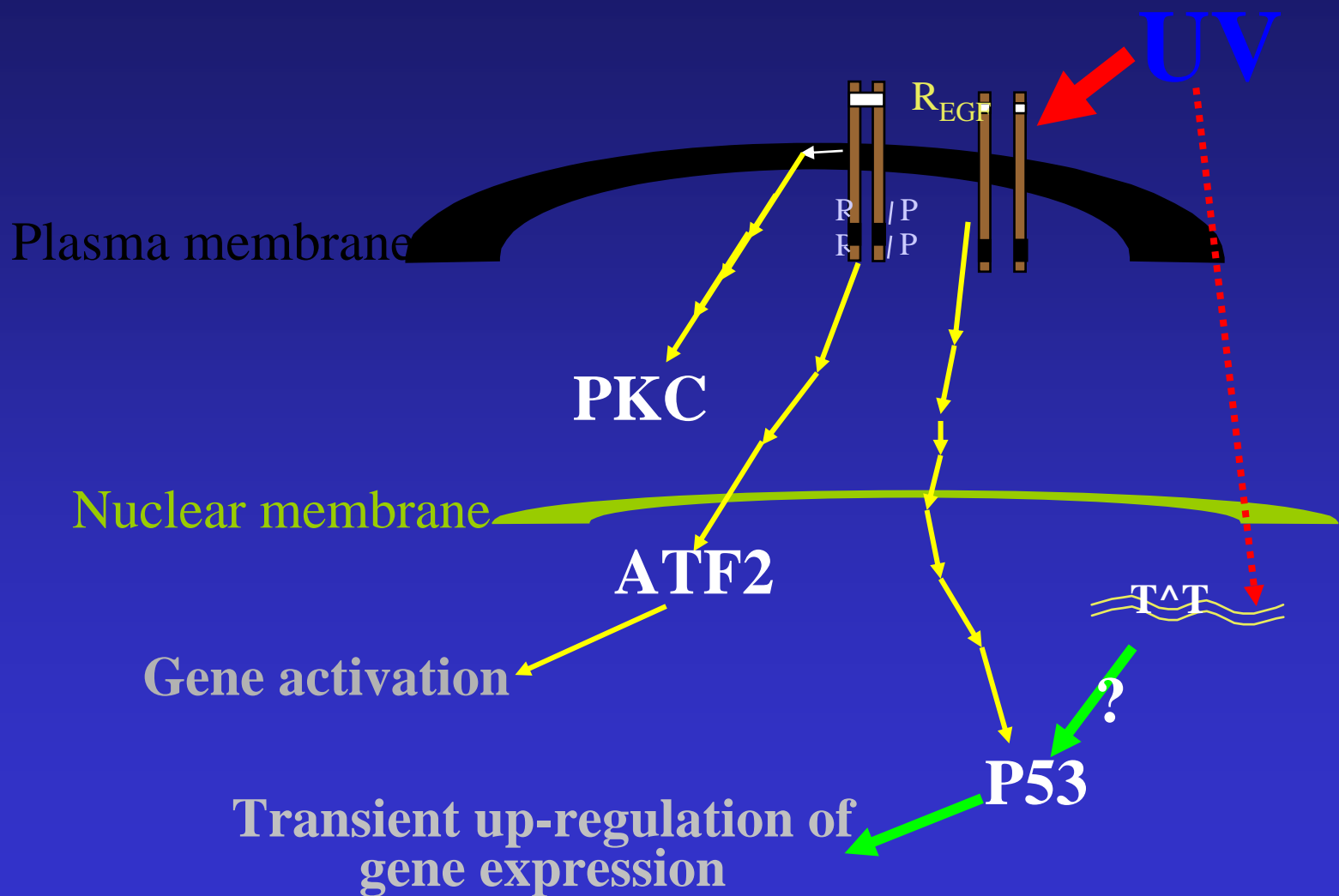


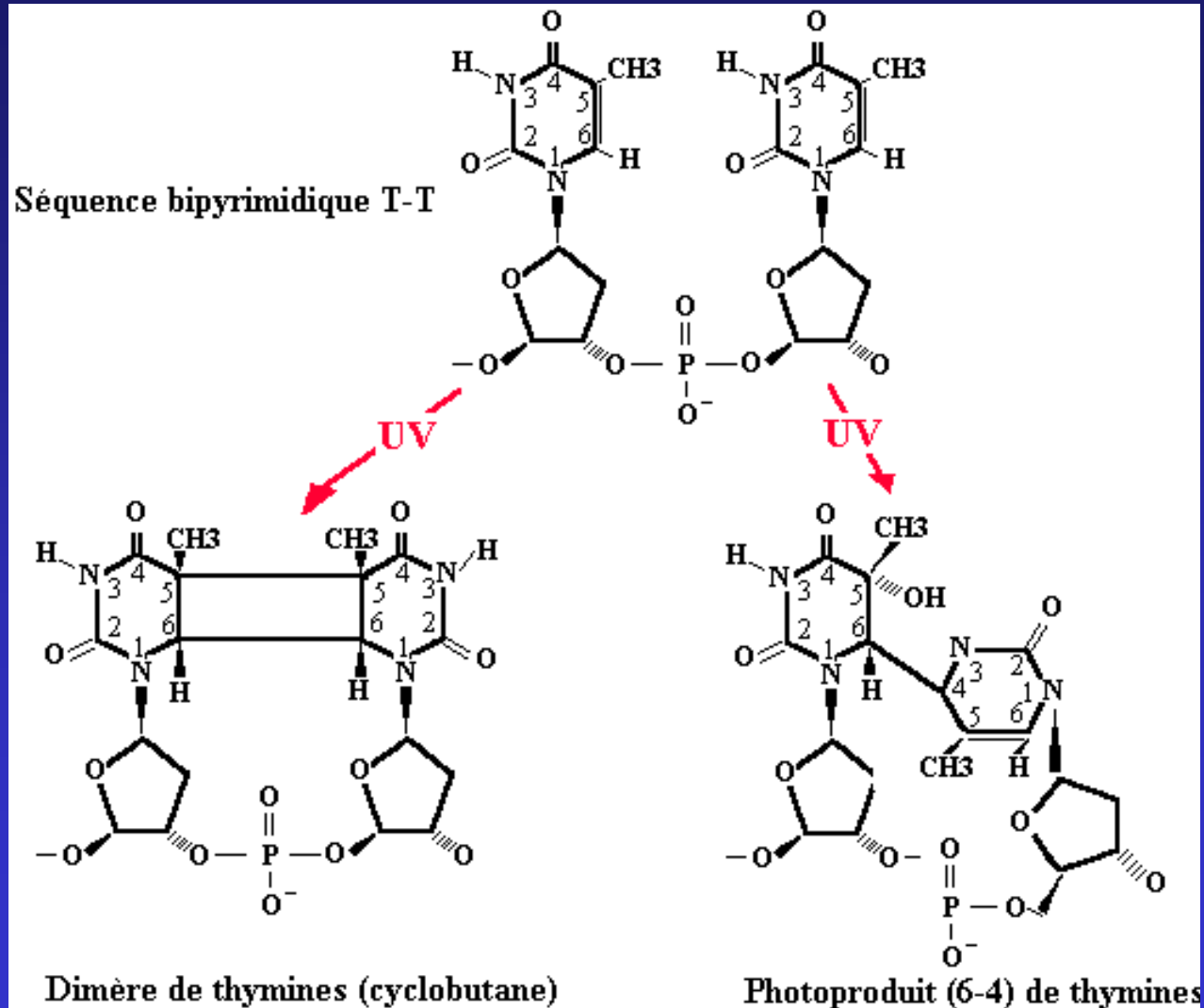


# **Le systèmes de réparation de l'ADN, une activité peut en cacher une autre**

# UVC-activation of signal transduction pathways



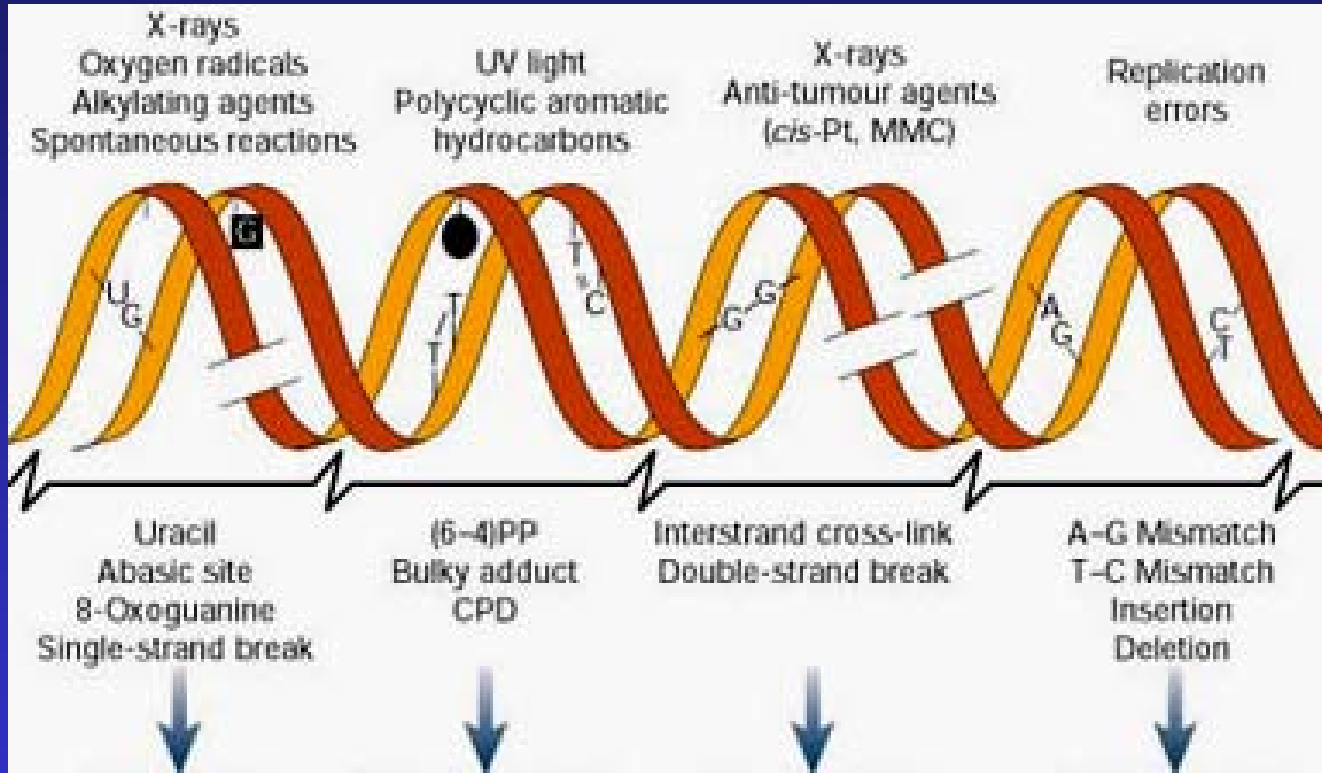
# Représentation d'un dimère provoqué par les UV pouvant générer des mutations



# Principal DNA repair pathways



## Damaging agent

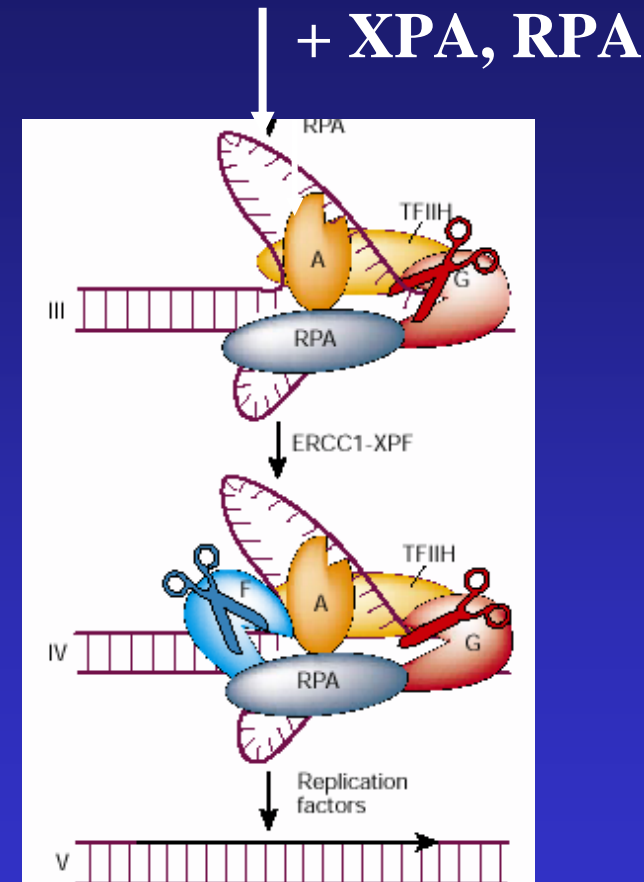
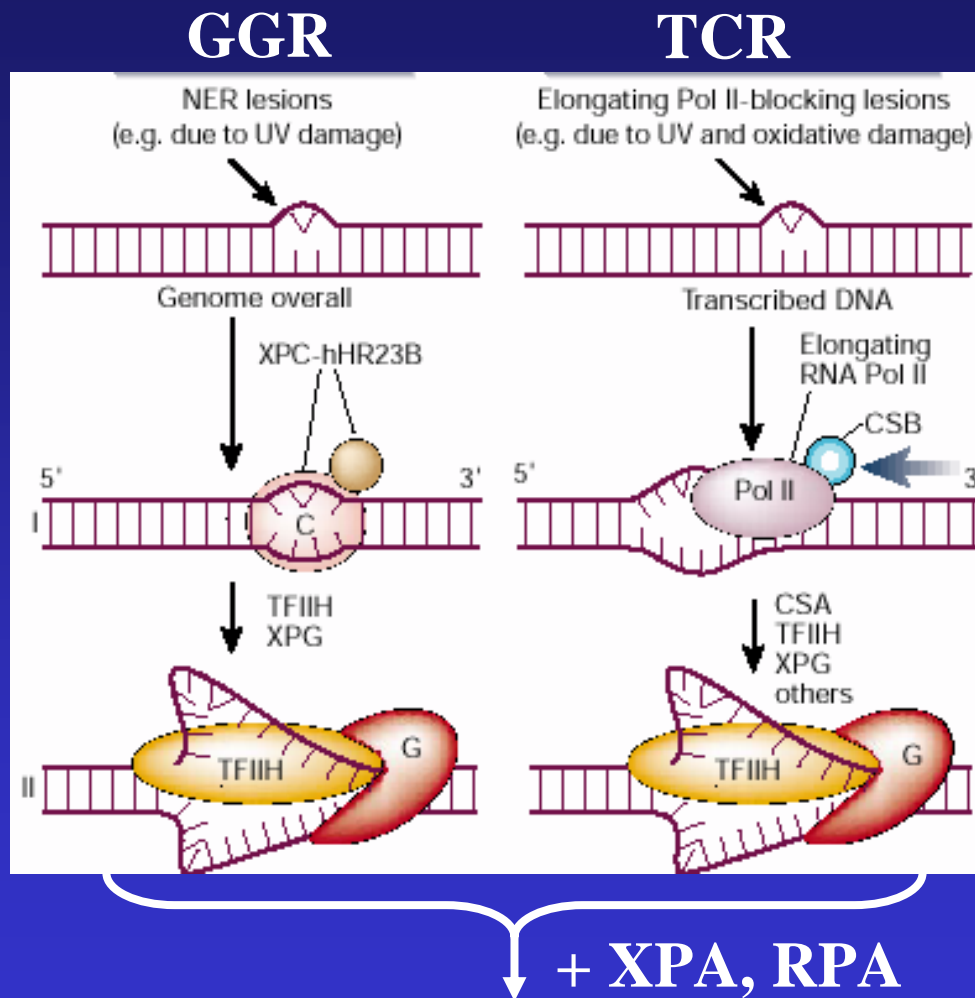


**BER    NER    HR EJ    MMR    PHR NIR**

## Repair process

After Jan H. J. Hoeijmakers, *Nature*, 411, 366 - 374 (2001)

# Nucleotide Excision Repair



After Jan H. J. Hoeijmakers, NATURE, 2001, 411, 366

# Properties of *KIN17*, a human gene involved in DNA replication

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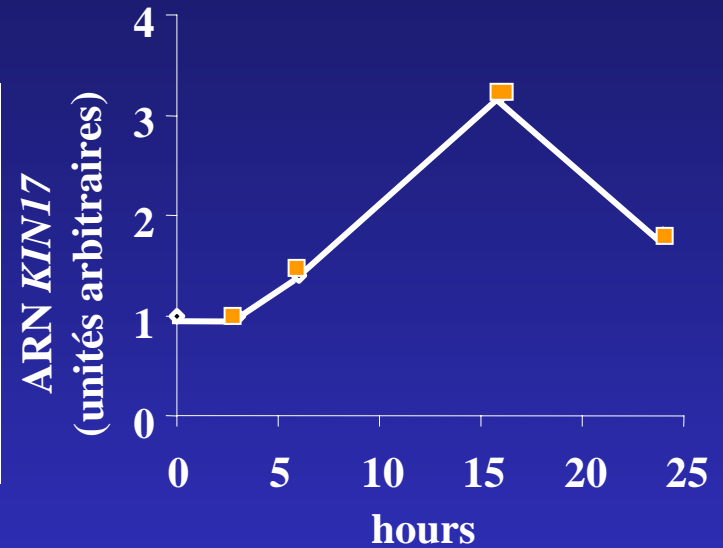
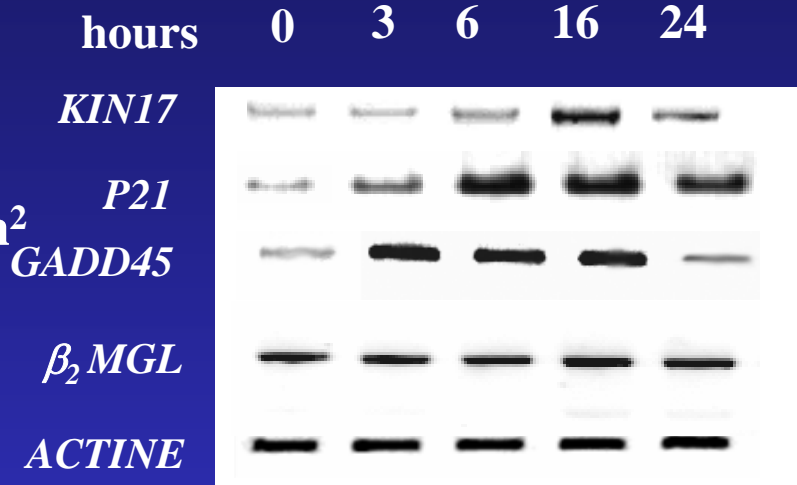


- It participates in a cellular response to diverse genotoxics which is conserved during evolution.
- KIN17* gene seems to be essential during cell proliferation, in transactions related to DNA replication.
- KIN17* gene expression is modified in human and mouse tumors and tumor-derived cell lines.

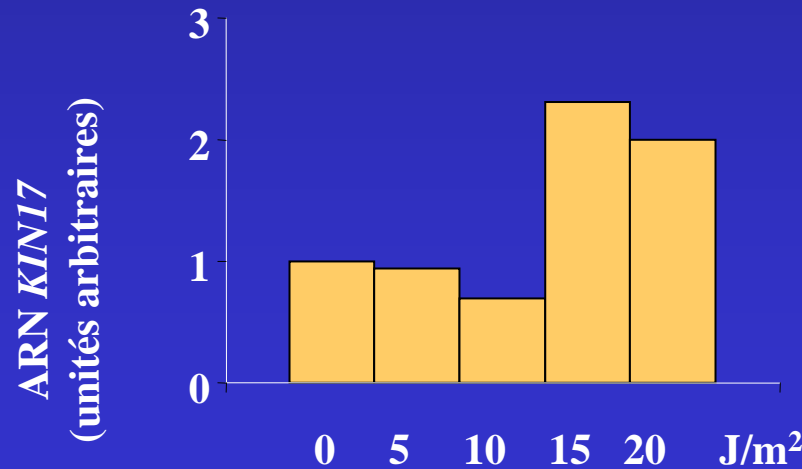
# UVC-irradiation of human primary cultured cells up-regulates *KIN17* RNA



• A 15 J/m<sup>2</sup>



• A 16 h

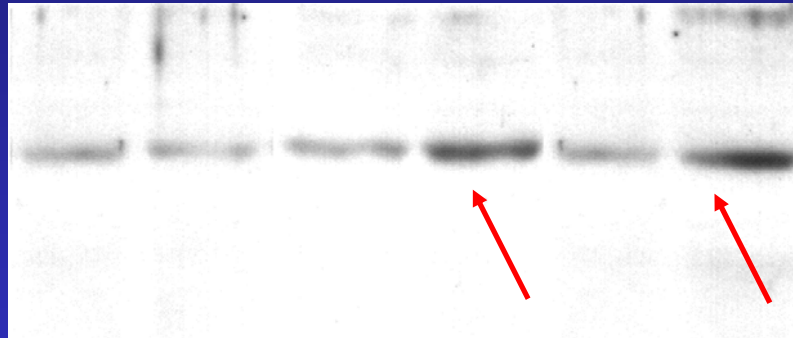


# UVC increases kin17 protein level and provokes an intranuclear accumulation



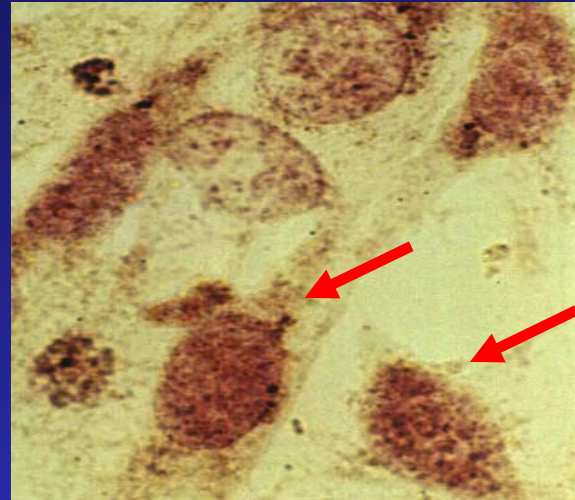
1 h                      13 h                      15 h

kin17  
(45 kDa)



J/m<sup>2</sup>    0    15    0    15    0    15

Western blot



15 J/m<sup>2</sup>

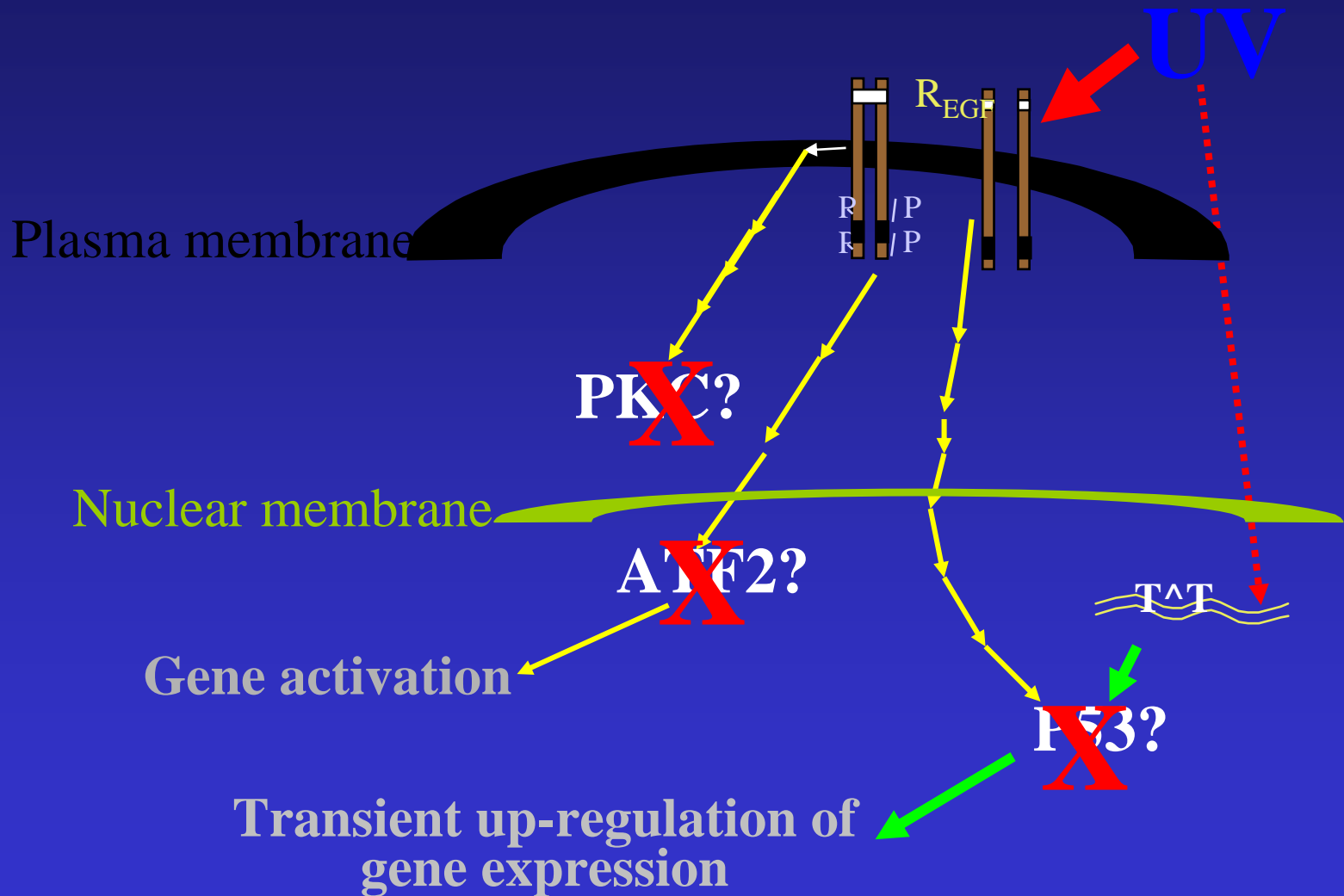


0 J/m<sup>2</sup>

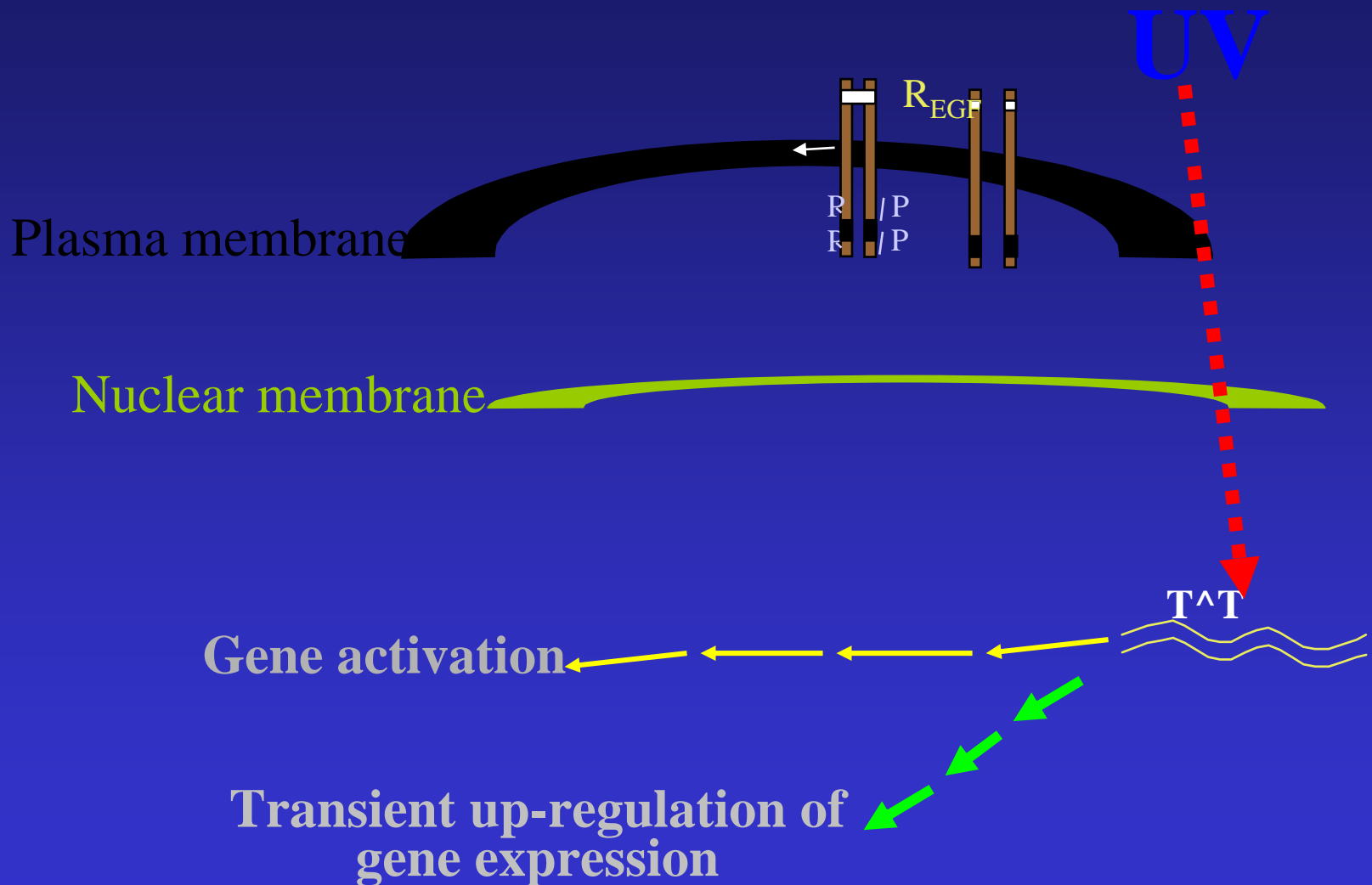
Immunocytochemistry



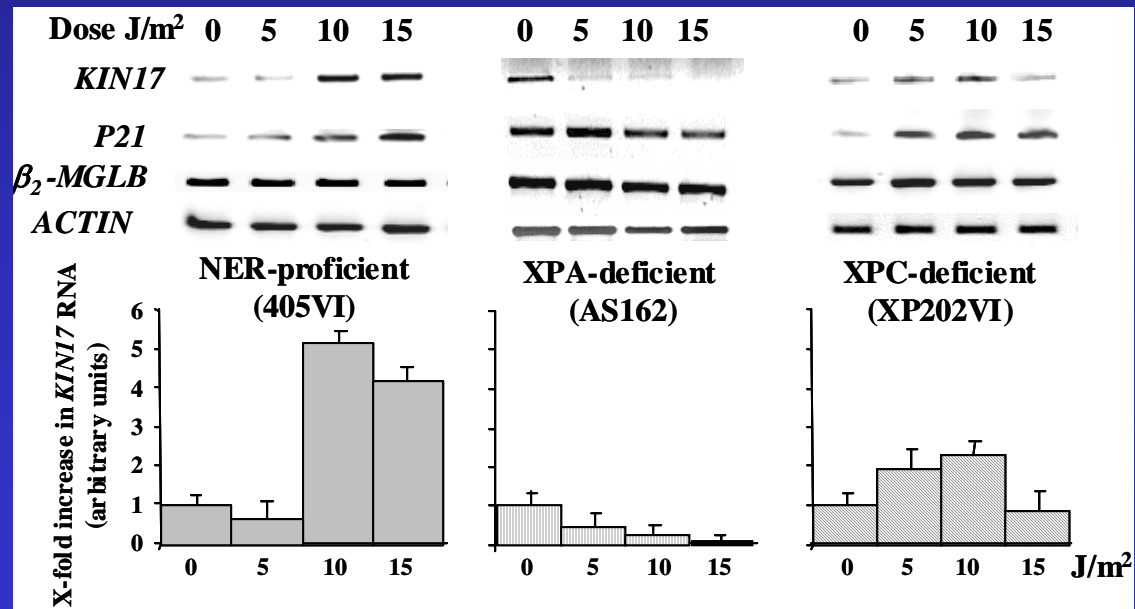
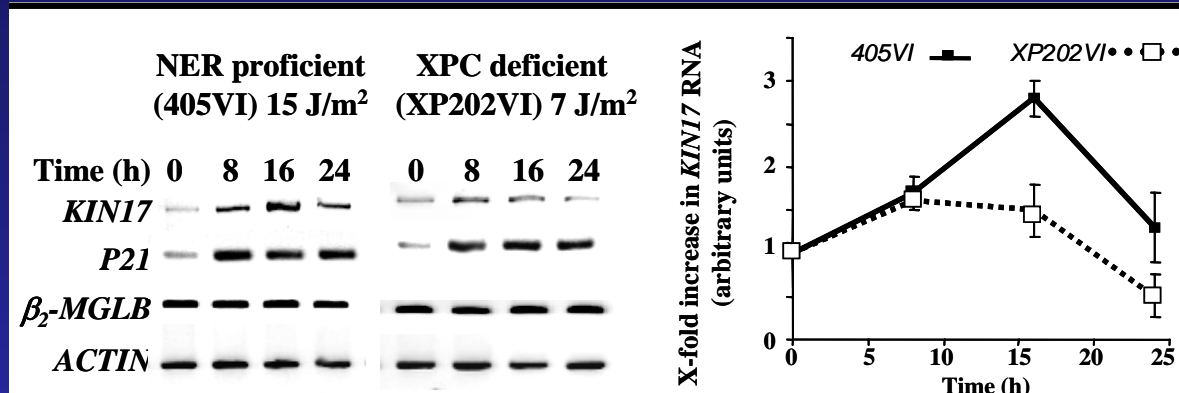
# What is the UV-induced transduction pathway that up-regulates the expression of *KIN17* gene?



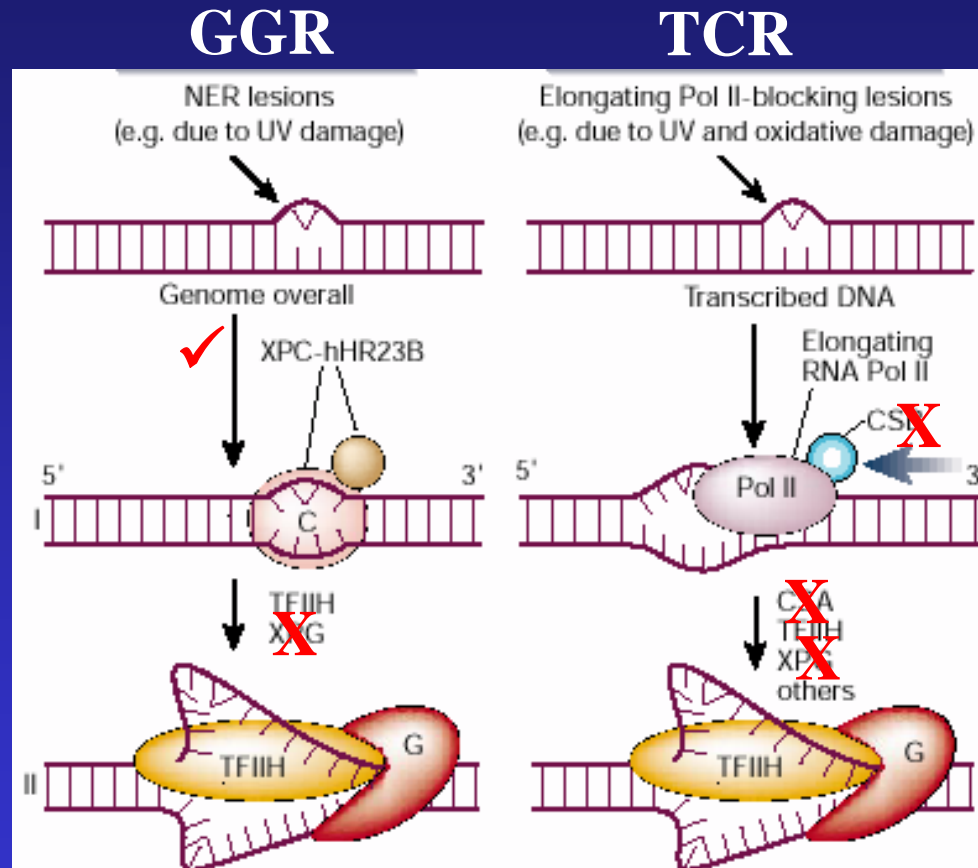
# Signal transduction by a novel nucleoplasmic pathway?



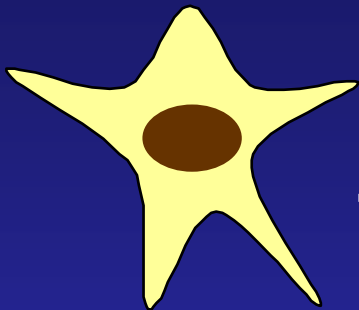
# Several NER deficient cells fail to up-regulate *KIN17* RNA



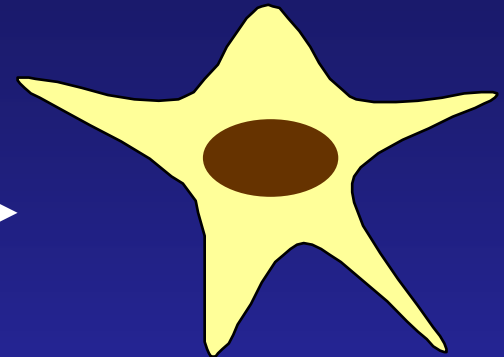
# NER defects inactivating the induction of *KIN17* gene



# Experimental approach: genetic complementation of a human established cell line $NER^{-/-}$

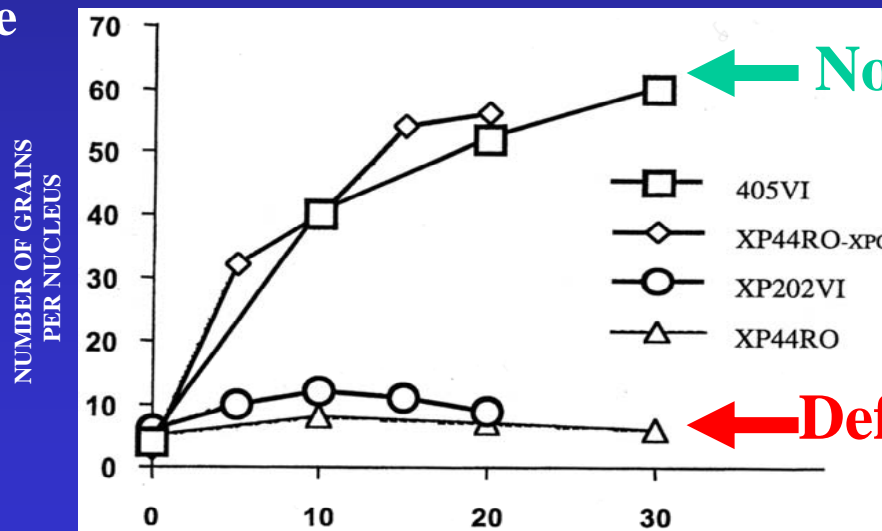


+ ADNc XPC  
antibiotic selection



XP44RO, cells derived from a testicular melanoma, carrying a XPC mutation, therefore  $NER-GGR$  deficient

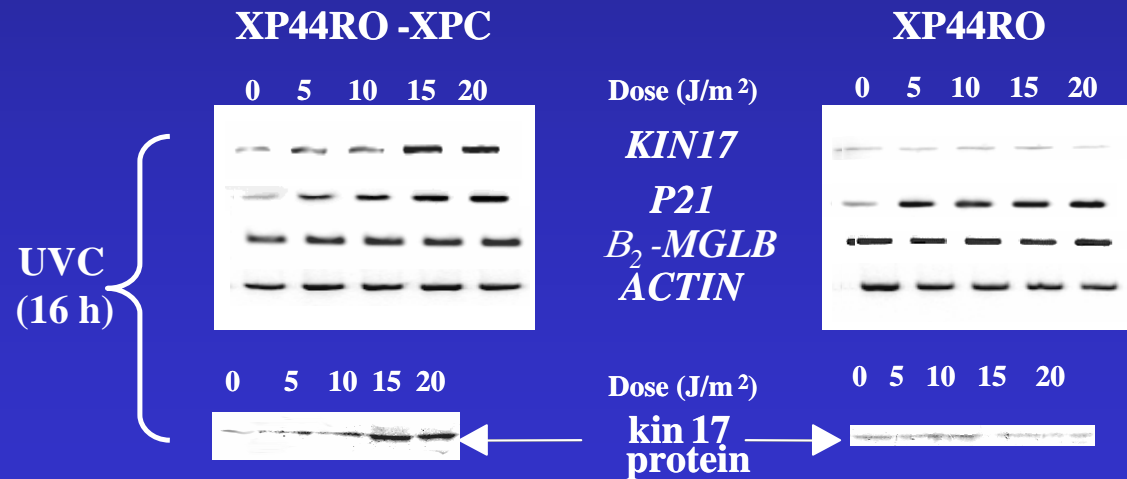
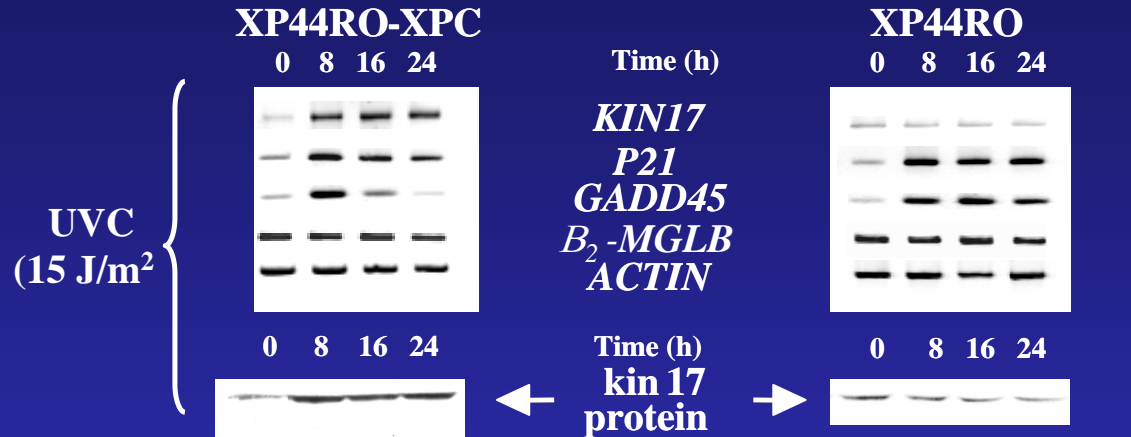
XP44RO-XPC



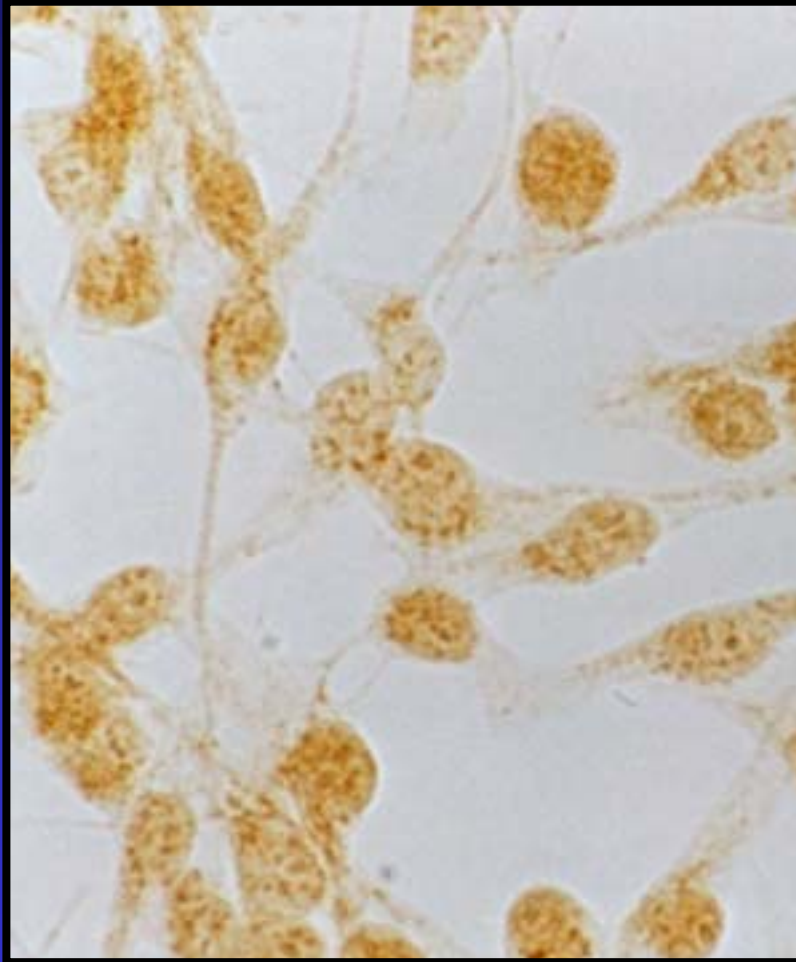
← Normal repair

← Deficient repair

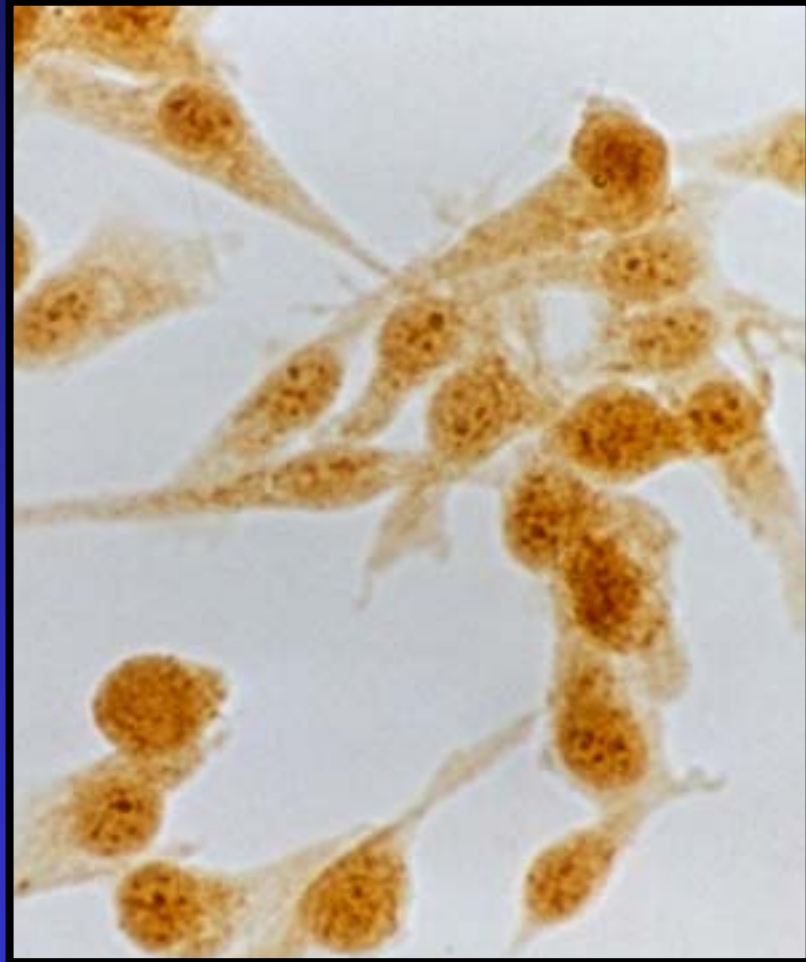
# Complemented XPC cells recover the up-regulation of *KIN17* RNA



# UVC-induced intranuclear accumulation of kin17 protein in complemented XPC cells



**XP44RO**



**XP44RO-XPC**

# Conclusions

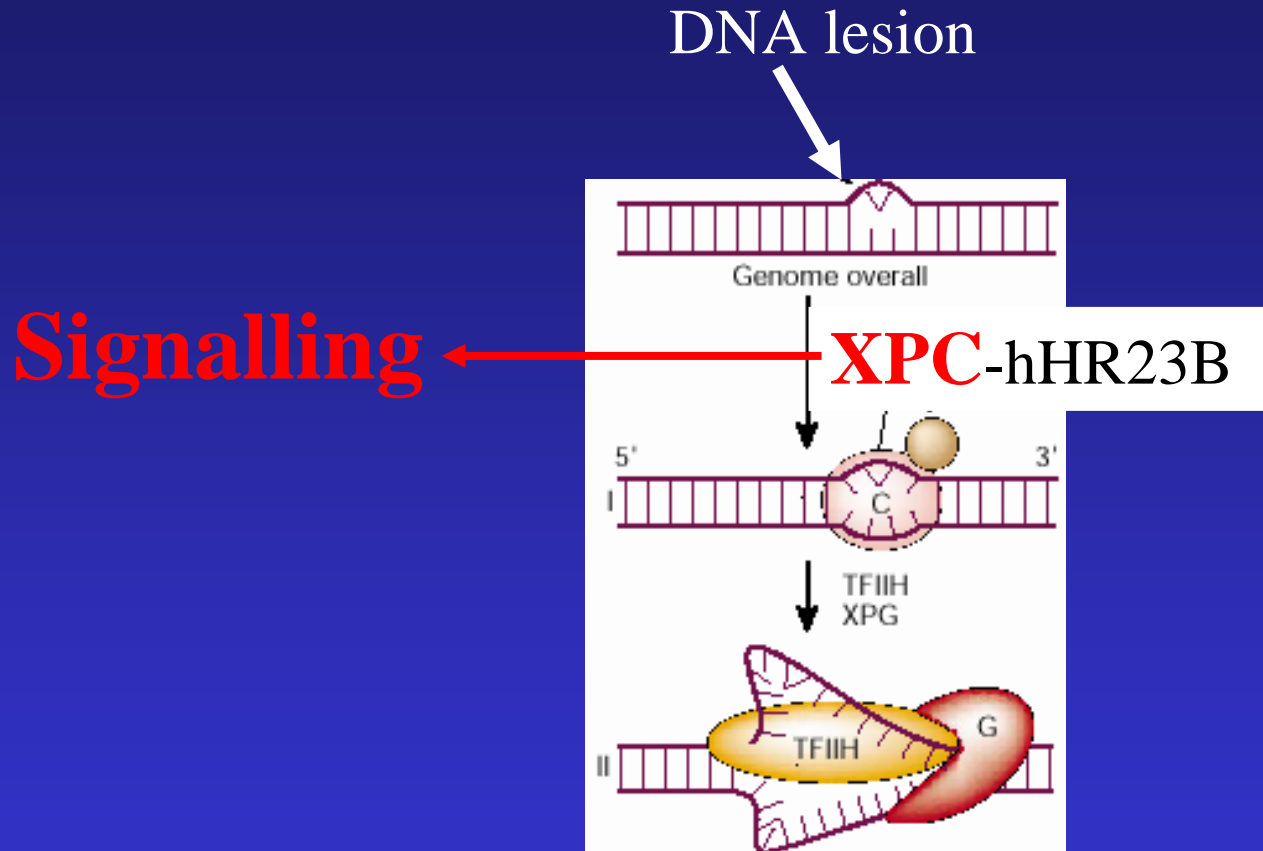
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- ***KIN17* RNA accumulation after UVC is independent of p53, ATF2 and the pathway controlled by the PKC.**
- **XPA and XPC proteins are essential for the UV-induced up-regulation suggesting their participation in a novel intranuclear signalling pathway.**



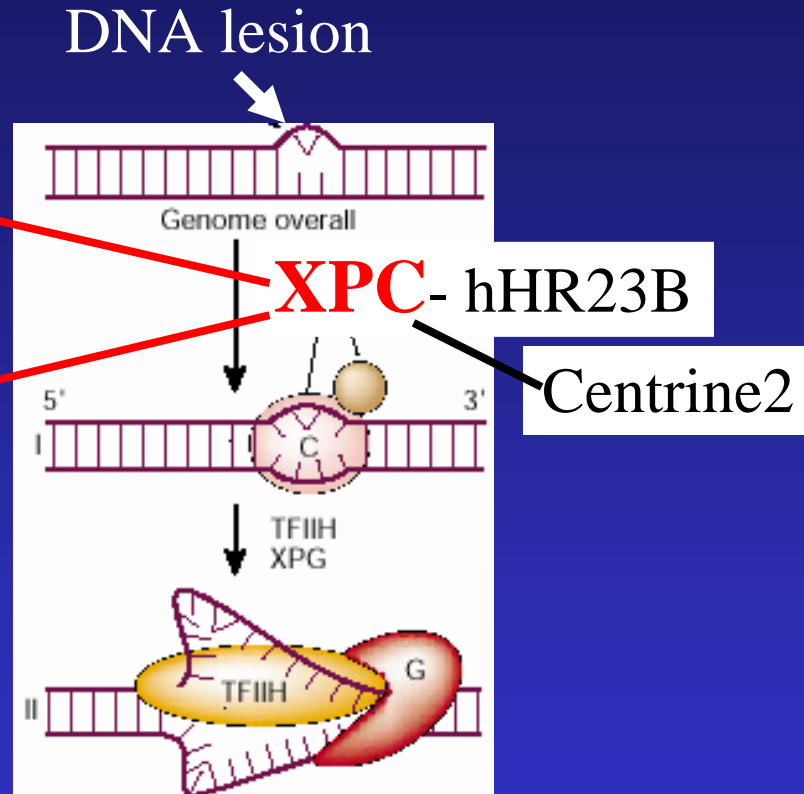
# A new role of XPC protein



# XPC protein regulates GG-NER



**Signalling**  
**Regulation**



- Centrine2 { Araki et al., (2001), J. Biol. Chem., 276, 18665-72  
Popescu et al., (2003), J. Biol. Chem., 278, 40252-61
- hHR23B Ng et al., (2003), Genes and Dev., 17, 1630-5

# Conclusions

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- **XPC protein is a multifunctional enzyme involved in DNA repair, transcriptional and postranscriptional regulation and in signalling the presence of lesions.**
- **The capacity of XPC protein to bind to a wide range of DNA structures and to bind to CEN2 suggest that the XPC cancer-prone phenotypes are partly due to defects in the mechanism that couples cell division to NER and/or in the repair reaction involving the XPC-HR23B-CEN2 complex.**

# Laboratoire de génétique de la radiosensibilité

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Laurent MICCOLI



Karène ANTOINE

# CREDITS

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**and Jacques GRASSI**  
**SPI, CEA, Saclay**

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**Karlsruhe, Allemagne**









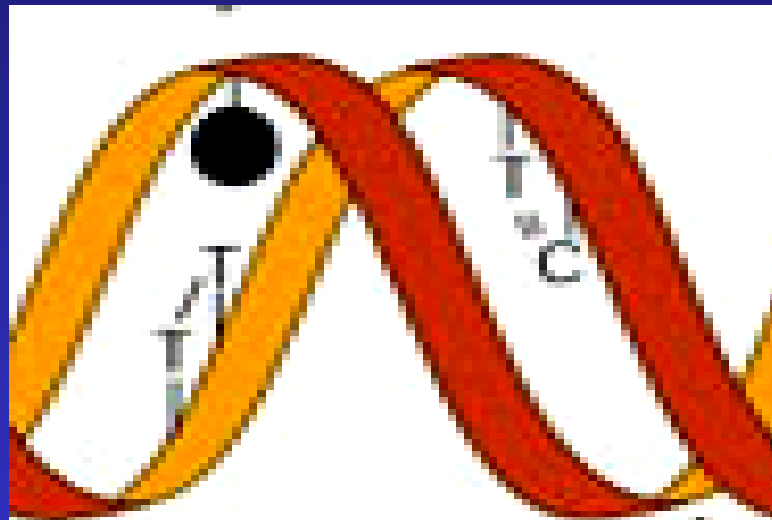


# Nucleotide Excision Repair of UV lesions



Polycyclic aromatic  
Hydrocarbons

UV



(6-4)PP  
Bulky adduct  
CPD

**NER**

After Jan H. J. Hoeijmakers, *Nature* 411, 366 - 374 (2001)