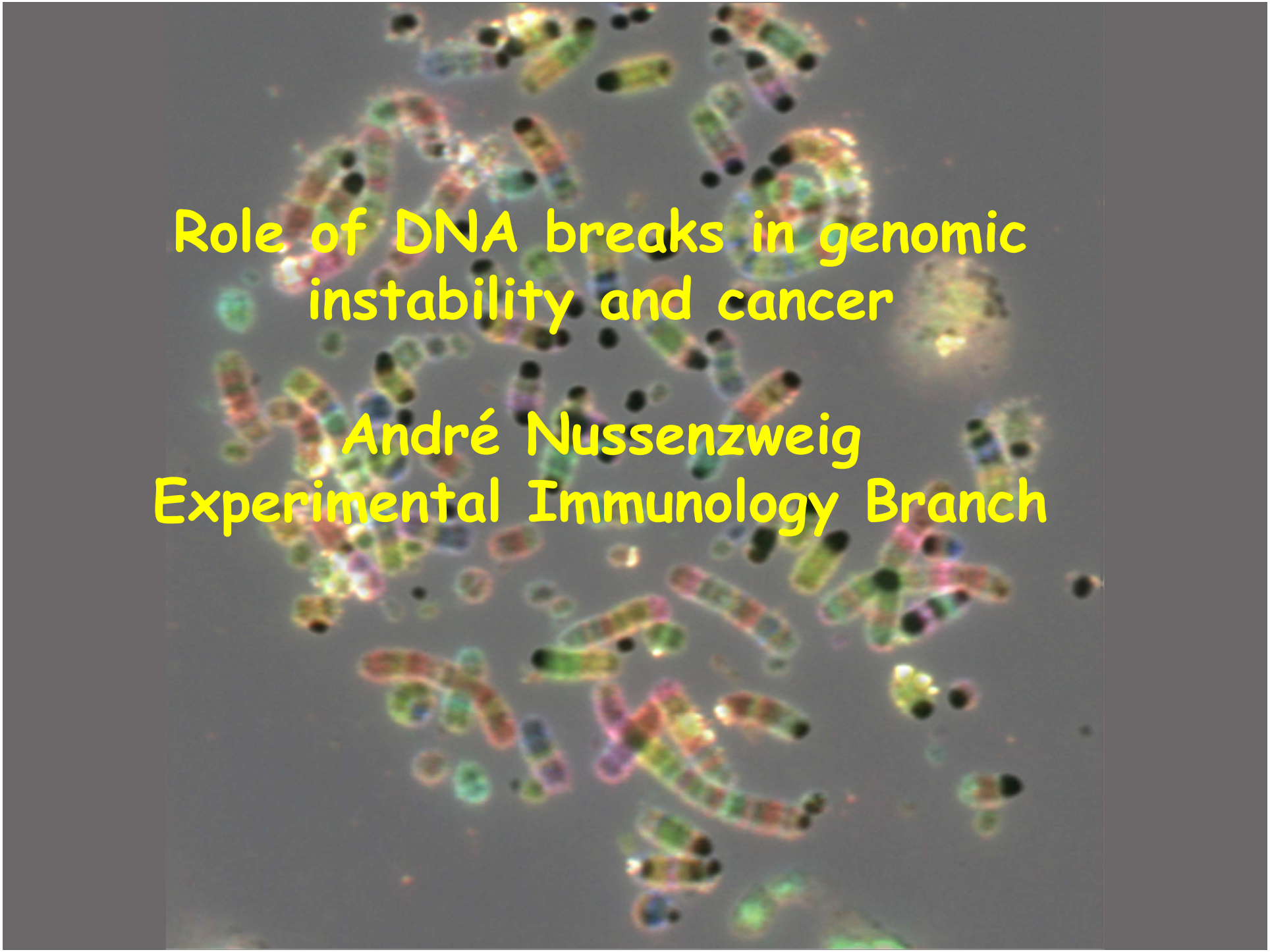
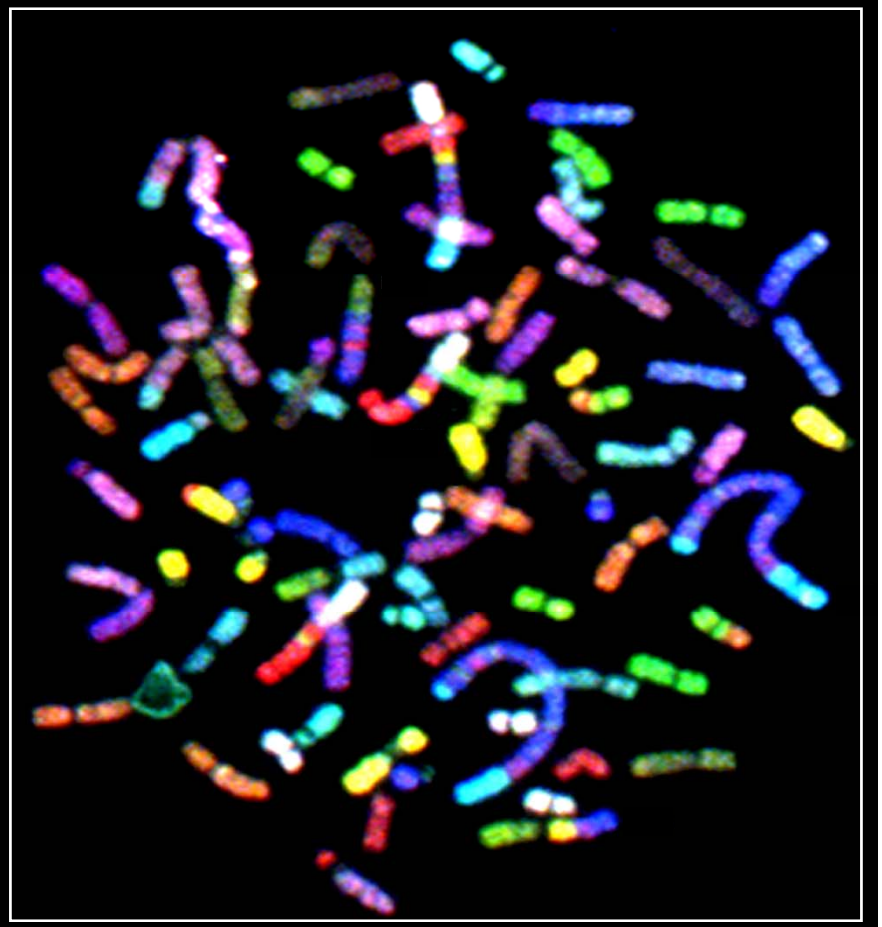
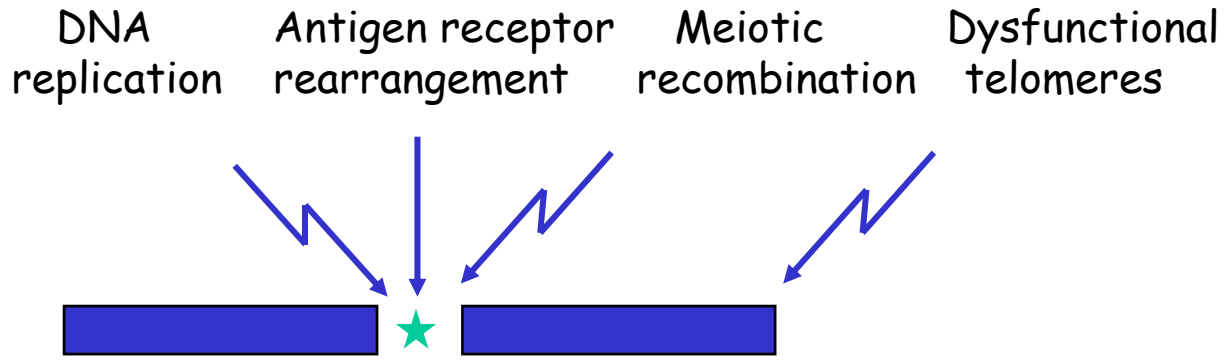

Role of DNA breaks in genomic instability and cancer
André Nussenzweig
Experimental Immunology Branch

Normal cell

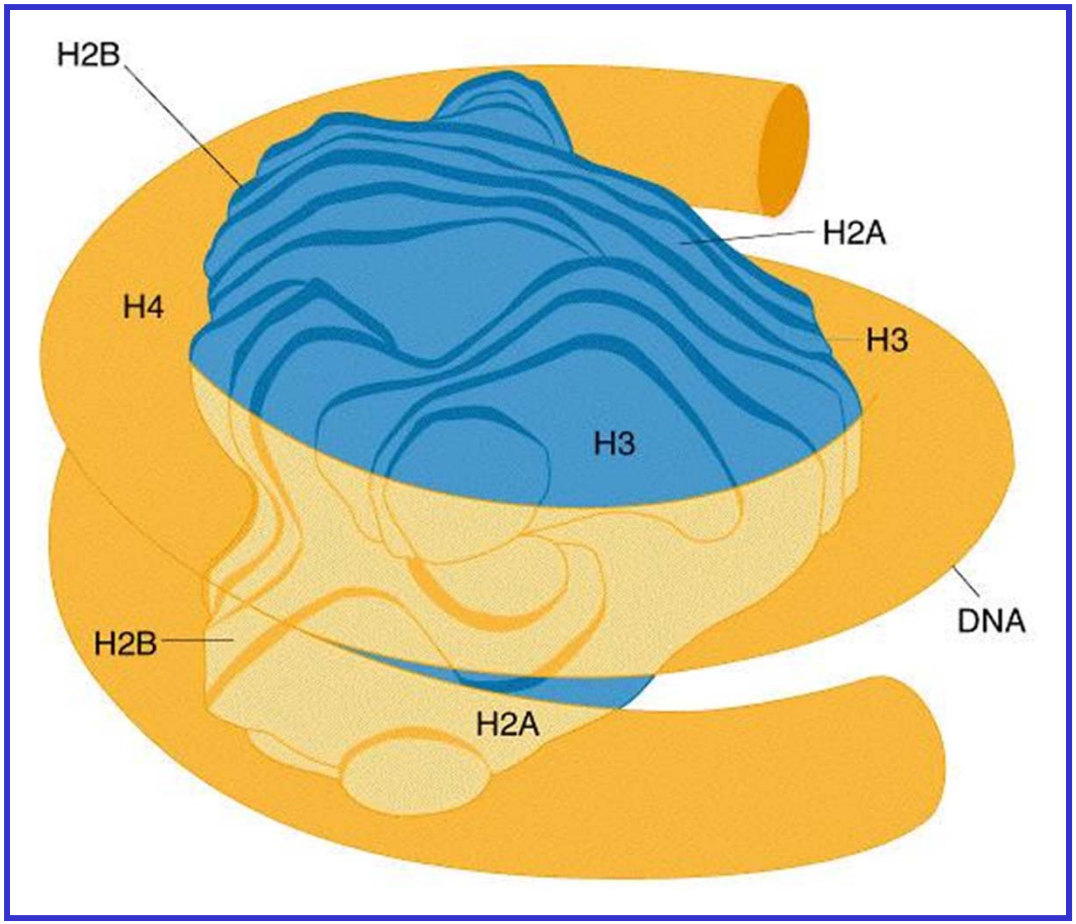
Cancer cell



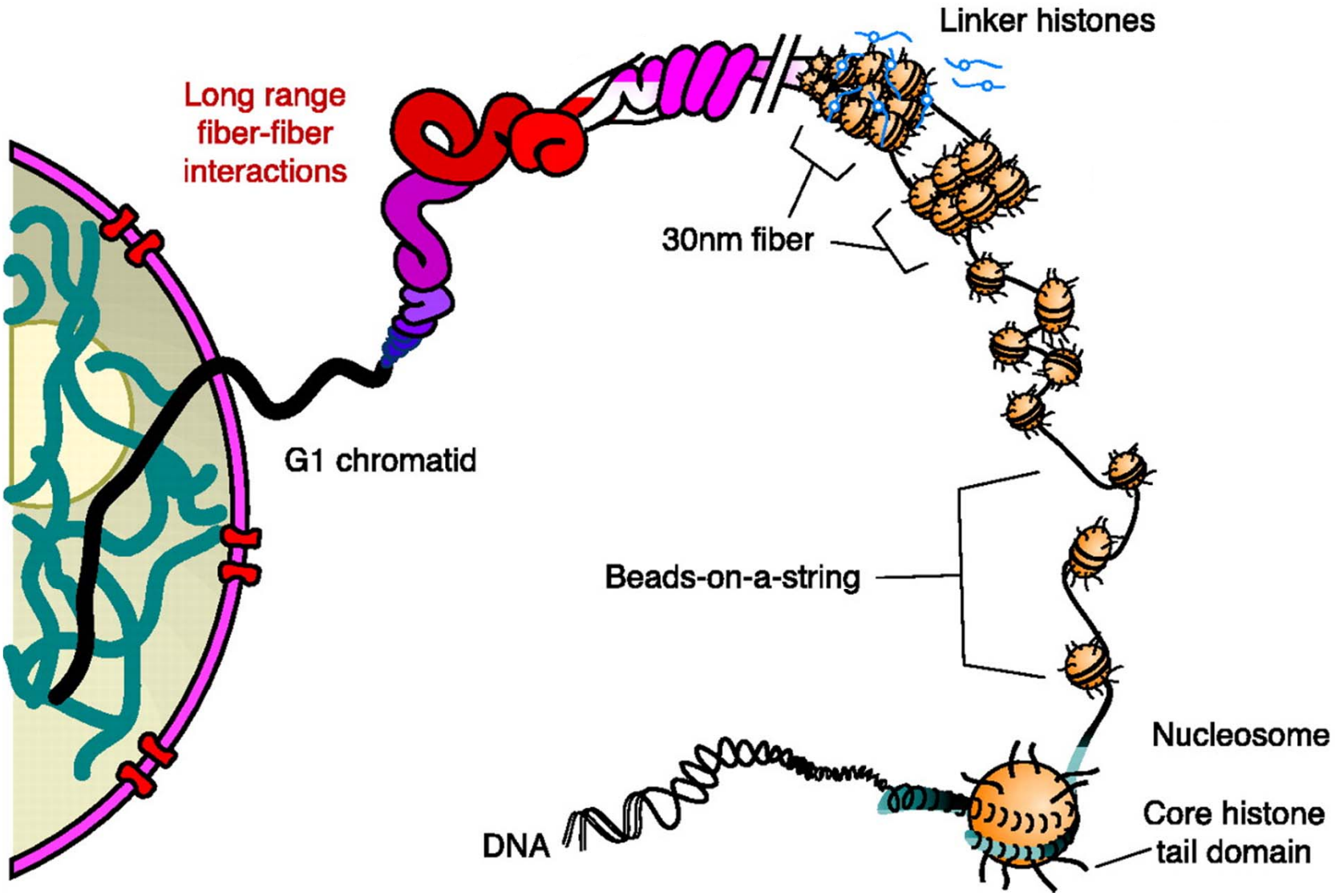
DNA double strand breaks



The nucleosome

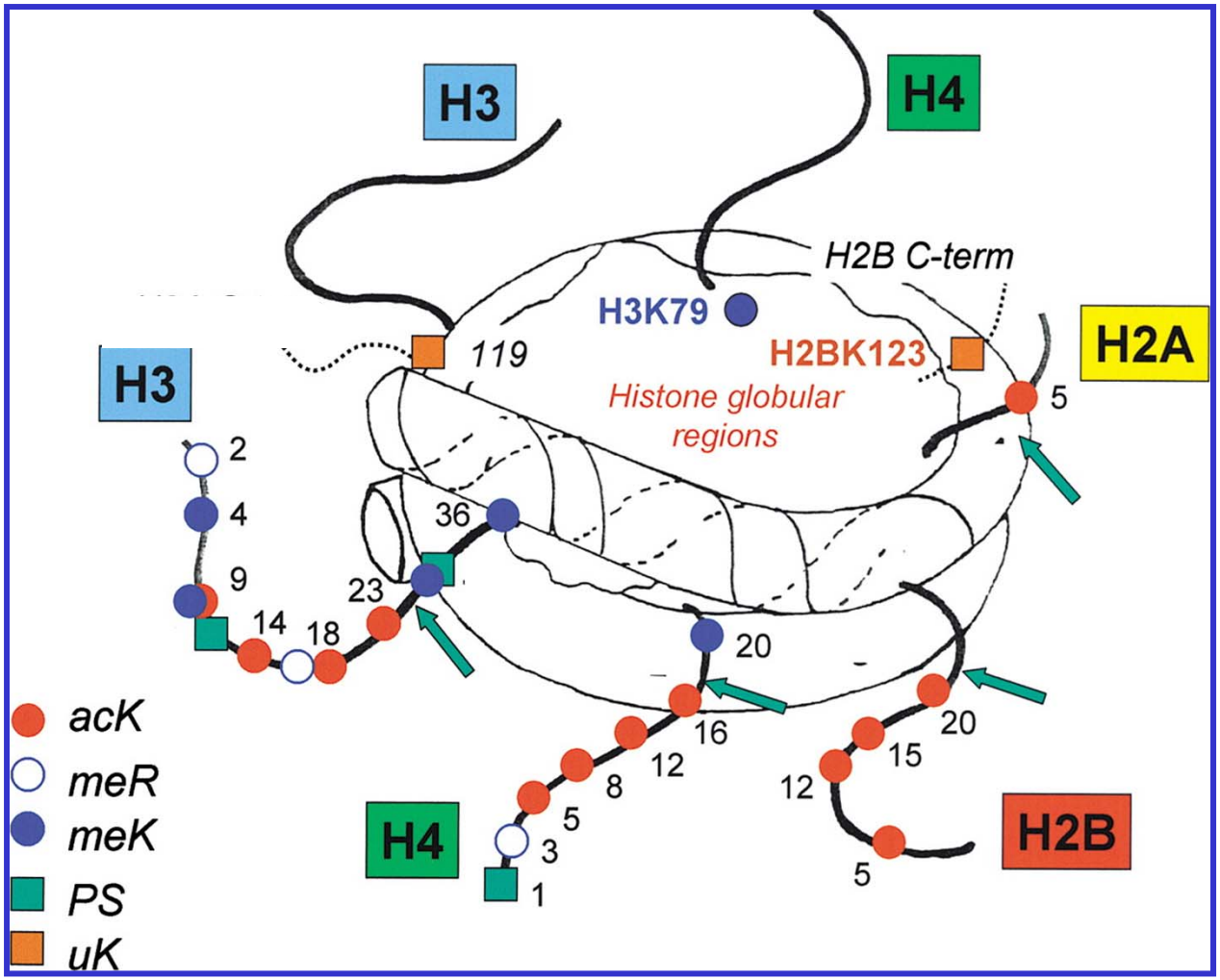


Nucleosomes package DNA into the nucleus

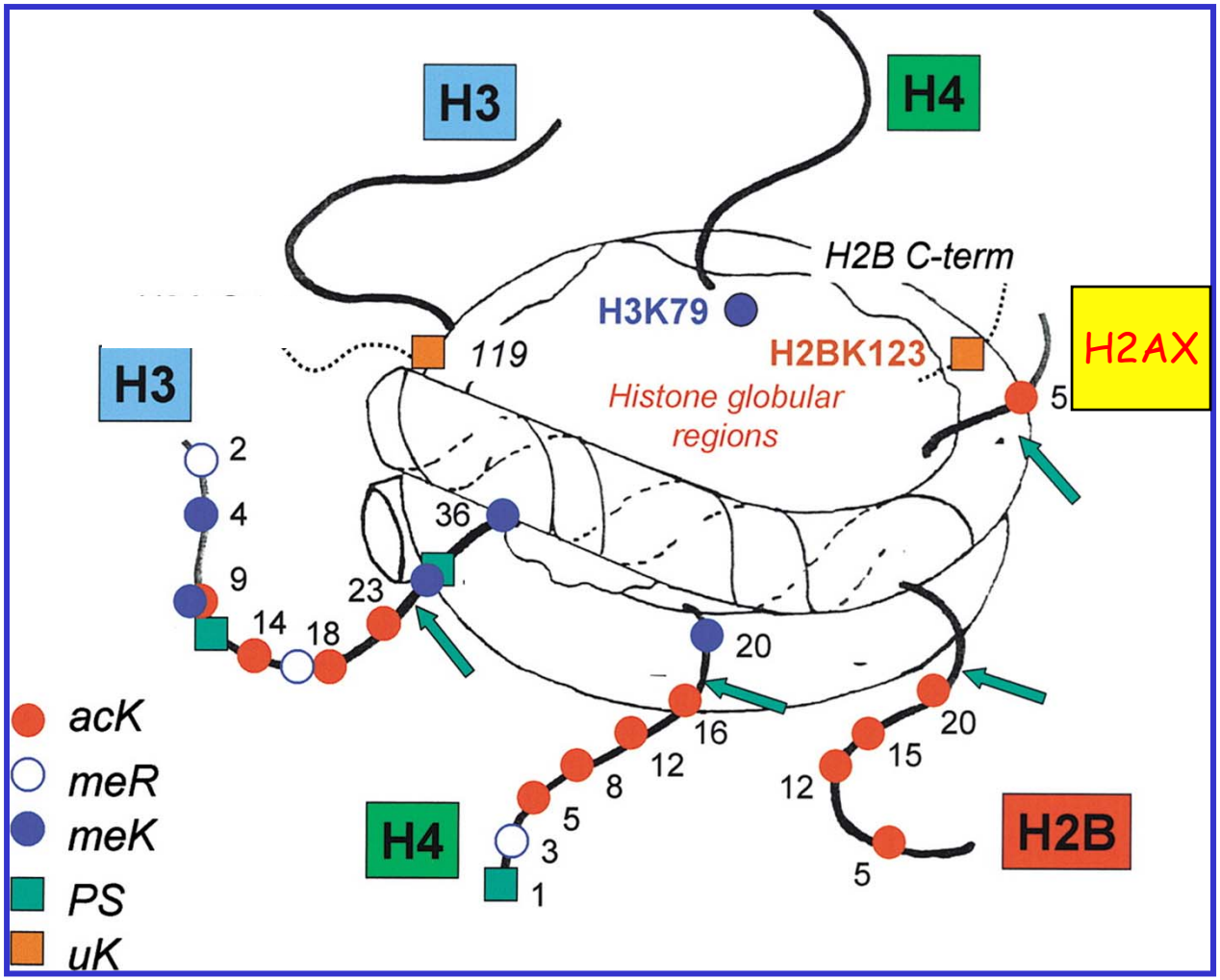


P. J. Horn et al. *Science* 2002

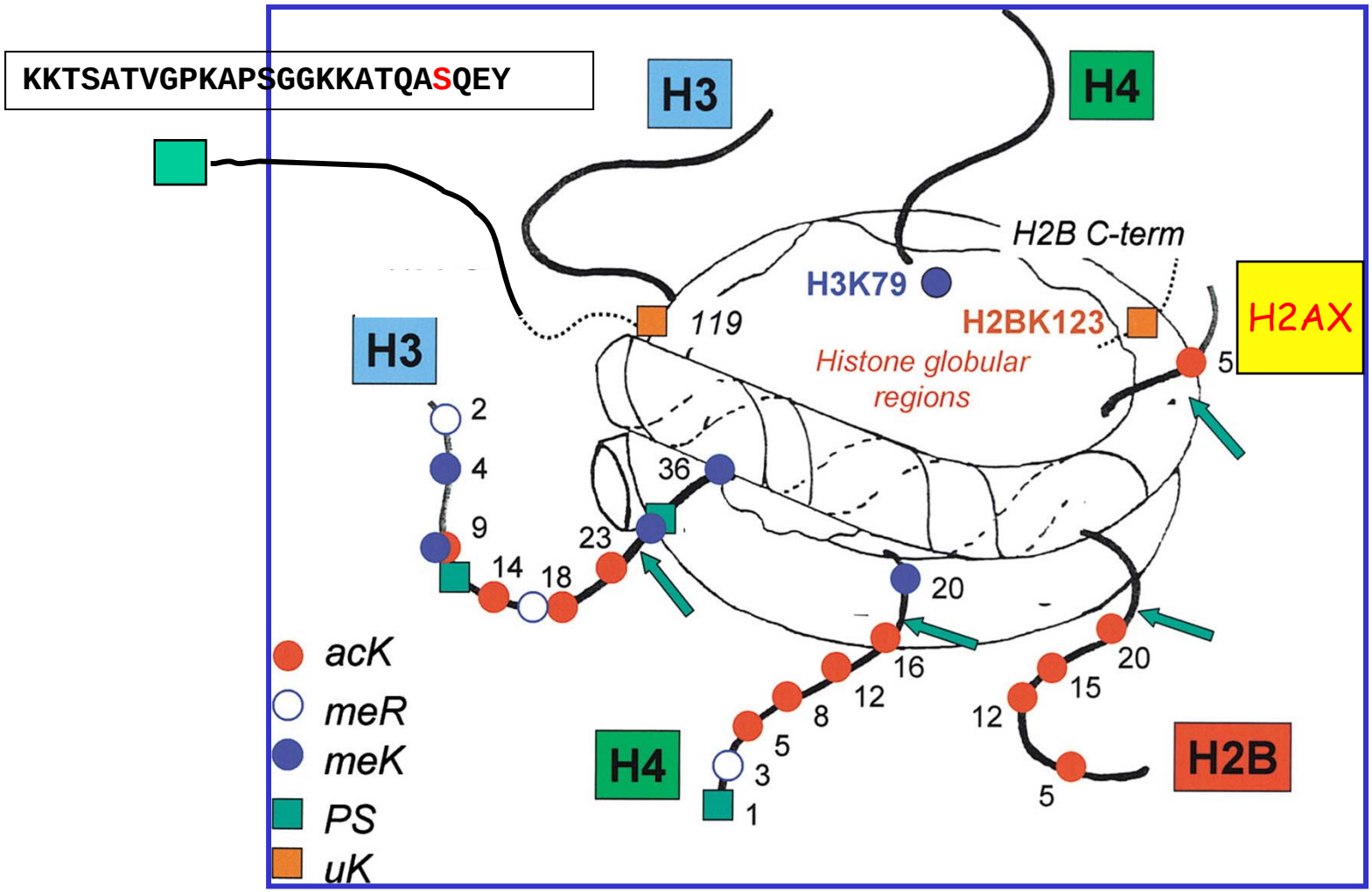
The histone code



The histone code



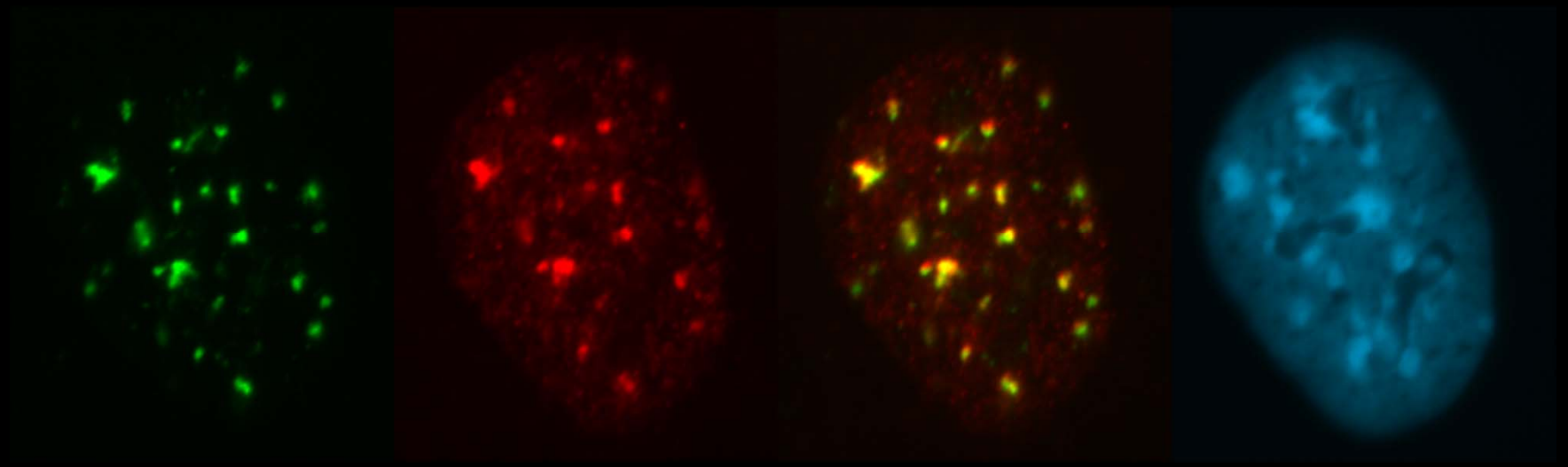
The histone code



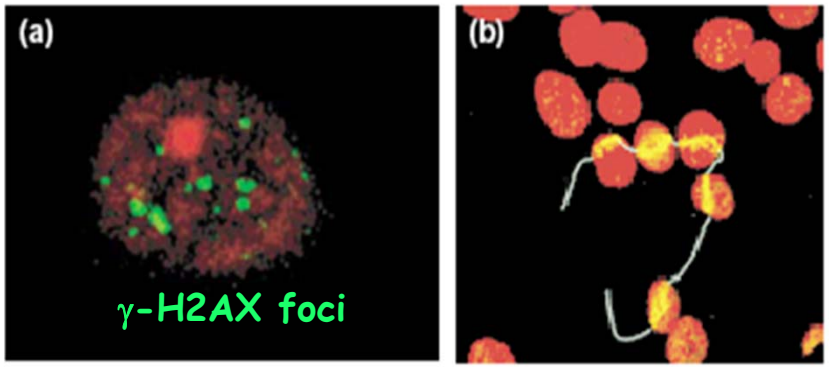
Visualizing DNA breaks

γ-H2AX foci

Nbs1 foci

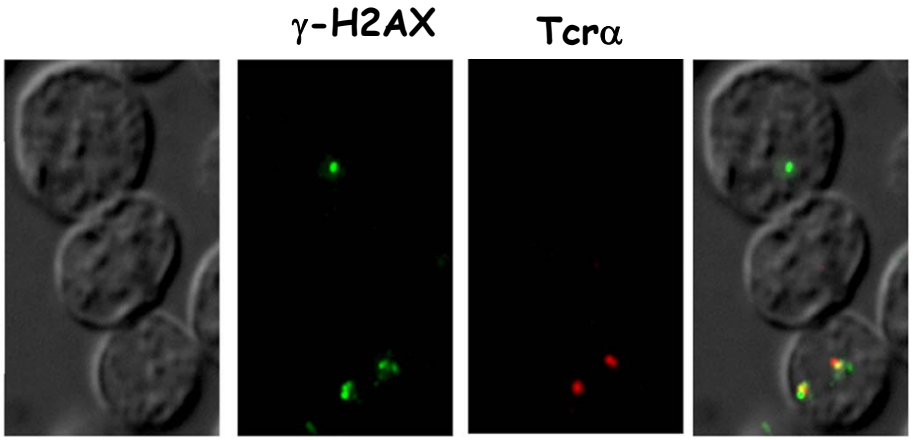


Ionizing radiation Laser scissors



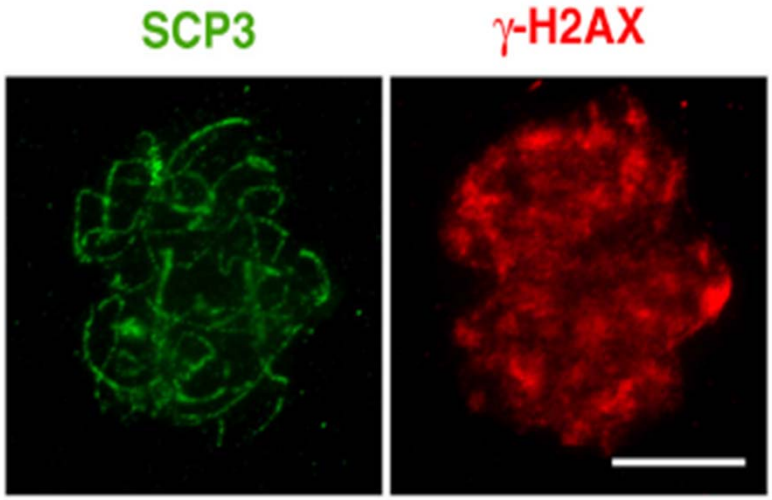
E. P. Rogakou et al. JCB 1999

V(D)J recombination



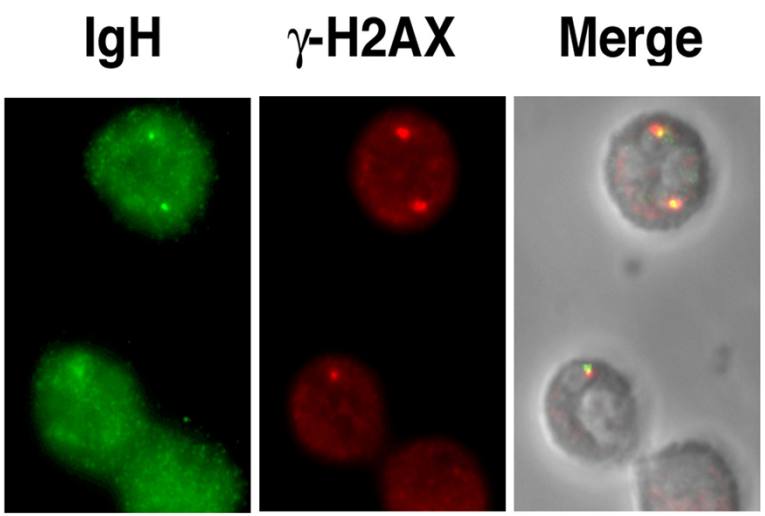
H. T. Chen et al. *Science* 2000

Meiotic recombination



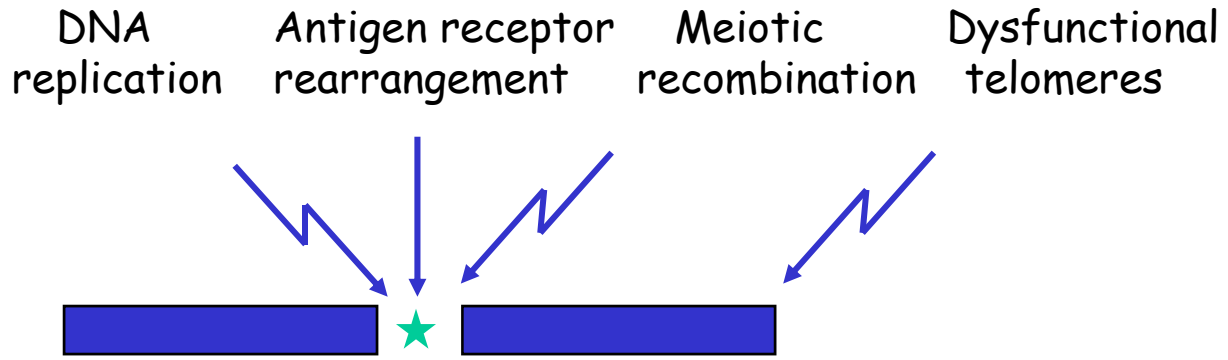
S.K. Mahadevaiah et al. *Nat. Genetics* 2001

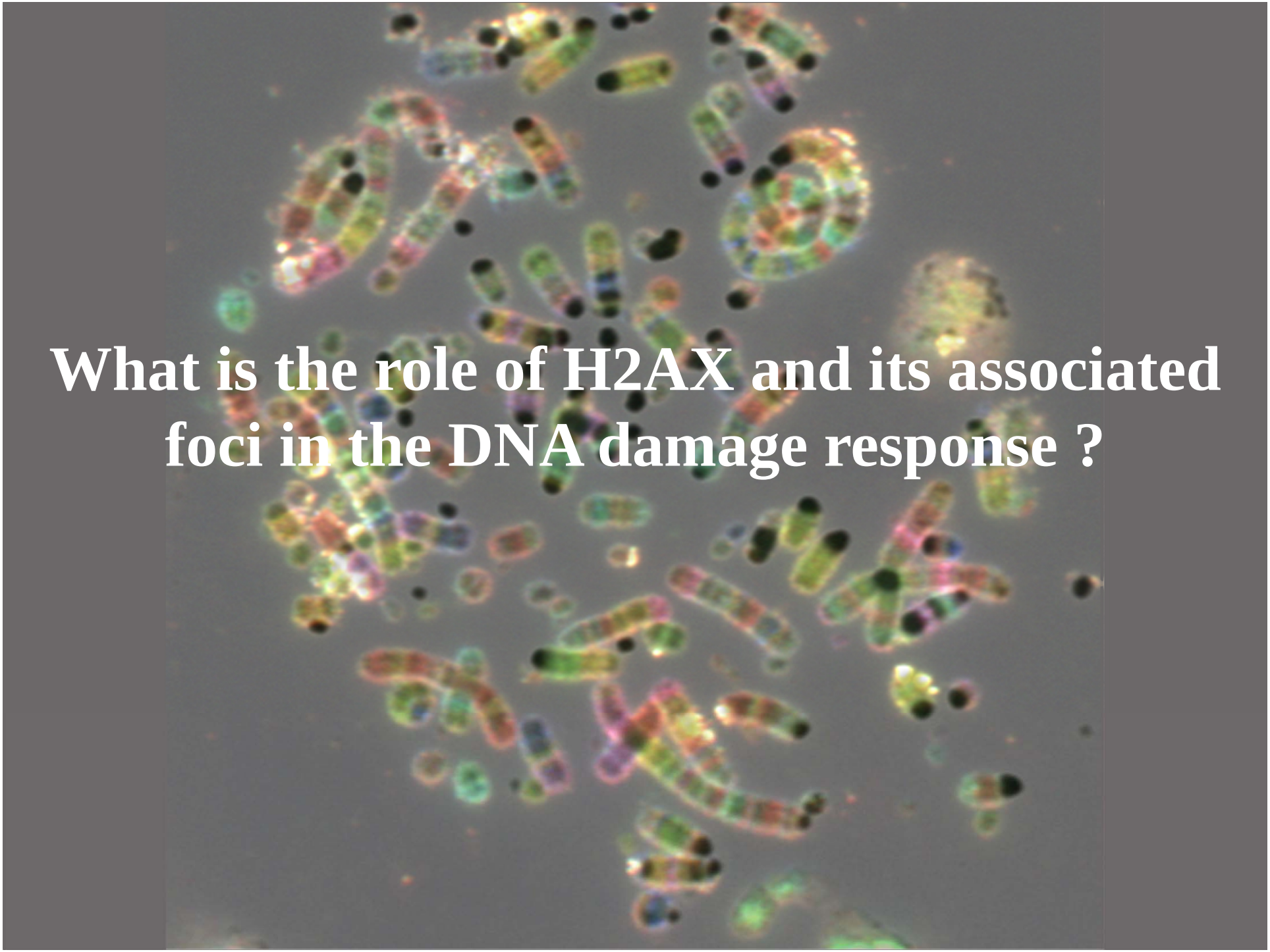
Class-switch recombination

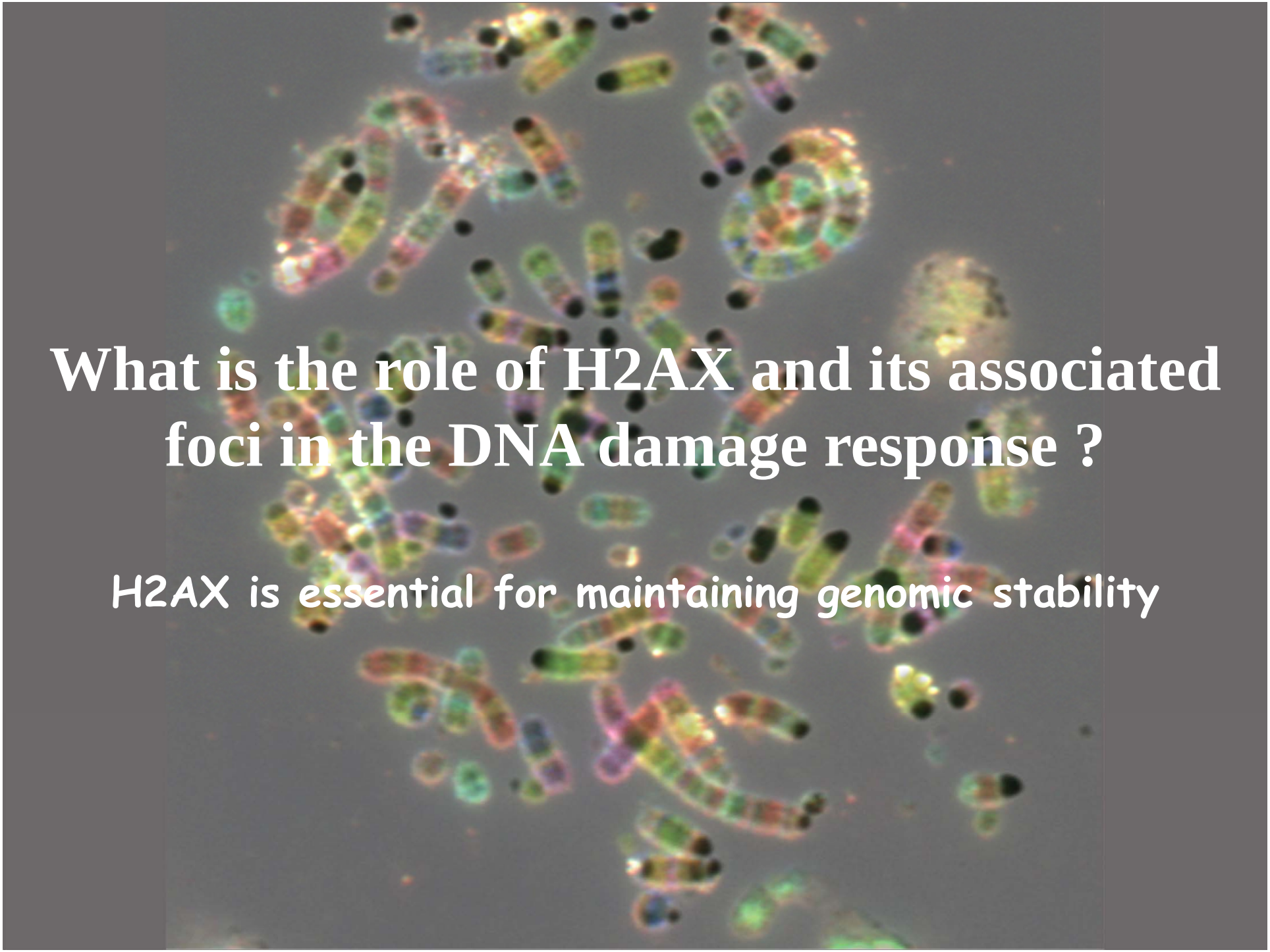


S. Petersen et al. *Nature* 2001

γ-H2AX "marks" sites of DNA breaks




What is the role of H2AX and its associated foci in the DNA damage response ?



What is the role of H2AX and its associated foci in the DNA damage response ?

H2AX is essential for maintaining genomic stability

H2AX deficiency leads to a chromosomal instability syndrome

Growth defects

Chromosomal fragility

Male sterility

Defective antigen receptor rearrangements

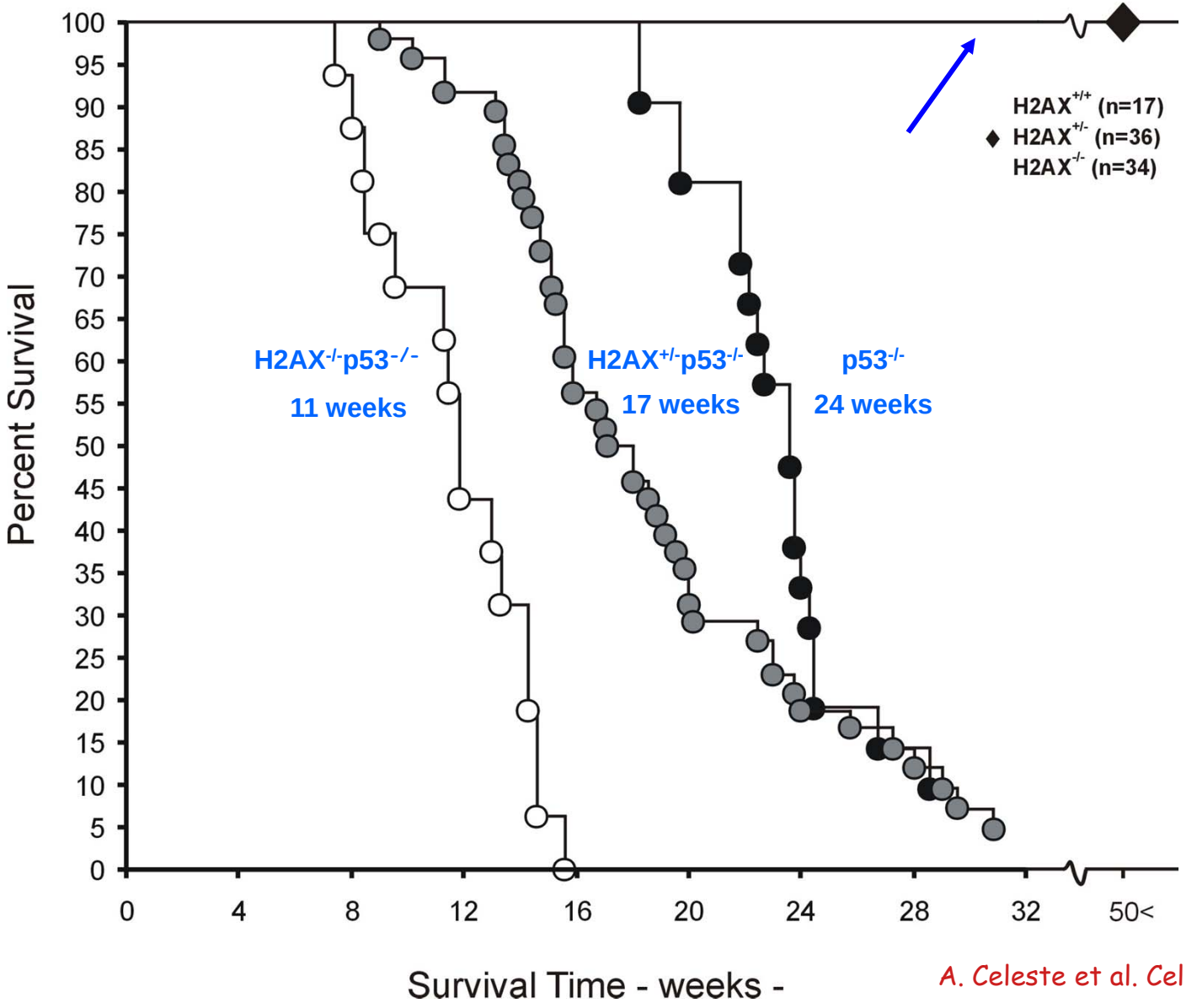
Hypersensitivity to radiation

Altered telomere topology

Impaired G2/M checkpoint

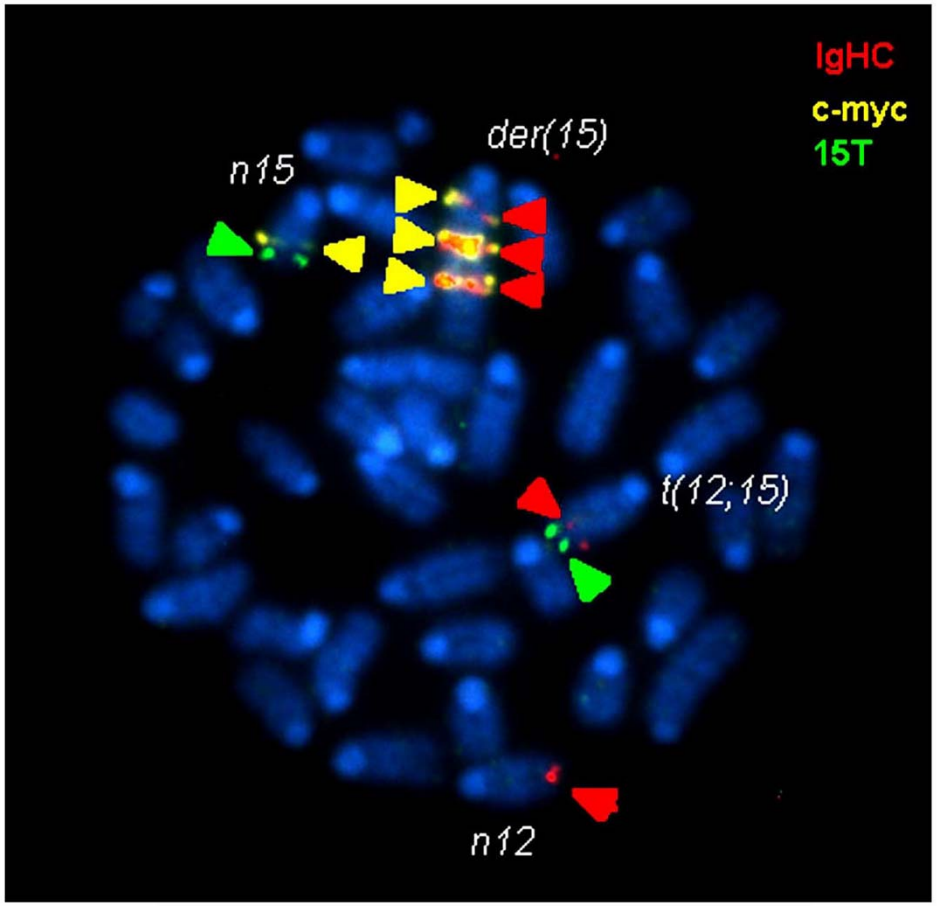
Enhanced tumorigenesis

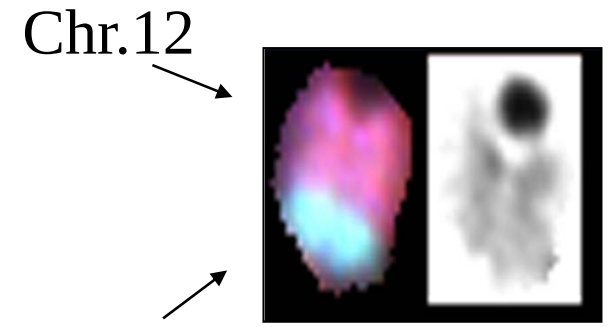
H2AX and p53 deficiency synergize in tumorigenesis



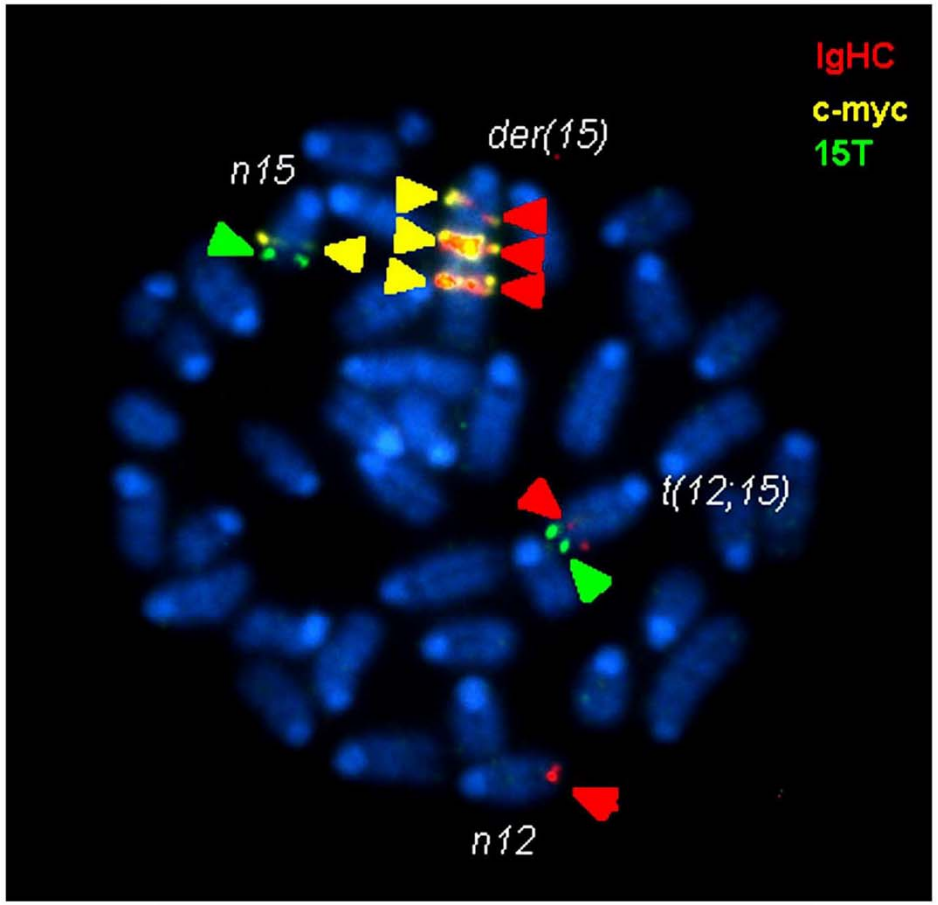
A. Celeste et al. Cell 2003

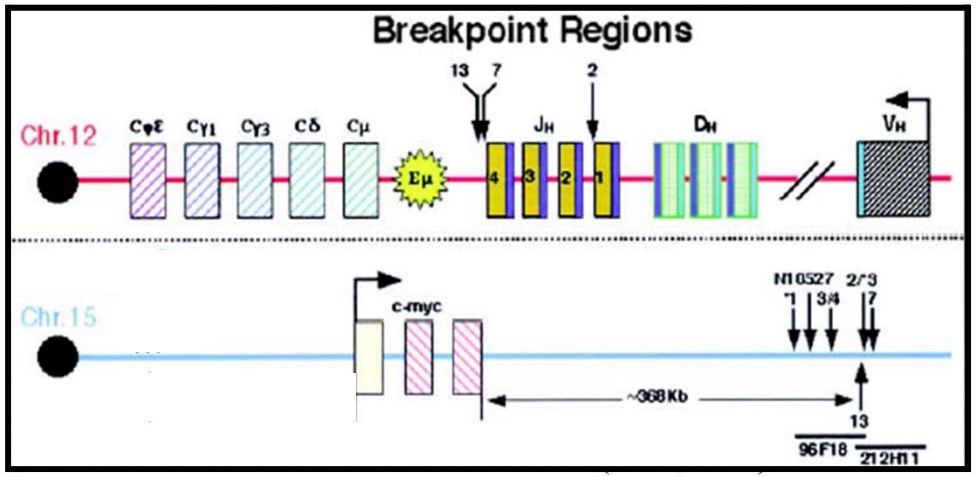
Translocation and amplification of c-myc and IgH in H2AX$^{-/-}$p53$^{-/-}$ pro B cell lymphomas





Translocation and amplification of c-myc and IgH in $H2AX^{-/-}p53^{-/-}$ pro B cell lymphomas





Summary

- Histone H2AX protects the genome from spontaneous, irradiation, and V(D)J and class-switch recombination induced double strand breaks, consistent with it's phosphorylation at these sites

H2AX and human Cancers

- The human H2AX gene maps to 11q23 (11 Mb 3' of *ATM*).
- *H2AX* resides within a minimal region hypothesized to contain a human tumor suppressor gene(s).
- A large number of human lymphomas and solid tumors contain deletions of 11q23 on a single allele (not necessarily involving *ATM*) .
- Thus, H2AX deficiency or *haploinsufficiency* may contribute to tumorigenesis in humans

What is the basis for the pleotropic phenotypes in H2AX$^{-/-}$ mice ?

Growth defects

Male sterility

Hypersensitivity to radiation

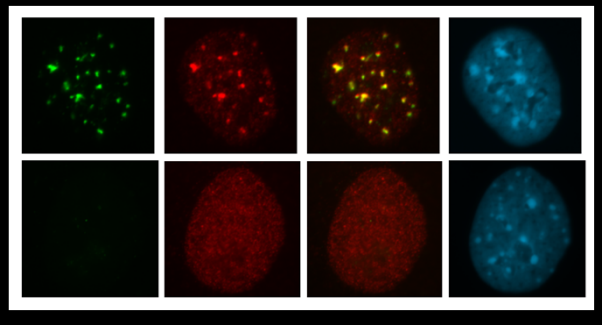
Altered telomere topology

Impaired G2/M checkpoint

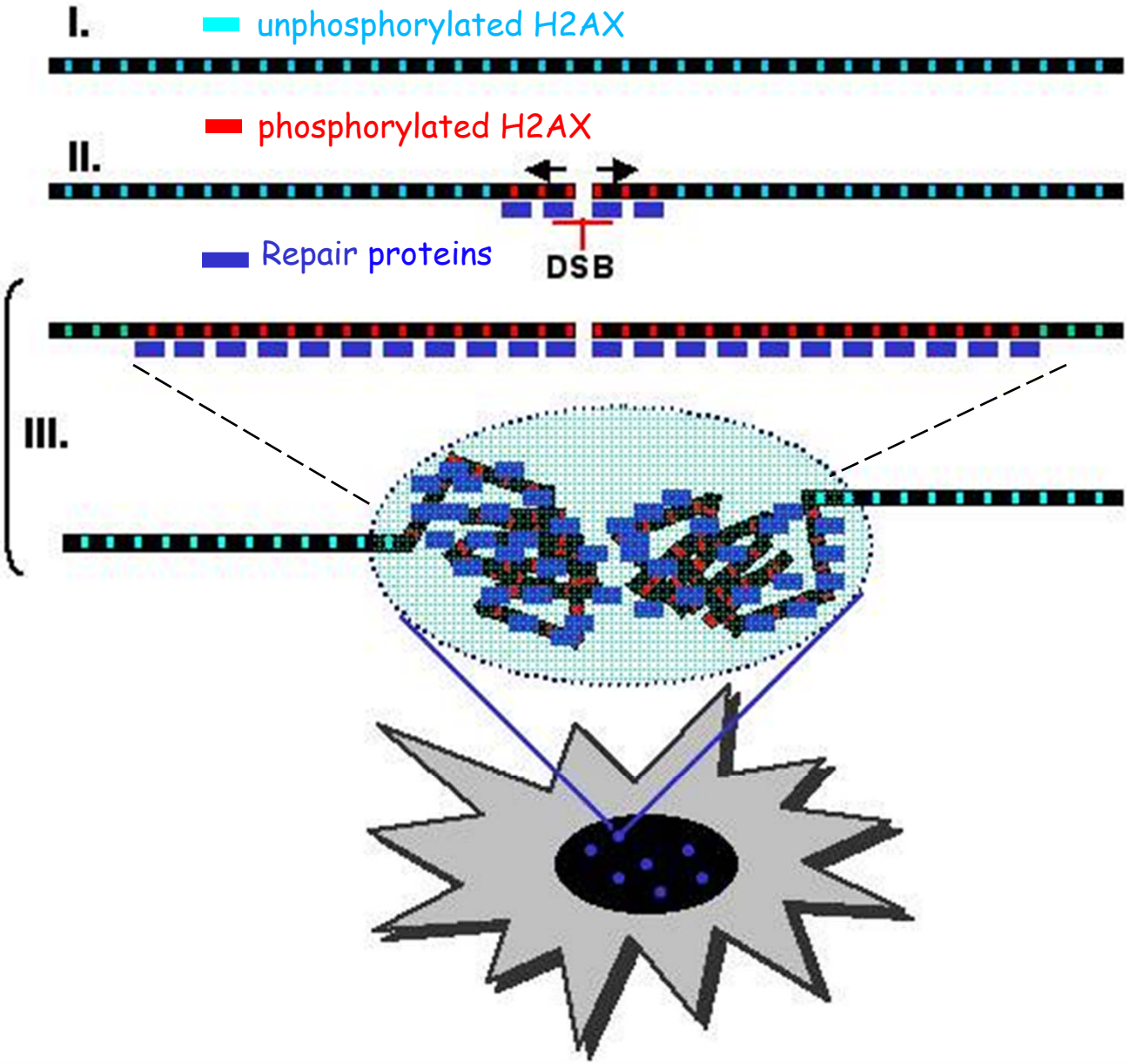
Defective antigen receptor rearrangents

?

Enhanced tumorigenesis



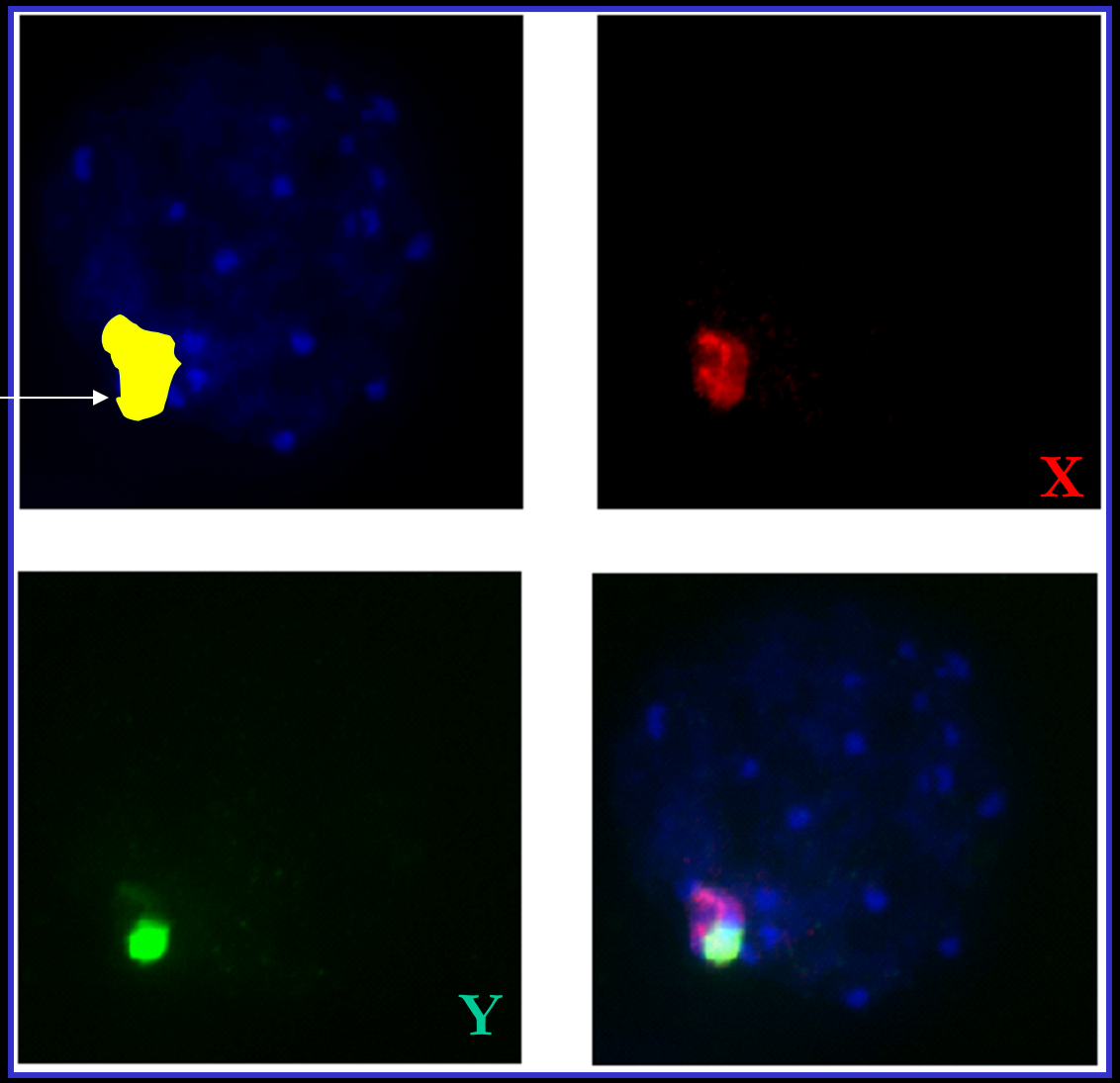
The chromatin model

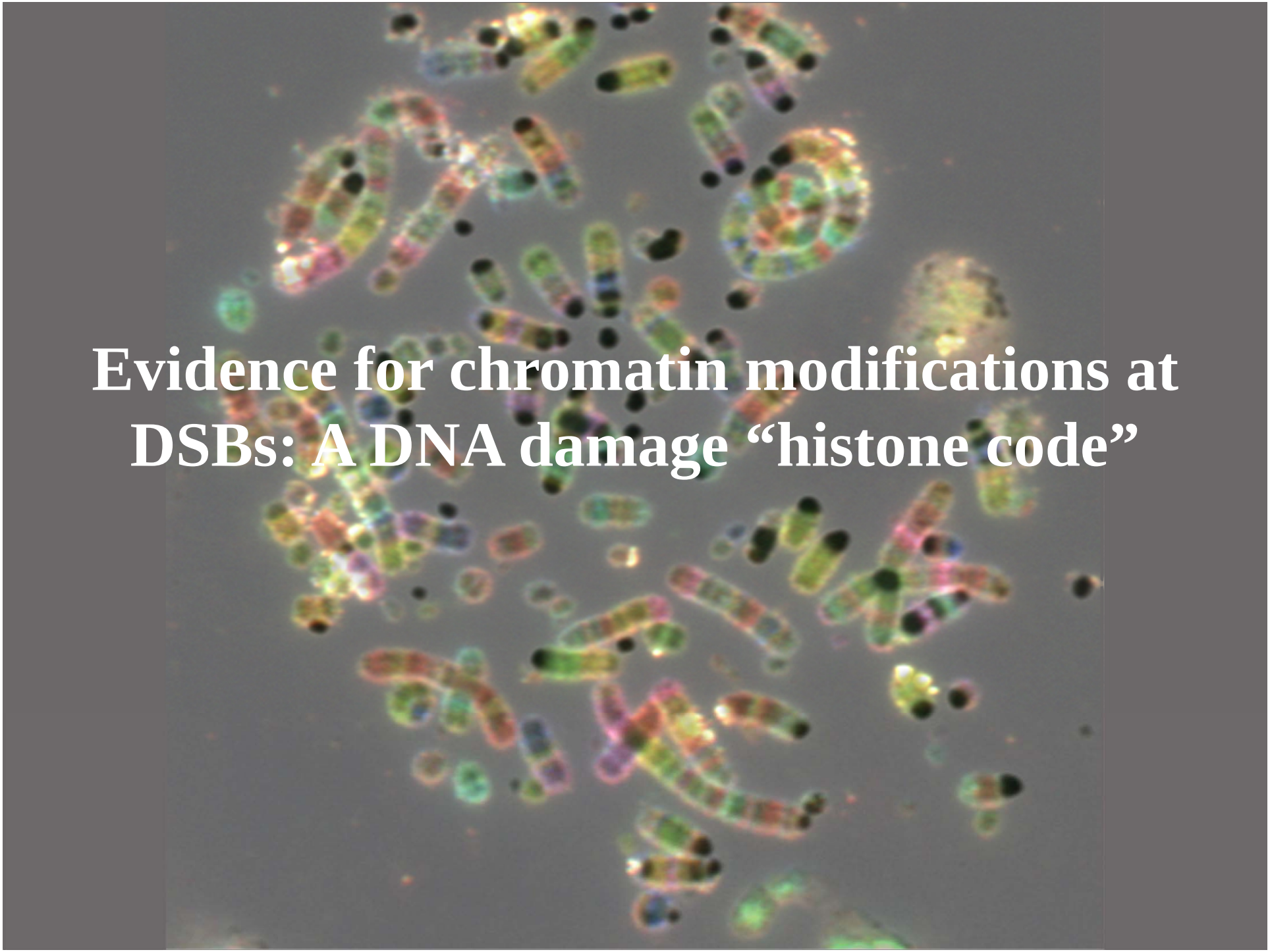


Hypothesis

Chromosomal fragility, radiation hypersensitivy, growth defects, dysfunctional antigen receptor rearrangements,and male sterility could be all be due to defective chromatin compaction in the absence of H2AX

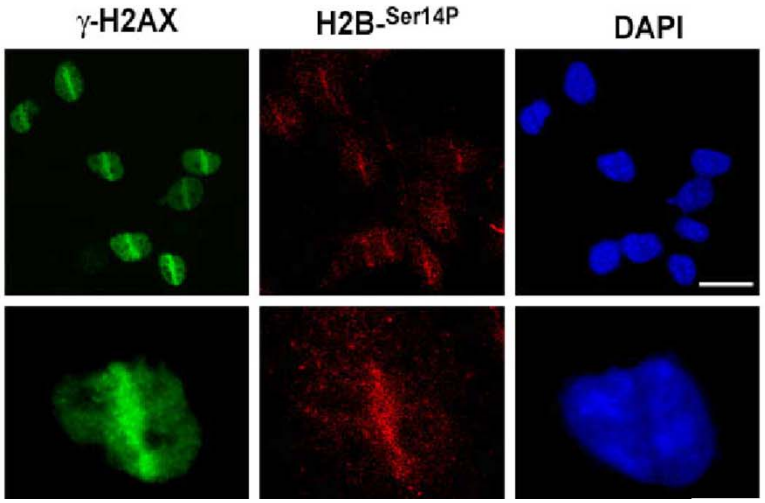
I. Role of H2AX in chromatin condensation

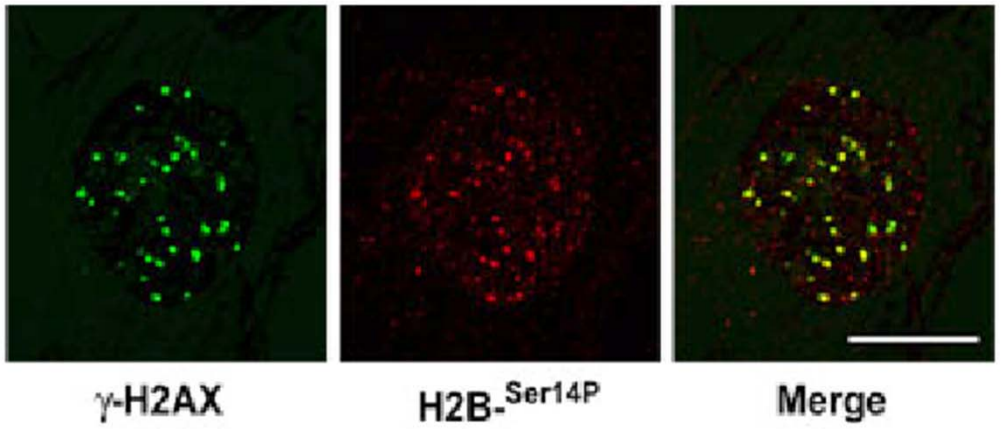


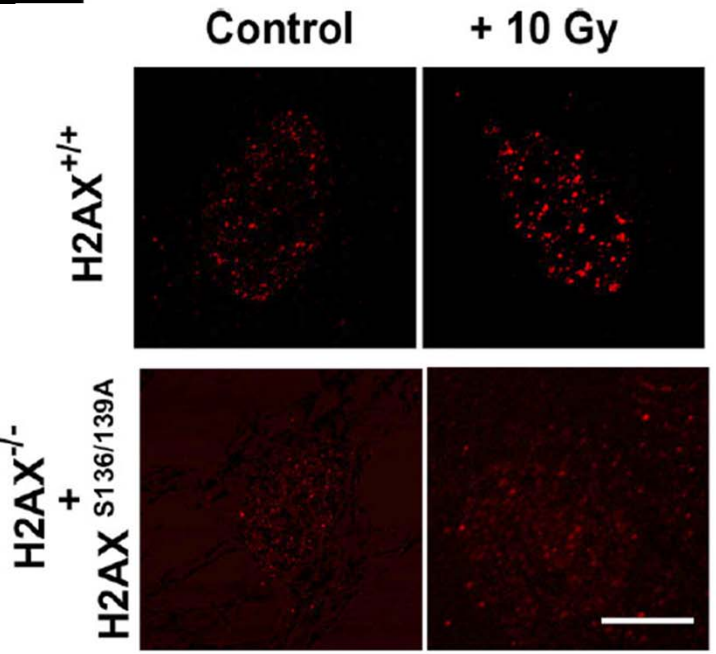


Evidence for chromatin modifications at DSBs: A DNA damage “histone code”

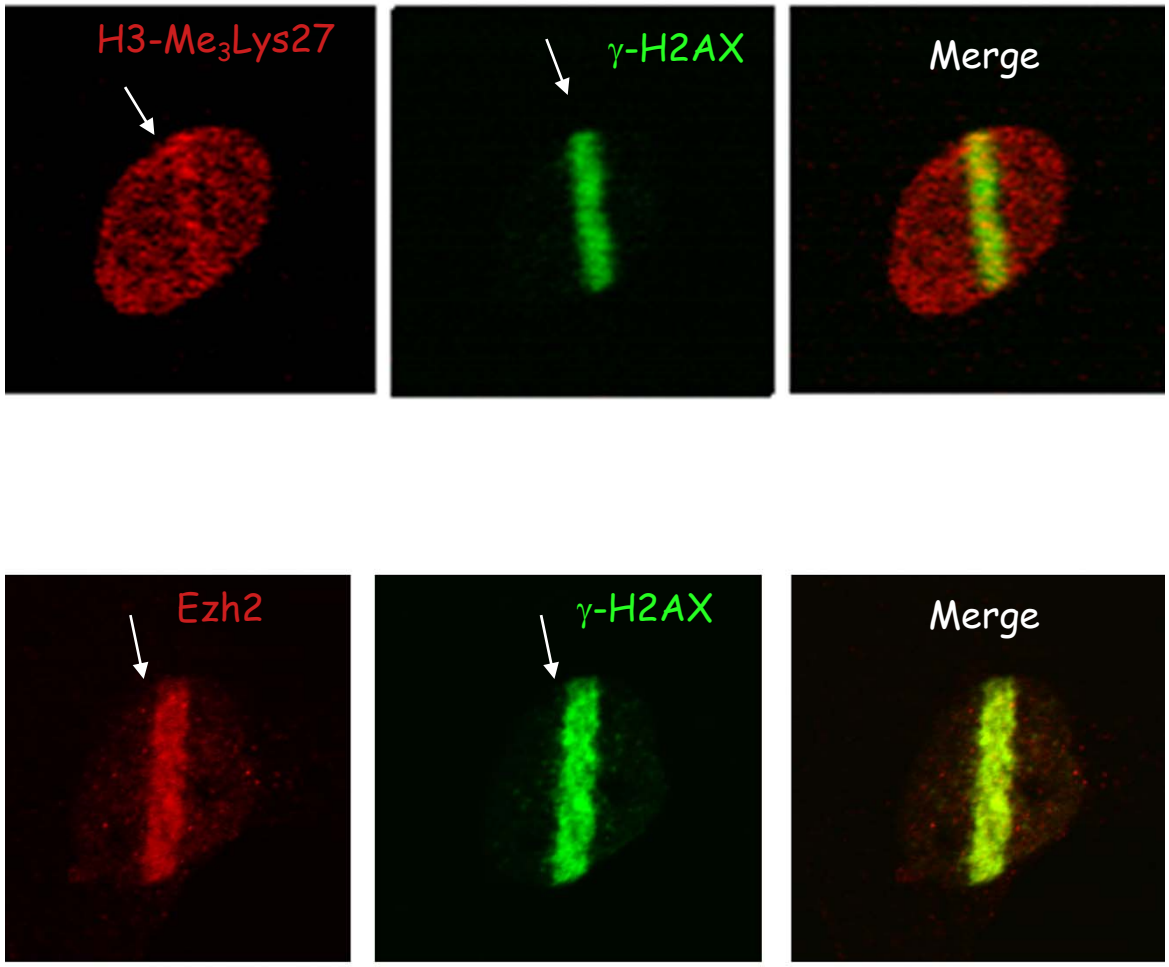
II. Another chromatin mark: phosphorylation of H2B-Ser14 at sites of DNA double strand breaks







III. Methylation of histone H3-Lys27 and recruitment of Ezh2 to sites of DNA double strand breaks



Links between EZH2 and cancer

The polycomb protein EZH2 is involved in progression of prostate cancer

Nature **Vol. 419, No. 6907 p. 624-9, 2002**

The EZH2 polycomb transcriptional repressor-a marker or mover of metastatic prostrate cancer?

Cancer Cell **Vol. 2, No.5 pp. 349-350 2002**

EZH2 is a marker of aggressive breast cancer and promotes neoplastic transformation of breast epithelial cells

Proc.Natl. Acad. Sciences **Vol. 100, No. 20 pp. 11606-616 2003**

EZH2 is downstream of the pRB-E2F pathway, essential for proliferation and amplified in cancer

The EMBO Journal **Vol. 22, No. 20 pp. 5323-5, 2003**

EZH2 controls B cell development through histone H3 methylation and IgH rearrangement

Nat. Immunol. **Vol. 4, No. 2 pp. 124-31, 2002**

Summary:

- demonstration that histone H2AX is a dosage dependent tumor suppressor
- discovery of new epigenetic marks in histones that may be involved in the maintenance of genomic stability

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