

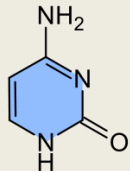


DNA

- Tüm canlıların evrensel genetik şifresi
- Watson - Crick çift sarmal modeli (1964)
- Hem yapısal hem de fonksiyonel proteinlerin - enzimlerin şifresi
- DNA: kendini kopyalayabilme (replikasyon)
proteinleri şifreleyebilme (translasyon)
- Şifre 4 harfli
- 4 Nükleotid:
 - Adenin - Timin
 - Guanin - Sitozin

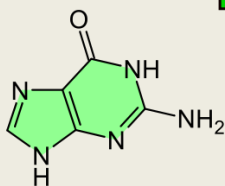


Cytosine



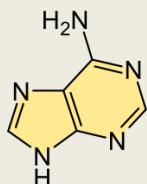
C

Guanine



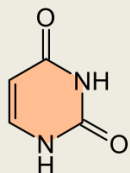
G

Adenine



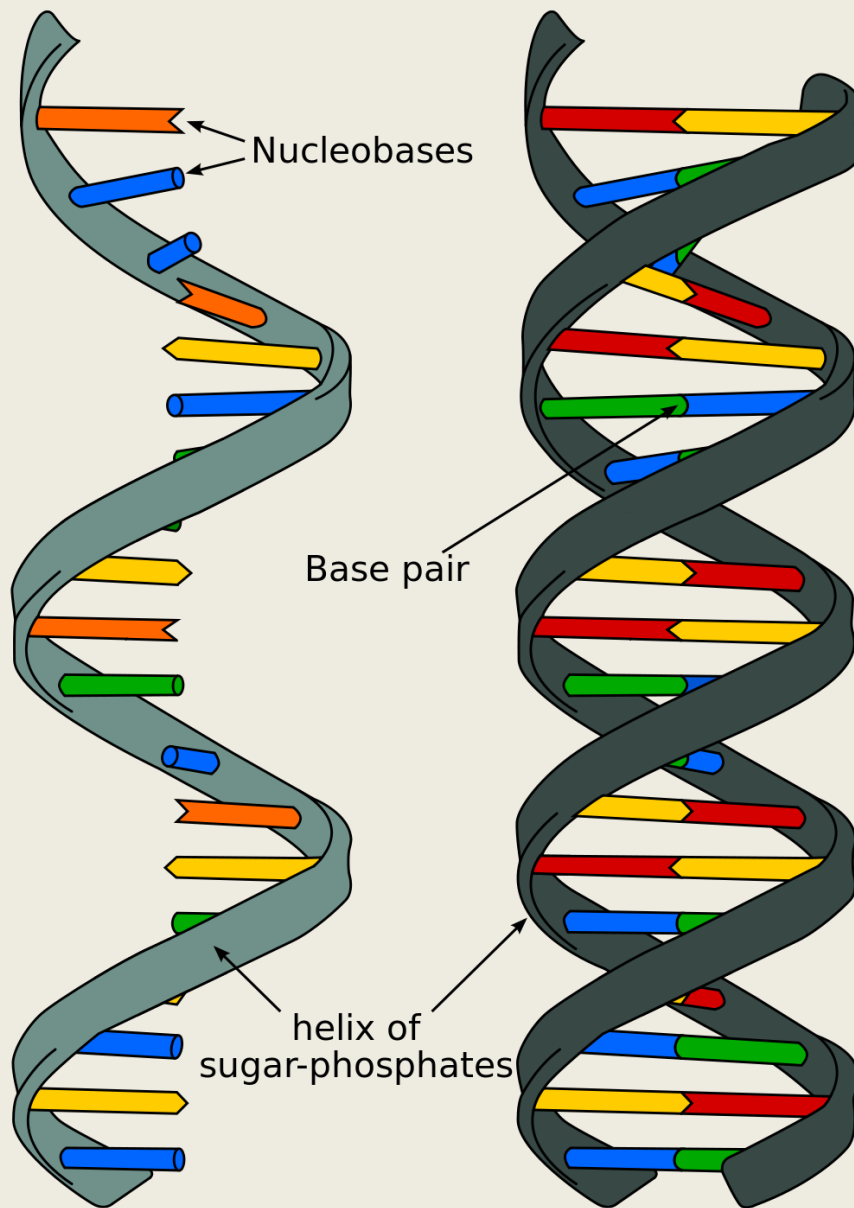
A

Uracil



U

Nucleobases
of RNA



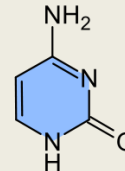
RNA

Ribonucleic acid

DNA

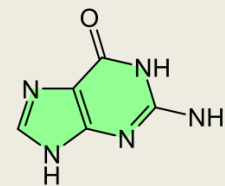
Deoxyribonucleic acid

Cytosine



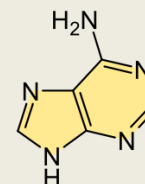
C

Guanine



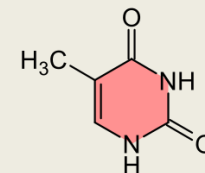
G

Adenine



A

Thymine



T

Nucleobases
of DNA

Mutasyon

- DNA çok dayanıklı bir molekül !
- DNA yapısı, baz dizisindeki değişiklikler:
mutasyon
 - Nokta mutasyonlar
 - Ekleme, çıkarma, değişme...
 - Çerçeve kayması (frameshift)
 - Kromozom bozuklukları
 - Yararlı, zararlı, nötral mutasyonlar
- Protein sentezi, yapısı, işlevinde bozukluk

Mutasyonlar

- DNA replikasyonu kusursuz değil !
- Devamlı mutasyonlar oluşuyor
- Dış etkenler bu hızı arttırıyor
 - Işınlr: UV ve iyonizan
 - Kimyasallar
 - Oksidatif stress

Mutasyonlar yaşamın gerekli bir ögesi

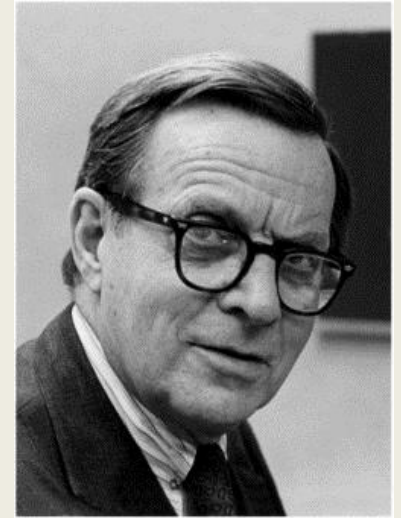
Mutasyon Oranları

Mutation rates of different genes in different organisms			
Organism	Mutation	Rate	Unit
Bacteriophage T2	Lysis inhibition	1×10^{-8}	Per replication
	Host range	3×10^{-9}	
<i>Escherichia coli</i>	Lactose fermentation	2×10^{-7}	Per cell division
	Histidine requirement	2×10^{-8}	
<i>Neurospora crassa</i>	Inositol requirement	8×10^{-8}	Per asexual spore
	Adenine requirement	4×10^{-8}	
Corn	Kernel color	2.2×10^{-6}	Per gamete
<i>Drosophila</i>	Eye color	4×10^{-5}	Per gamete
	Allozymes	5.14×10^{-6}	
Mouse	Albino coat color	4.5×10^{-5}	Per gamete
	Dilution coat color	3×10^{-5}	
Human	Huntington's disease	1×10^{-6}	Per gamete
	Achondroplasia	1×10^{-5}	
	Neurofibromatosis (Michigan)	1×10^{-4}	
	Hemophilia A (Finland)	3.2×10^{-5}	
	Duchenne muscular dystrophy (Wisconsin)	9.2×10^{-5}	

DNA'nın gerek mucizesi hafife samalamasıdır.

Bu zellik olmasaydı bizler hala anaerob bakteriler olarak kalırdık ve mzik olmazdı.

*Lewis Thomas
1913-1993
Notes Of A Biology Watcher*



Lewis Thomas

DNA Zedelenmesi

1. Pirimidin (timin) dimerleri

- * Ultraviyole

2. DNA'ya bağlanmalar

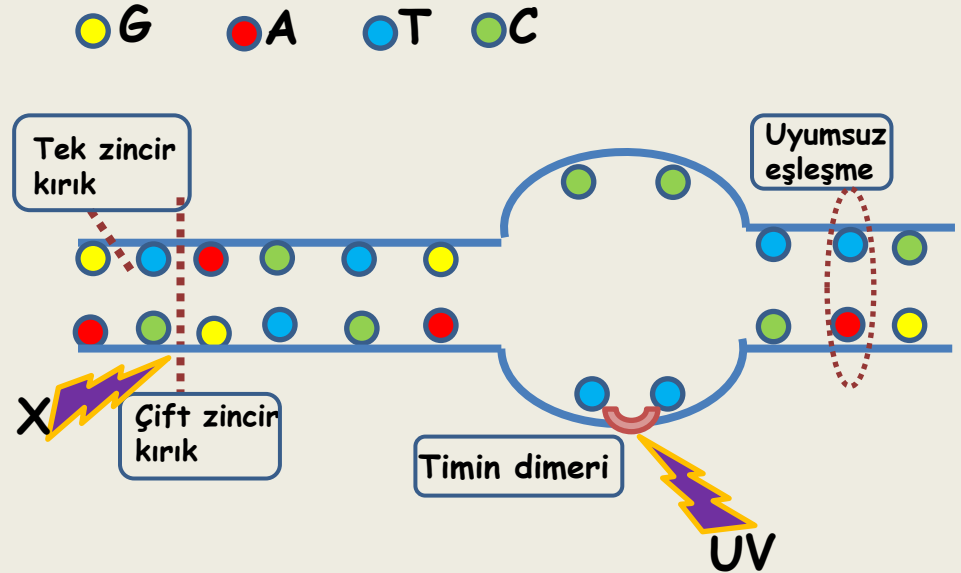
- Kimyasallar
- Kemoterapötikler

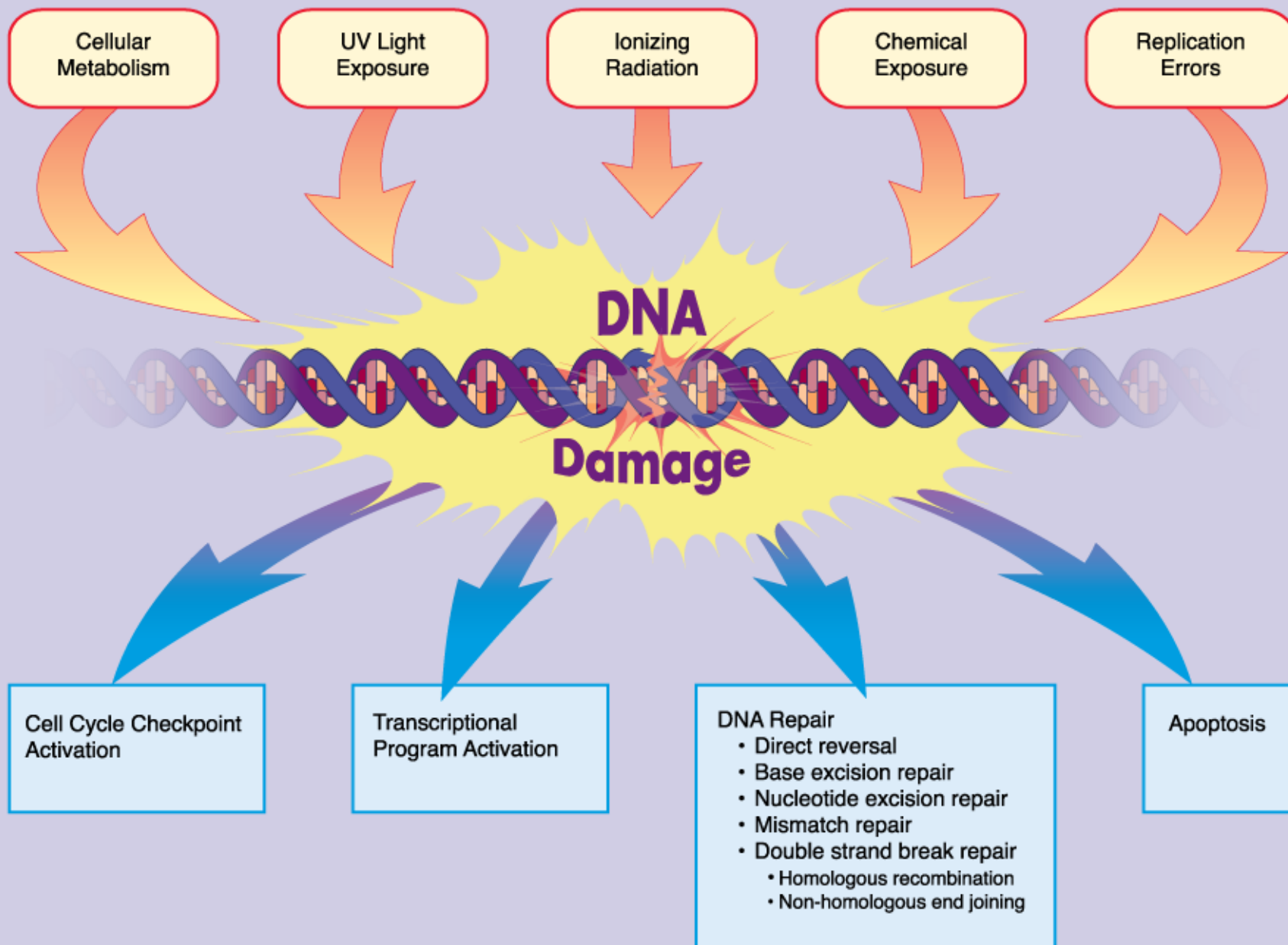
3. Zincir kırıkları

- * İyonizan radyasyon
- * Serbest radikaller
- * Alkilleyici ajanlar

4. Uyumsuz eşleşme (mismatch)

- * DNA replikasyon hataları
- * Mutajenler





DNA Onarımı

1. Doğrudan düzeltme: Fotoreaktivasyon (fotoliyaz), mavi ışık, bakteriler
2. Baz eksizyonu onarımı: zedelenmiş tek bazı değiştirme (glikozilaz)
3. Nükleotid eksizyon onarımı: zedelenmiş bölgeyi çevresi ile çıkararak yeni sentez yapmak
4. Uyumsuz eşleşme onarımı: zincirdeki uyumsuz eşleşmeleri tanıyıp çıkararak yeniden sentezlemek



Nobelpriset i kemi 2015

The Nobel Prize in Chemistry 2015

Nobelpriset i kemi 2015

KUNGL.
VETENSKAPS-
AKADEMIEN
THE ROYAL SWEDISH ACADEMY OF SCIENCES



Tomas Lindahl

Francis Crick Institute and
Clare Hall Laboratory,
Hertfordshire, UK



Paul Modrich

Howard Hughes Medical
Institute and Duke University
School of Medicine, Durham,
NC, USA



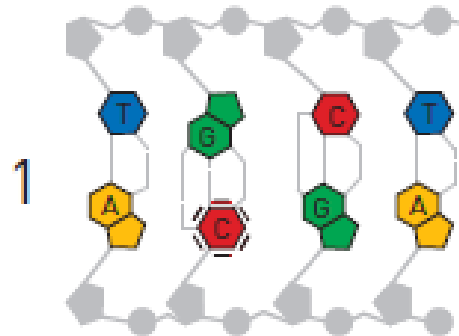
Aziz Sancar

University of North Carolina,
Chapel Hill, NC, USA

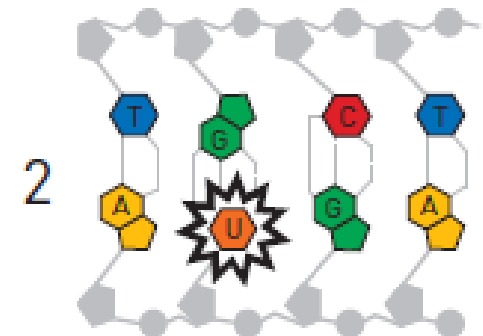
"för mekanistiska studier av DNA-reparation"
"for mechanistic studies of DNA repair"

Base excision repair

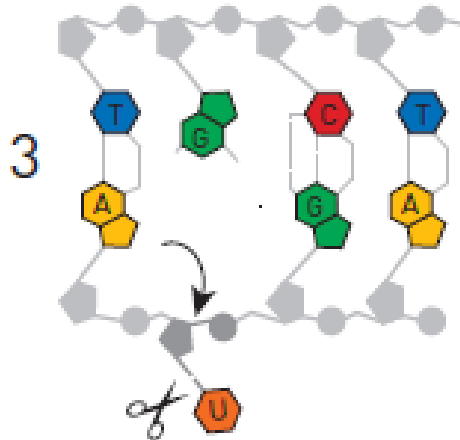
Base excision repairs DNA when a base of a nucleotide is damaged, for example cytosine.



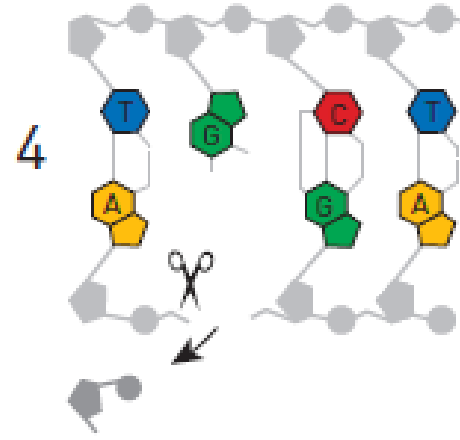
Cytosine can easily lose an amino group, forming a base called uracil.



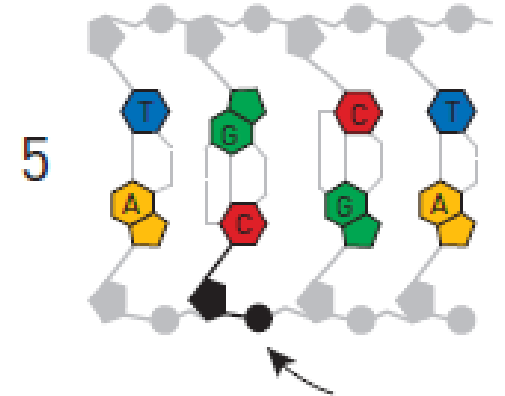
Uracil cannot form a base pair with guanine.



An enzyme, glycosylase, discovers the defect and excises the base of uracil.



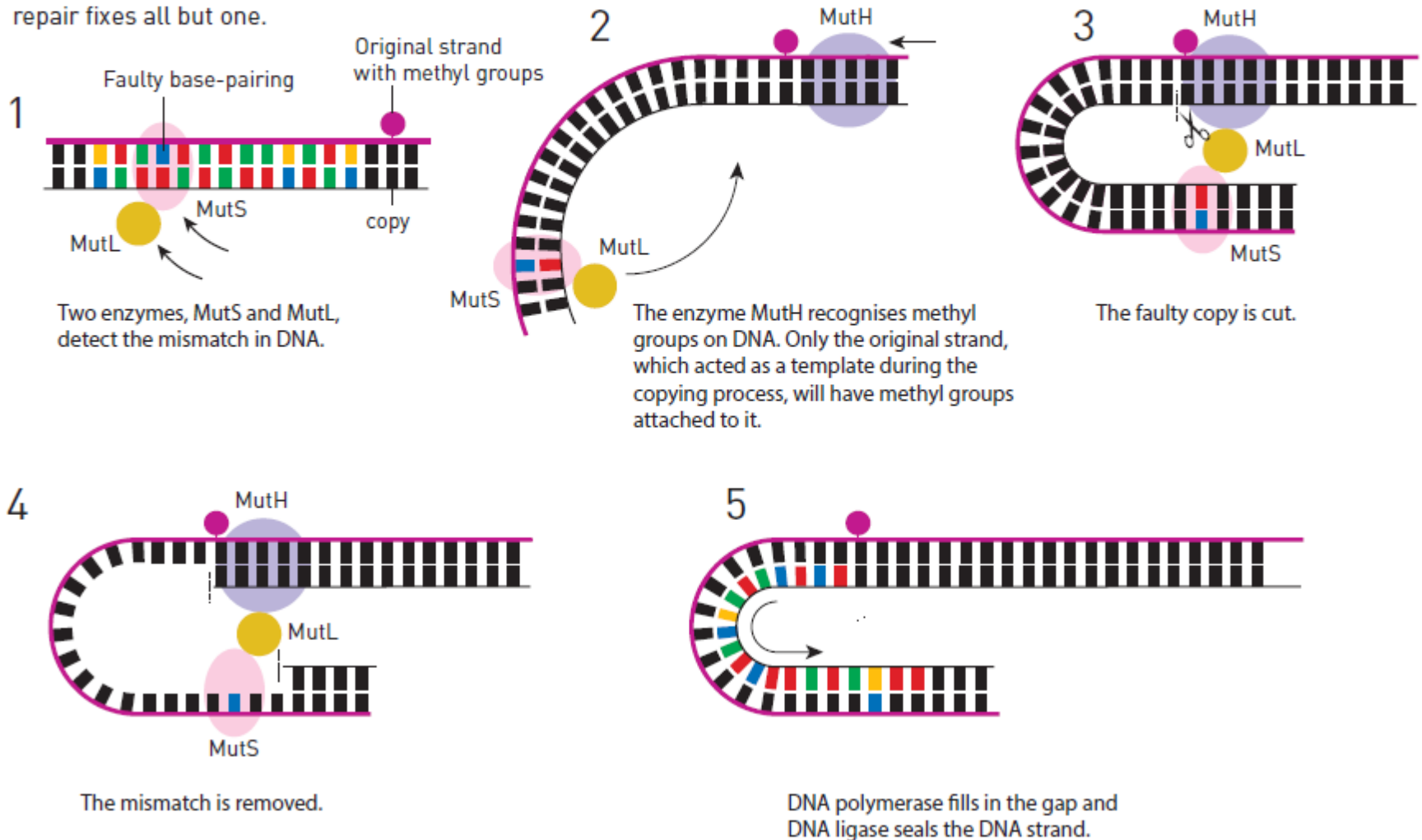
Another couple of enzymes remove the rest of the nucleotide from the DNA strand.



DNA polymerase fills in the gap and the DNA strand is sealed by DNA ligase.

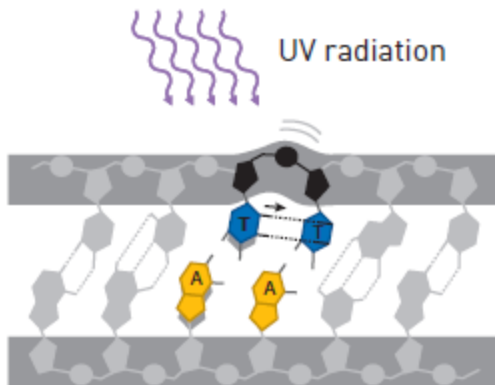
Mismatch repair

When DNA is copied during cell division, mismatching nucleotides are sometimes incorporated into the new strand. Out of a thousand such mistakes, mismatch repair fixes all but one.

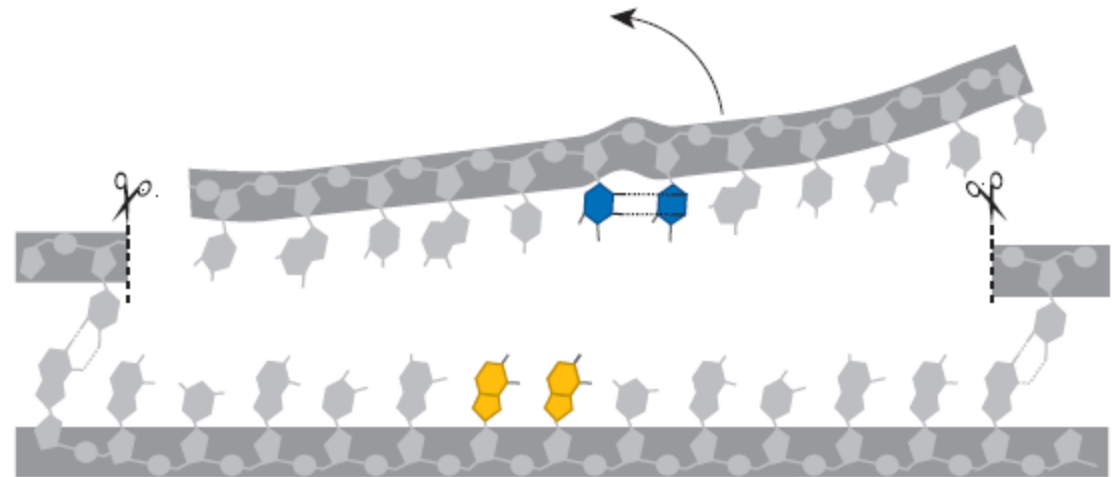


Nucleotide excision repair

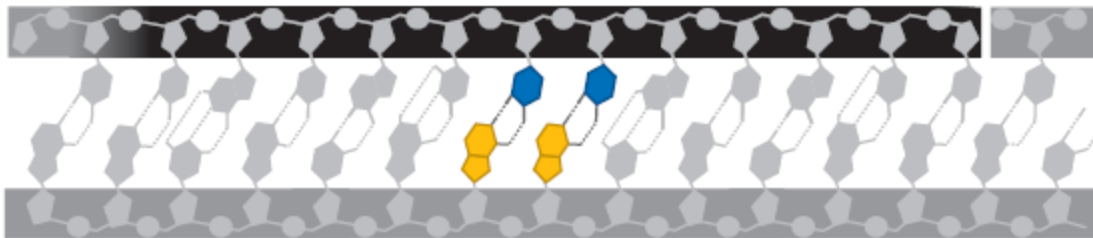
Nucleotide excision repairs DNA-injuries caused by UV radiation or carcinogenic substances like those found in cigarette smoke.



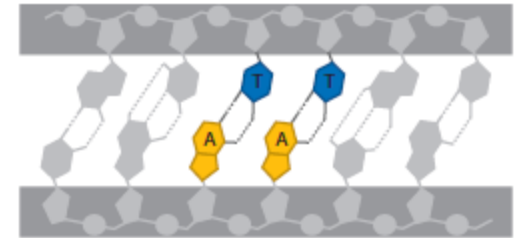
- 1 UV radiation can make two thymines bind to each other incorrectly.



- 2 The enzyme exonuclease finds the damage and cuts the DNA strand. Twelve nucleotides are removed.



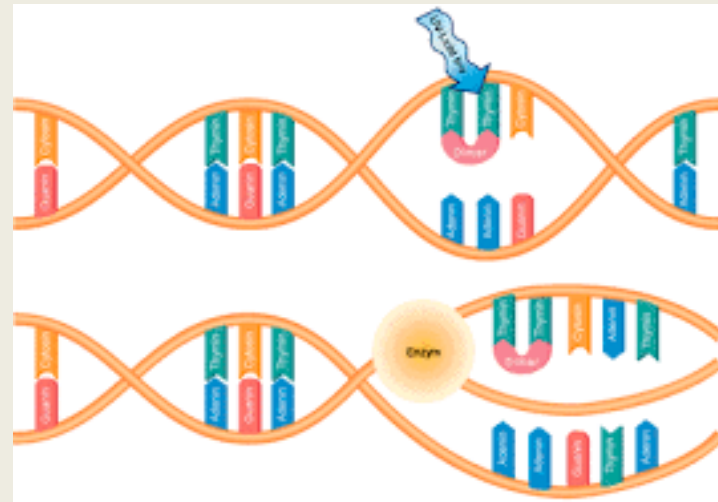
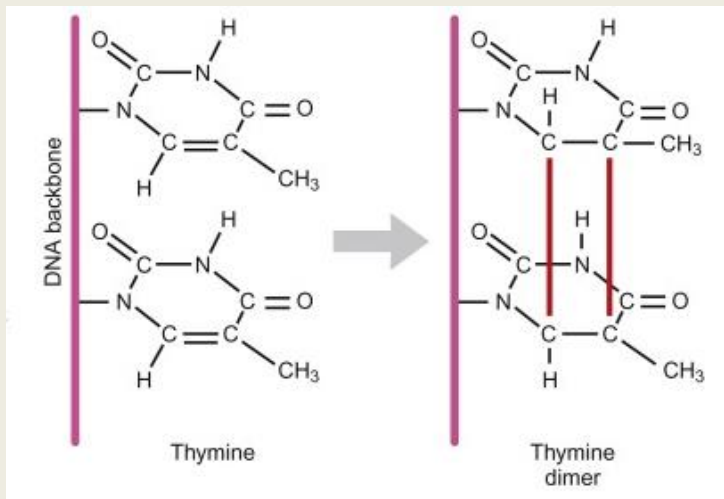
- 3 DNA polymerase fills in the resulting gap.

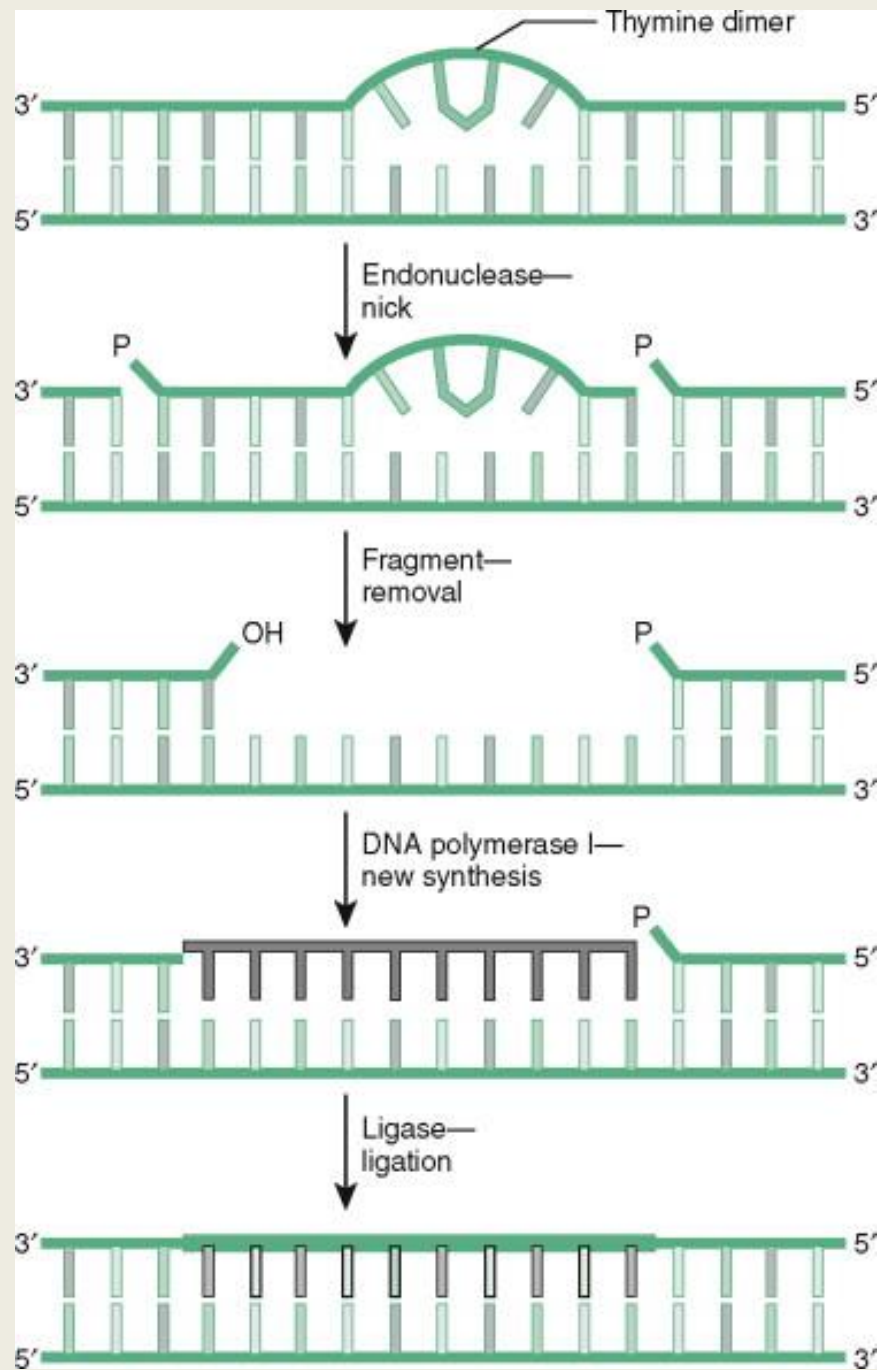


- 4 DNA ligase seals the DNA strand. Now the injury has been dealt with.

Ultraviyole ve DNA

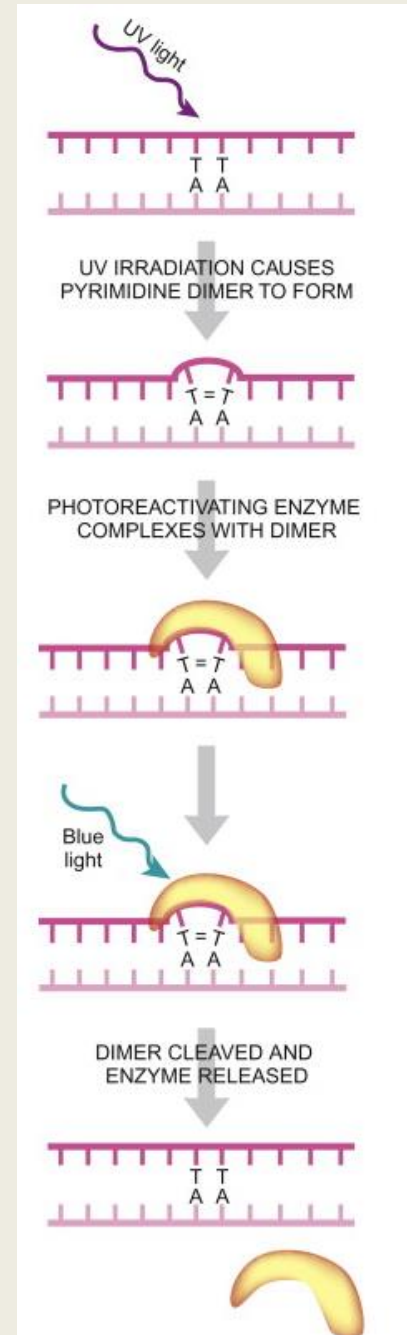
- UVB ışınları (280-315nm) DNA'da timin dimerleri oluşturur.
- Sterilizasyon
- Mutasyonlar: bakteri ve memeli hücreleri
- İnsanda deri kanserleri: melanom ve diğer

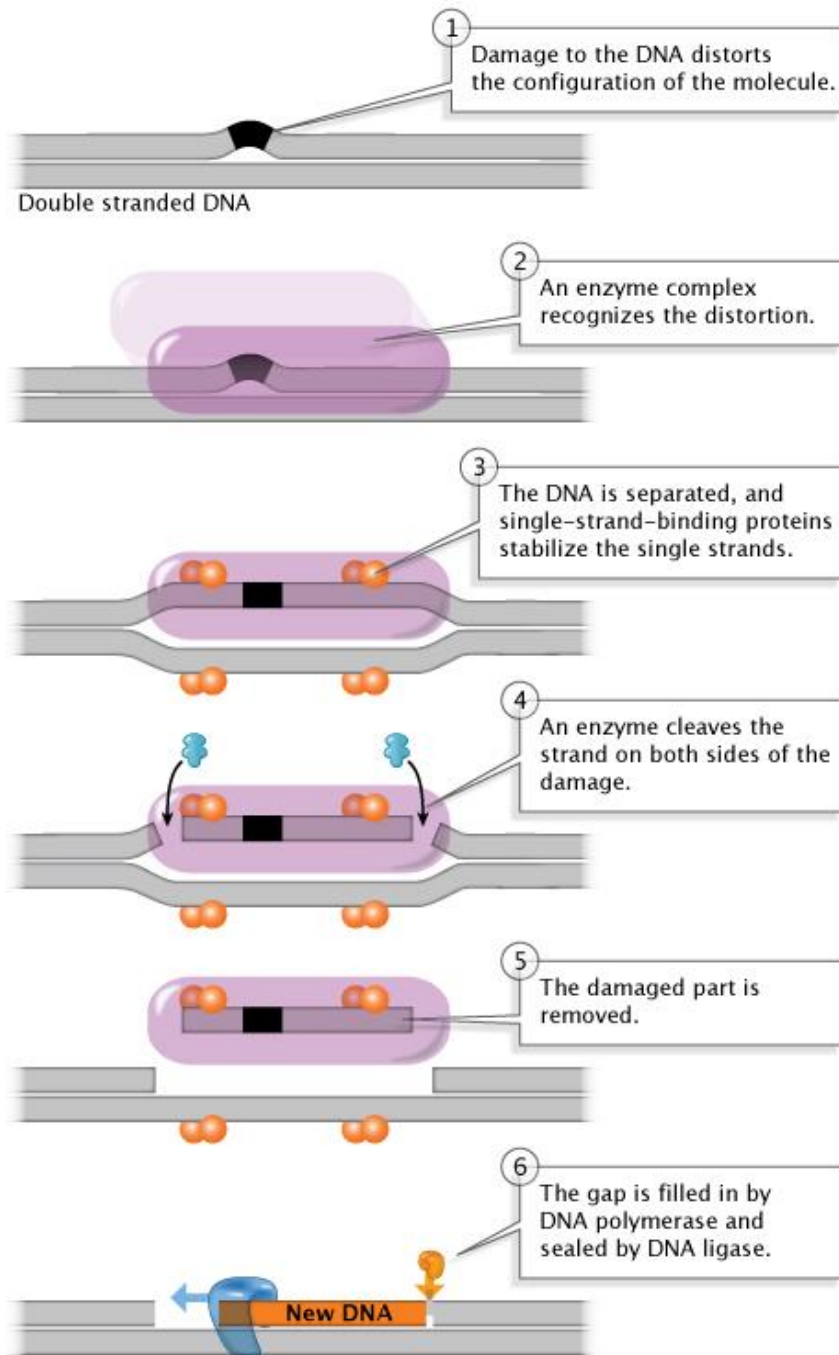




R. J. KAUFMAN

**Fotolizaz enzim kompleksi
görünür (mavi) ışık etkisiyle
timin dimerini onarır
(bakteri)**

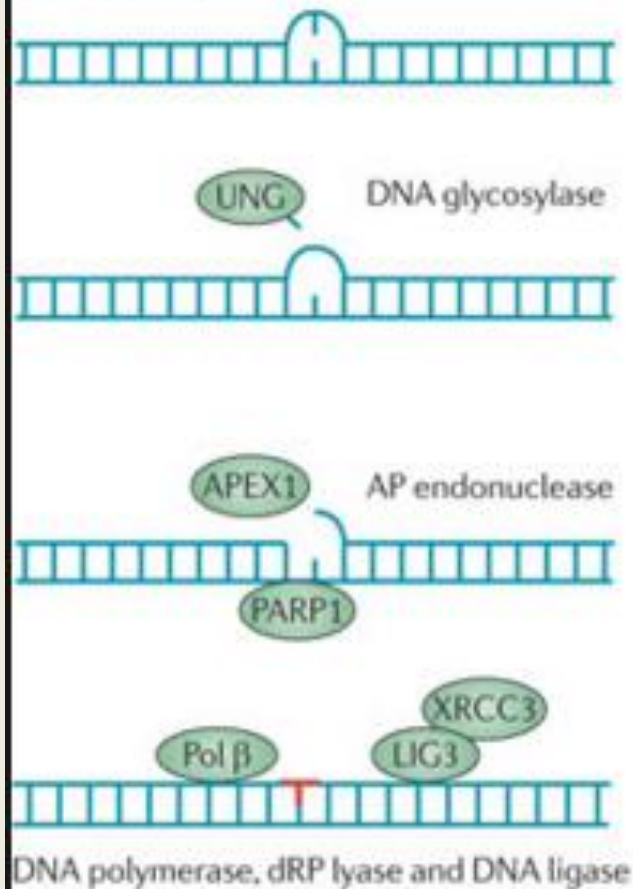




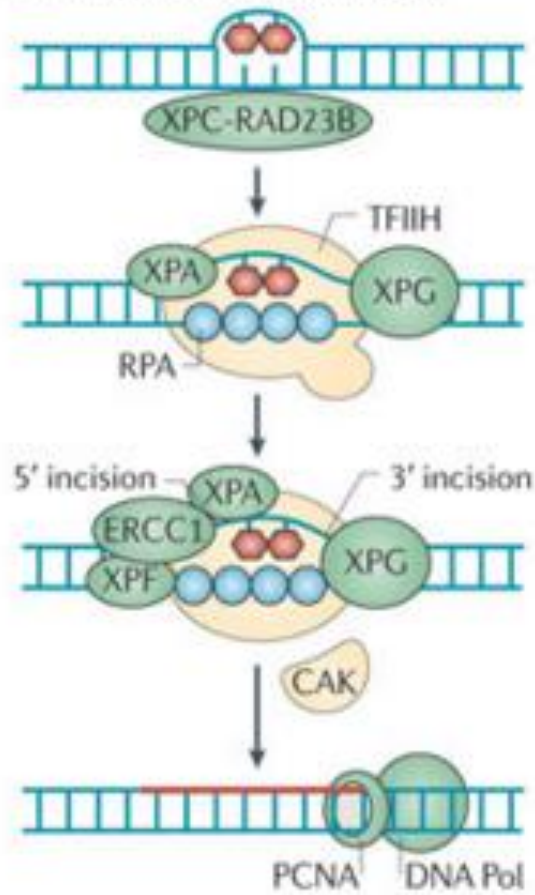
Bakterilerde 3 enzim

İnsanda 18 enzim

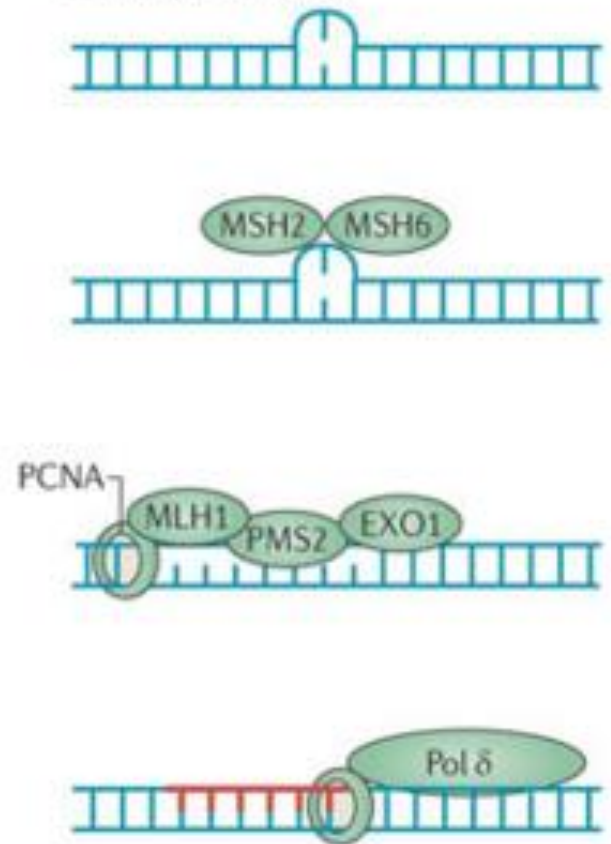
a Base excision repair



b Nucleotide excision repair



c Mismatch repair



UV ve Kanser

- UVB deri kanserine yol açar
- Denizciler, bahçıvanlar, Avustralya'ya göç eden İngilizler...
- Güneşe maruz bölgelerde kanserler
- Melanom ve diğer kanserler

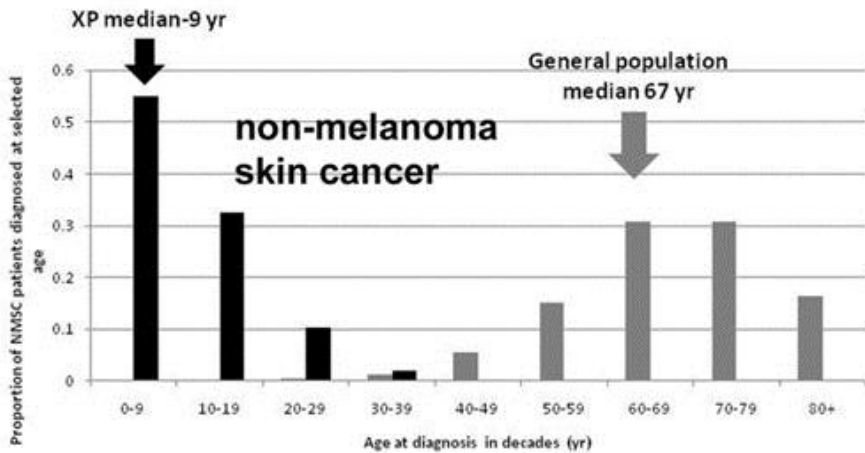


Xeroderma Pigmentosum

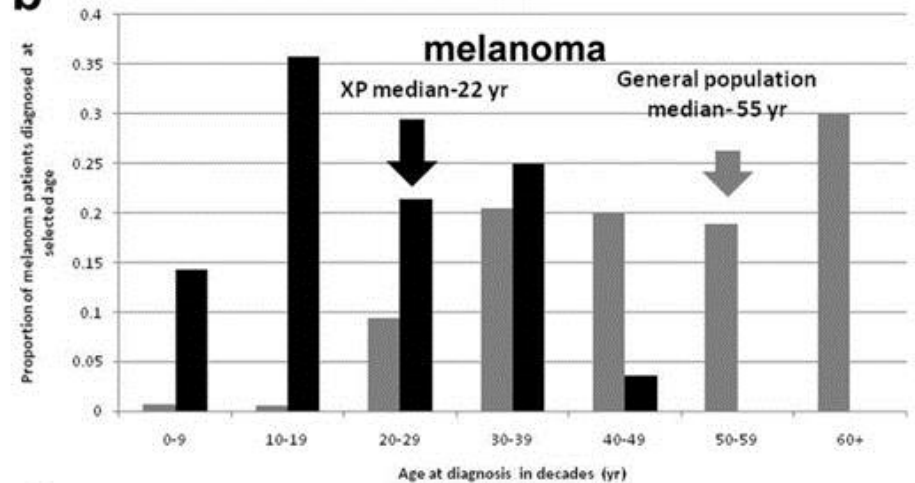
- Otozomal resessif deri hastalığı
- Sıklığı: 1/250 000 (Japonya: 1/40 000)
- Bebeklikten başlayarak fotosensitivite, pigmentasyon, deri kanserler, nörolojik belirtiler
- UV etkisiyle oluşan DNA zedelenmesinin onarımında bozukluk (Cleaver 1968)
- Timin dimerlerini DNA zincirinden eksize etme bozukluğu

Xeroderma Pigmentosum ve Kanser

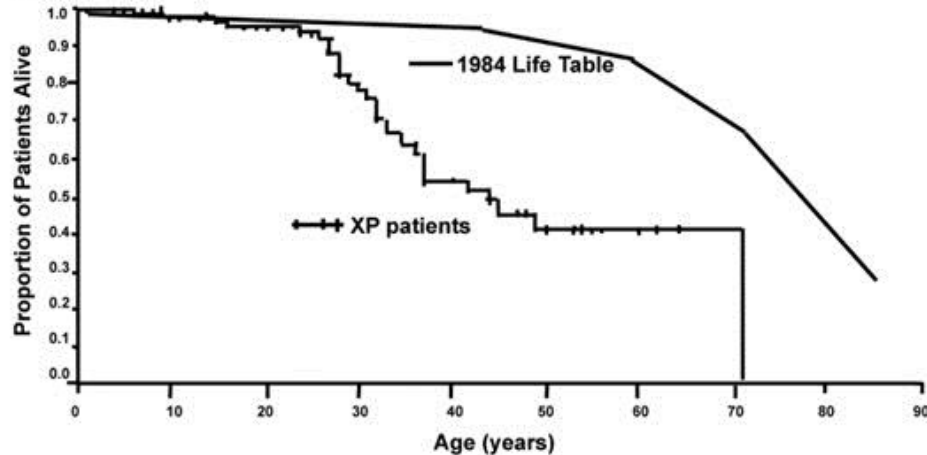
a



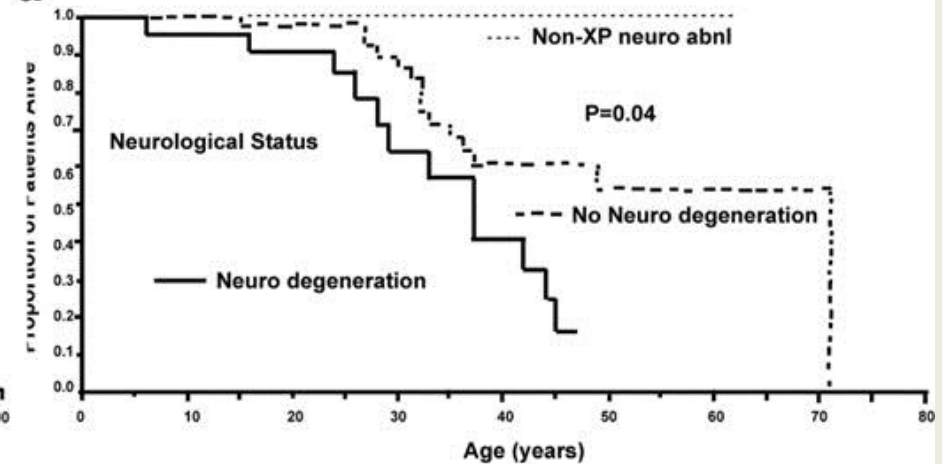
b



c



d



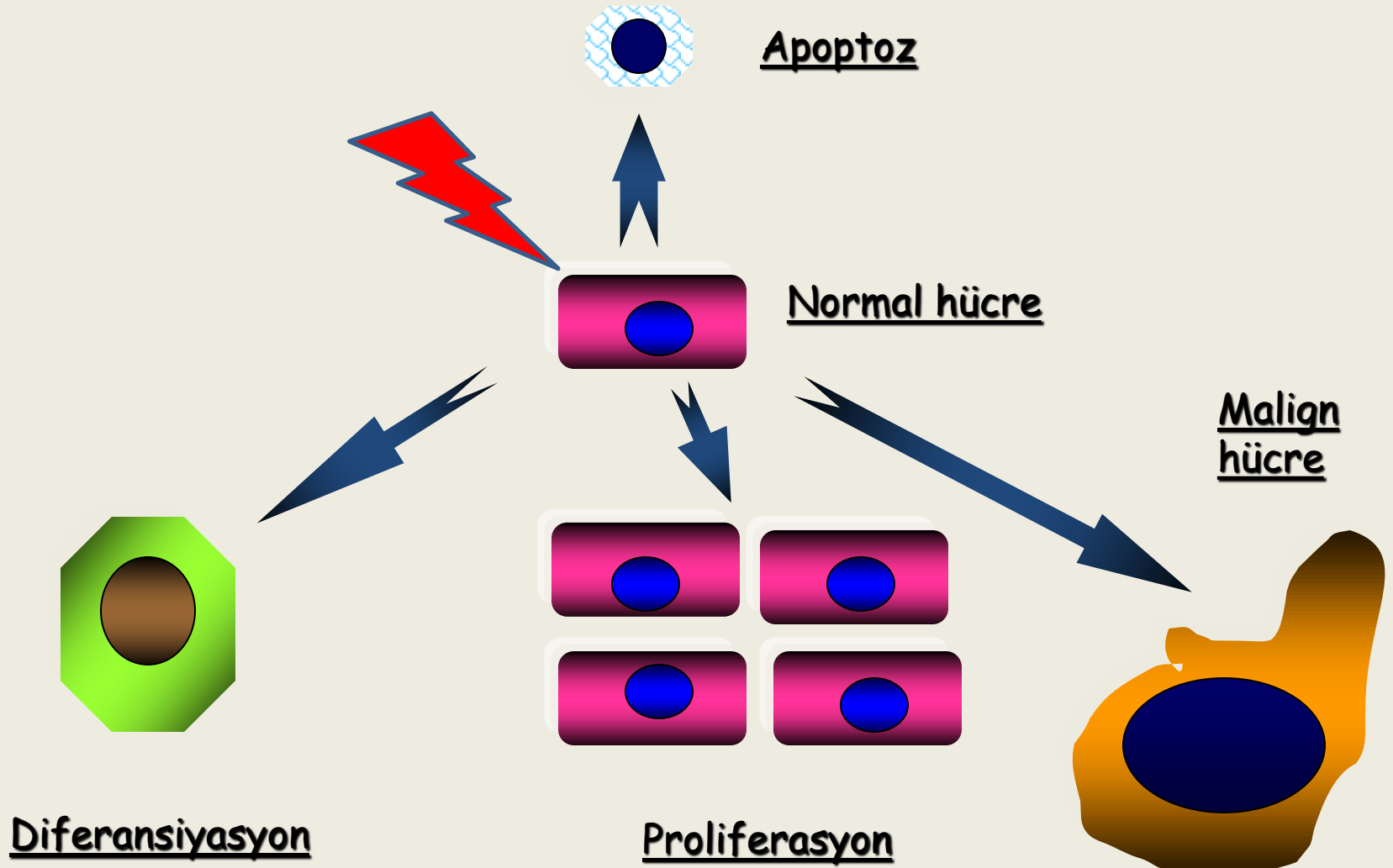
DNA Onarımı Bozuklukları

- Nükleotid Eksizyon Onarımı:
 - Xeroderma pigmentosum ve benzerleri
 - Mental gerilik
- İyonizan Radyasyon Zedelemeesi:
 - Ataksi telanjiektazi
- Uyumsuz Eşleşme Onarımı:
 - Kalıtsal kolon kanseri (HNPCC)

Genetic diseases associated with defects in DNA repair systems

Disease	Symptoms	Genetic defect
Xeroderma pigmentosum	Frecklelike spots on skin, sensitivity to sunlight, predisposition to skin cancer	Defects in nucleotide–excision repair
Cockayne syndrome	Dwarfism, sensitivity to sunlight, premature aging, deafness, mental retardation	Defects in nucleotide–excision repair
Trichothiodystrophy	Brittle hair, skin abnormalities, short stature, immature sexual development, characteristic facial features	Defects in nucleotide–excision repair
Hereditary nonpolyposis colon cancer	Predisposition to colon cancer	Defects in mismatch repair
Fanconi anemia	Increased skin pigmentation, abnormalities of skeleton, heart and kidneys, predisposition to leukemia	Possibly defects in the repair of interstrand cross–links
Ataxia telangiectasia	Defective muscle coordination, dilation of blood vessels in skin and eyes, immune deficiencies, sensitivity to ionizing radiation, predisposition to cancer	Defects in DNA damage detection and response
Li–Fraumeni syndrome	Predisposition to cancer in many different tissues	Defects in DNA damage response

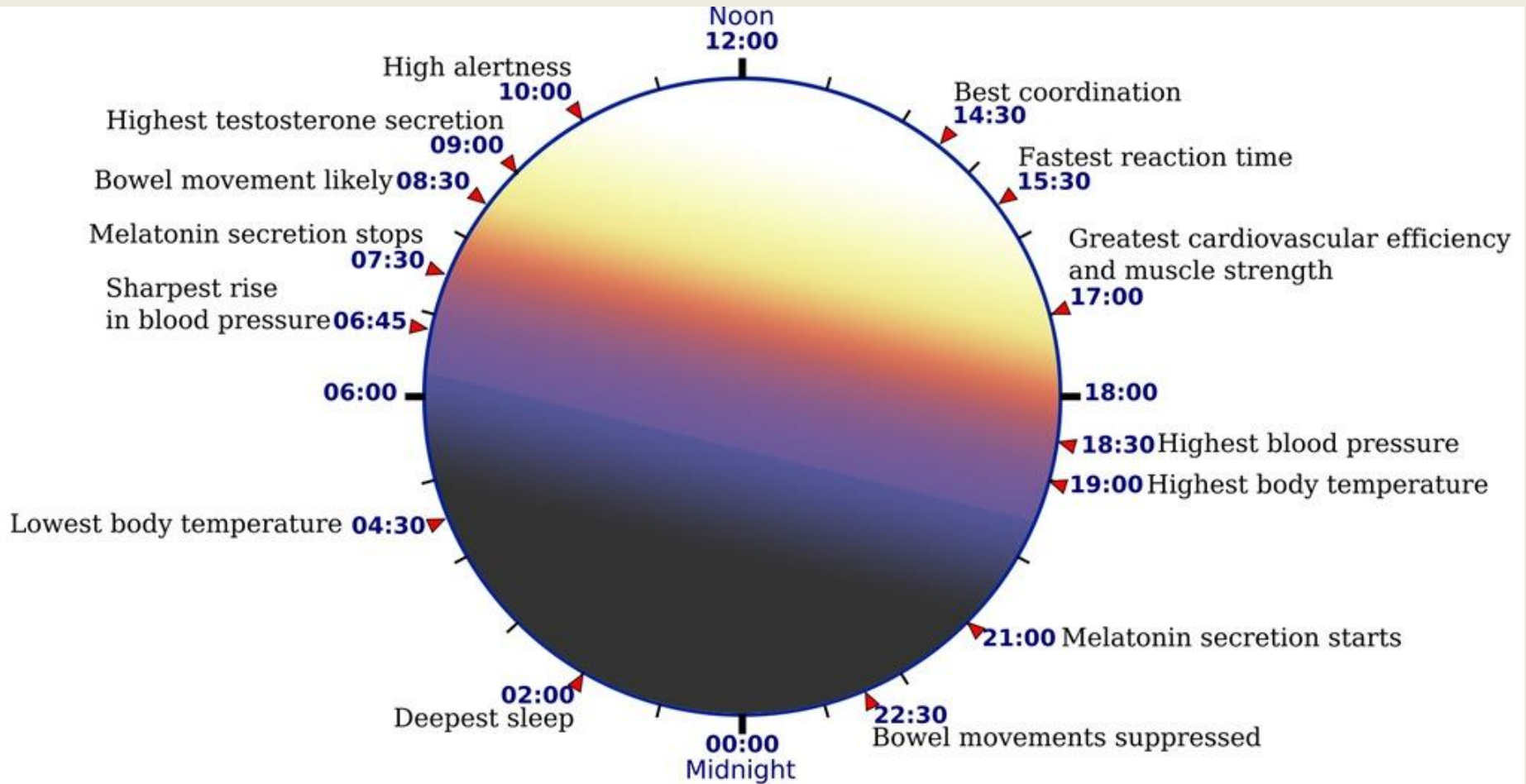
Hücrenin Kaderi

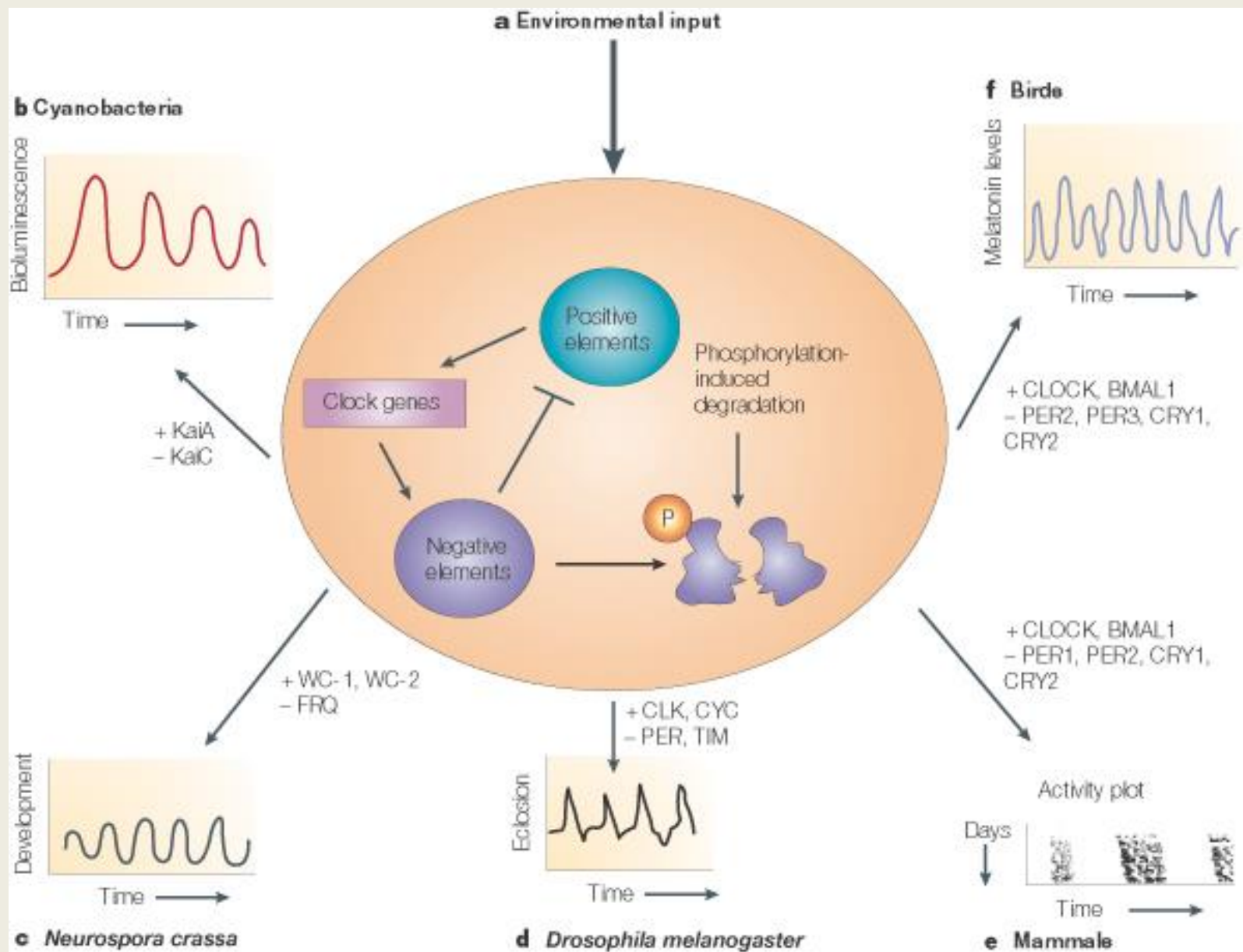


Biyolojik Saat

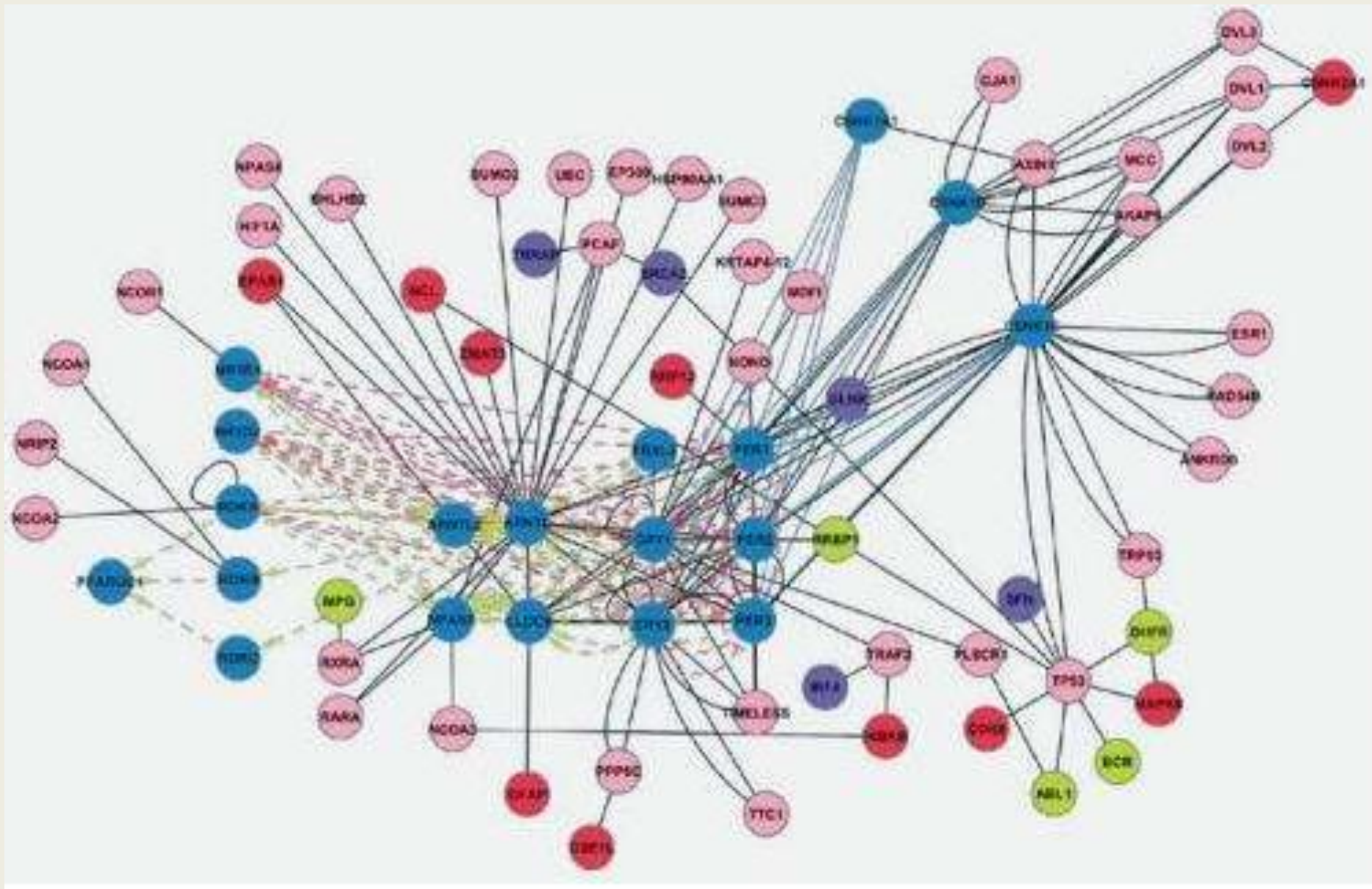
- Sirkadyen ritim
- Tüm canlılarda ort.24 saatlik siklus
- İç ve dış ayarlar
- Sancar'ın klonladığı fotoliyaz geninin memelilerdeki eşi: kriptogenleri
- Birçok gen saati oluşturuyor

Biyolojik Saatler





Biyolojik Saat - Enzimatik Bağlantılar



Biliyor musun ?
Genetik şifreyi
çözdüm !

Ama hala
kadınları
anlamıyorum

HUMAN GENO



CHAMPATTE

Vehbi Koç Vakfı Ödülü 2007



