Basic Nuclear Engineering 4
(原子核工学基礎第四)
(5) Effects of radiation (2)

Department of Transdisciplinary
Science and Engineering

Institute of Integrated Research
Laboratory for Zero-Carbon Energy

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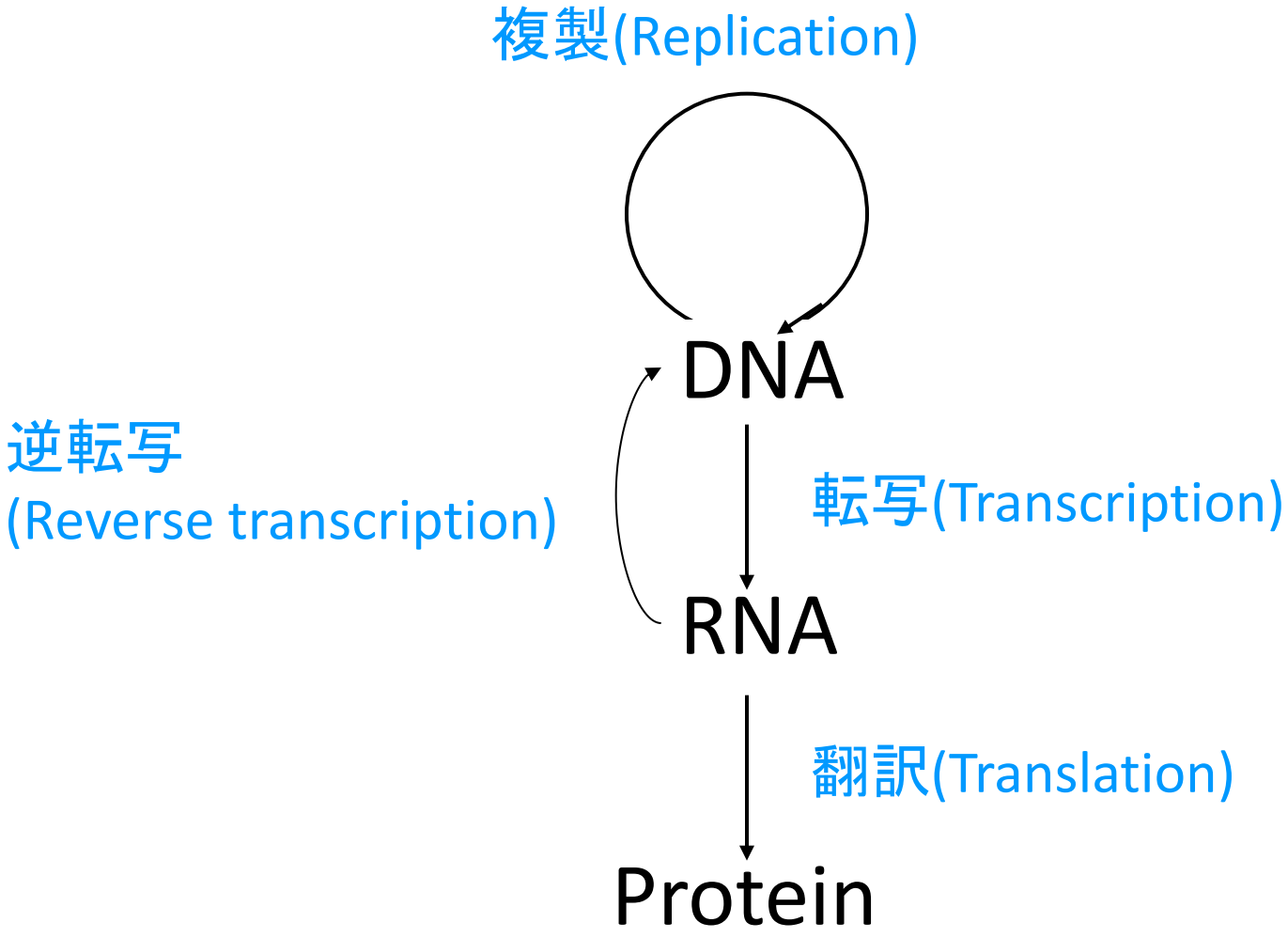
1. DNA as the target of radiation

Central dogma: Flow of genetic information



Transcription and translation

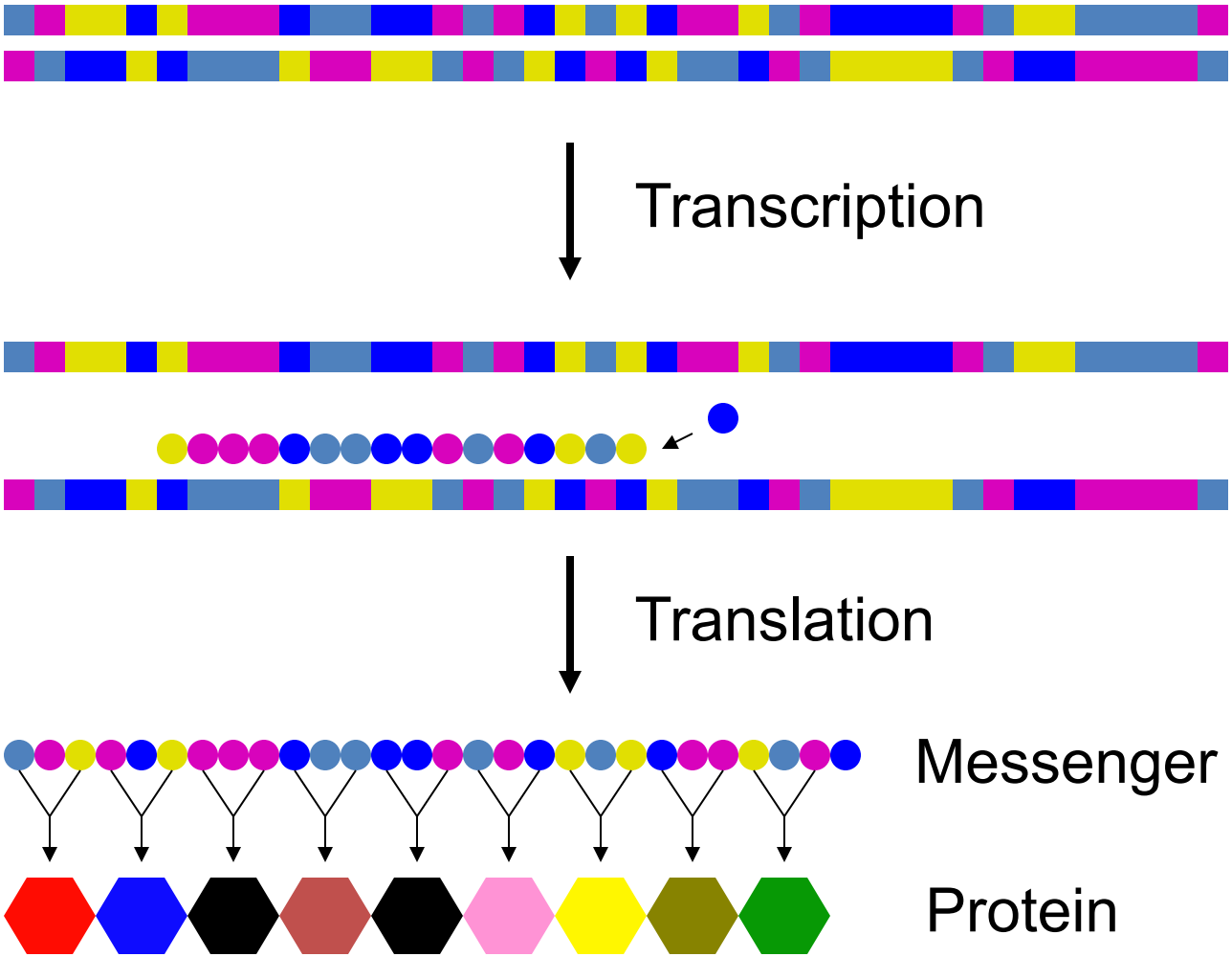
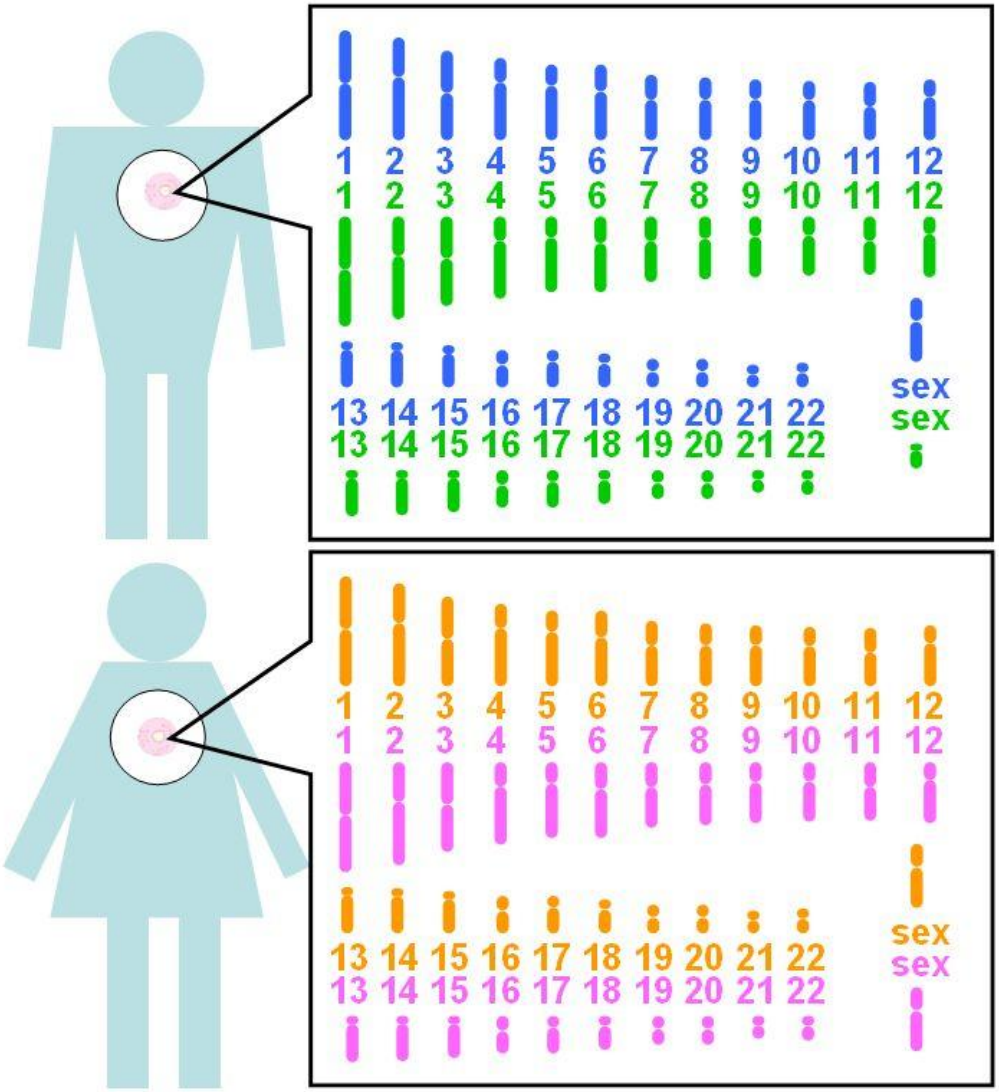


Table of Genetic Code (遺伝暗号表、コドン表)

2文字目→ ↓1文字目	U		C		A		G	
U	UUU	Phe(F)	UCU	Ser(S)	UAU	Tyr(Y)	UGU	Cys©
	UUC		UCC		UAC		UGC	
	UUA	Leu(L)	UCA		UAA	Stop	UGA	Stop
	UUG		UCG		UAG		UGG	Trp(W)
C	CUU	Leu(L)	CCU	Pro(P)	CAU	His(H)	CGU	Arg(R)
	CUC		CCC		CAC		CGC	
	CUA		CCA		CAA	Gln(Q)	CGA	
	CUG		CCG		CAG		CGG	
A	AUU	Ile(I)	ACU	Thr(T)	AAU	Asn(N)	AGU	Ser(S)
	AUC		ACC		AAC		AGC	
	AUA		ACA		AAA	Lys(K)	AGA	Arg(R)
	AUG	Met(M)	ACG		AAG		AGG	
G	GUU	Val(V)	GCU	Ala(A)	GAU	Asp(D)	GGU	Gly(G)
	GUC		GCC		GAC		GGC	
	GUA		GCA		GAA	Glu(E)	GGA	
	GUG		GCG		GAG		GGG	

Human chromosomes



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Terminology of chromosome

Autosome : 2 copies exists in male and female. In human, 22 sets

Sex chromosome : In human, female has two X chromosomes, whereas male has one X and one Y chromosomes.

Homologous chromosome : A pair of chromosome inherited from father and mother. Genetic information is slightly different

Sister chromatid: A pair of chromosome produced by DNA replication. Genetic information is identical.

Why is DNA a special target of radiation? (1)Importance

DNA is a “blueprint” of life

DNA encodes protein or RNA, which maintain cellular function and structure.

Loss of a part of DNA

↓

Proteins or RNAs encoded in the region of DNA is not produced.

↓

Cellular dysfunction

On the other hand,

Proteins or RNA can be produced, if DNA remains intact.

Why is DNA a special target of radiation? (2)Uniqueness, no alternative

DNA exists as a single copy in the cell in G1 state and only two copies after replication.

Loss of one copy brings significant results.

Why is DNA a special target of radiation? (3)Extreme length

Size of human genome (diploid) 6 billion base pairs on 46 chromosomes.

1 base pair = 0.3nm in length

∴Total length 2m, 4cm on average for chromosome.

Packed in nucleus with 10μm diameter.

Extremely long molecule:
Mechanically fragile (although chemically stable)

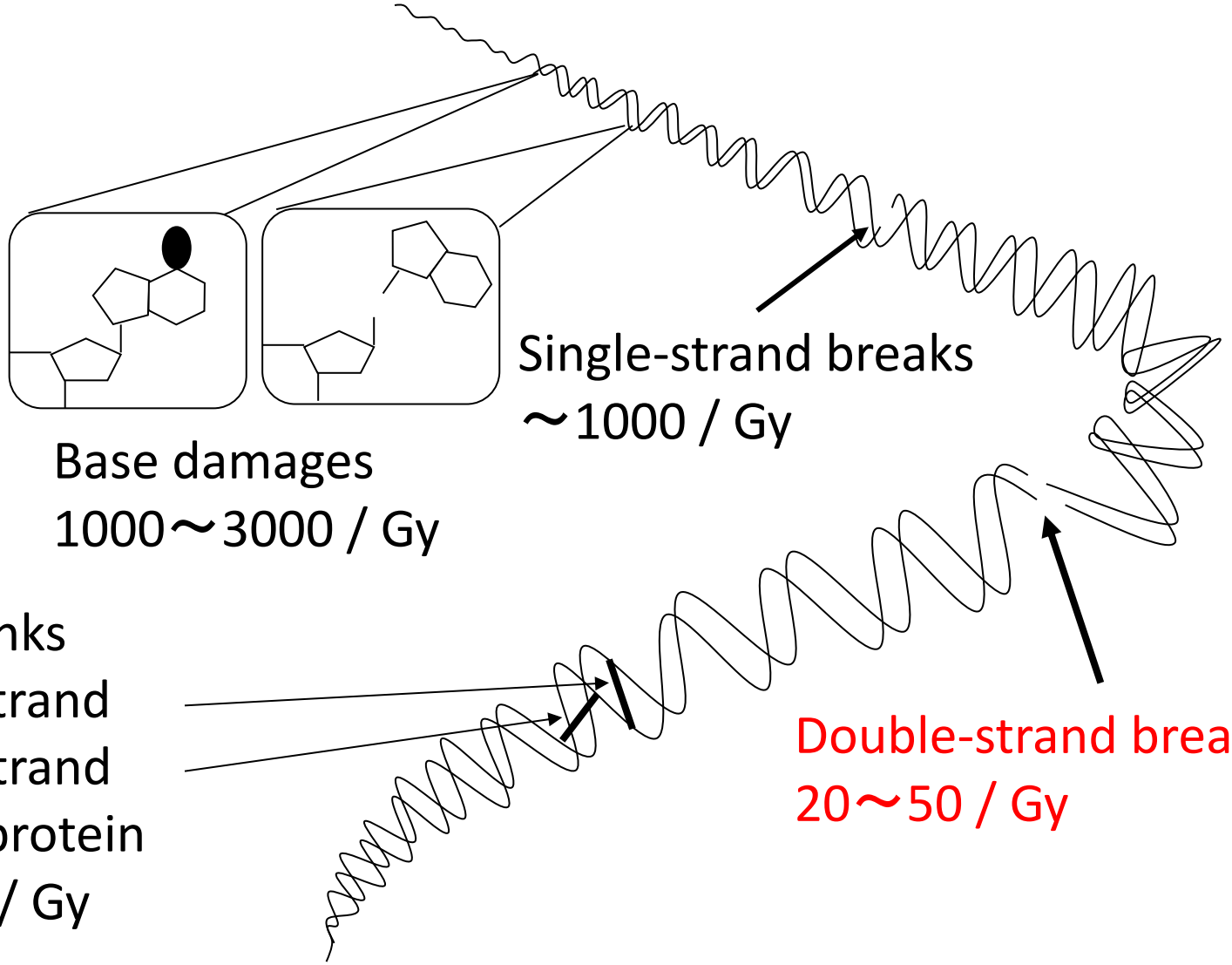
DNA carries vast amount of “information”
Extreme length is inevitable but also an “Achele’s heel”.

Why is DNA a special target of radiation?
(4)Extreme sensitivity to break

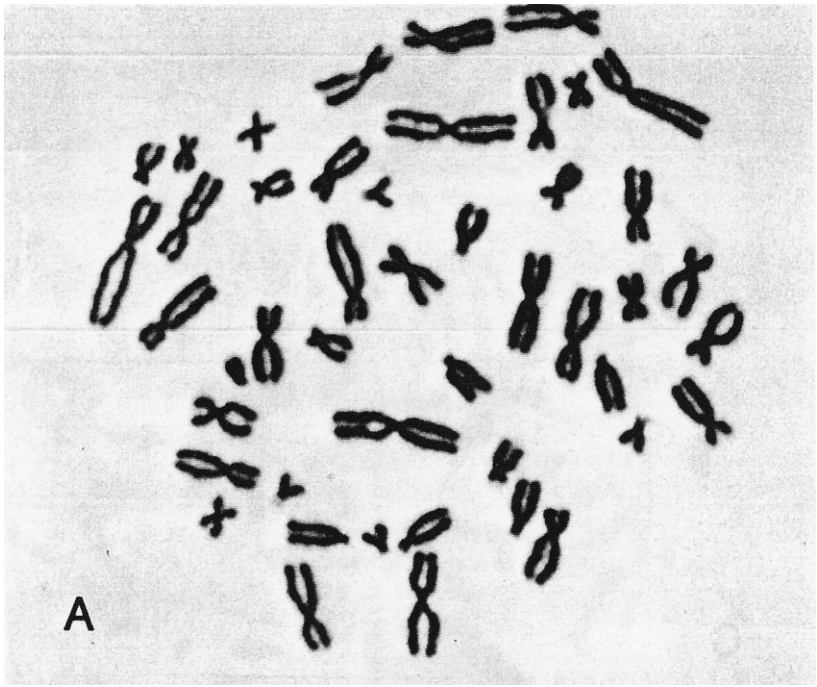
- DNA is "information molecule".
  Order of sequence is vital for its function.

- DNA must be
  faithfully replicated and accurately divided
  in cell division cycle.
  ↓
  Lesion or break significantly impedes
  proper replication or division of DNA.

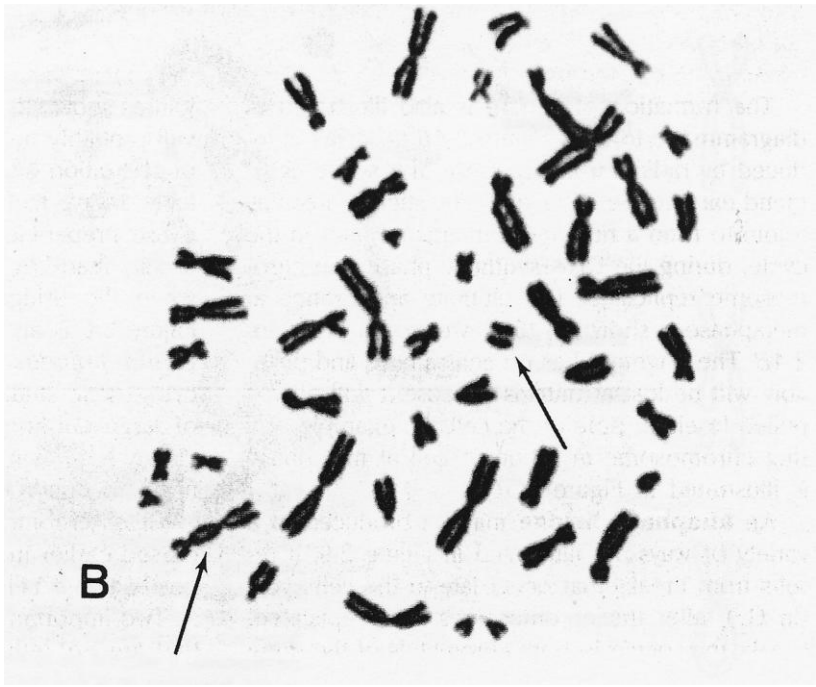
Radiation-induced DNA damages



Radiation-induced chromosome aberration



Chromosomes of unirradiated human lymphocyte



Chromosomes of irradiated human lymphocyte

(Hall and Giaccia, Radiobiology for the Radiologists)

Chromosome aberrations

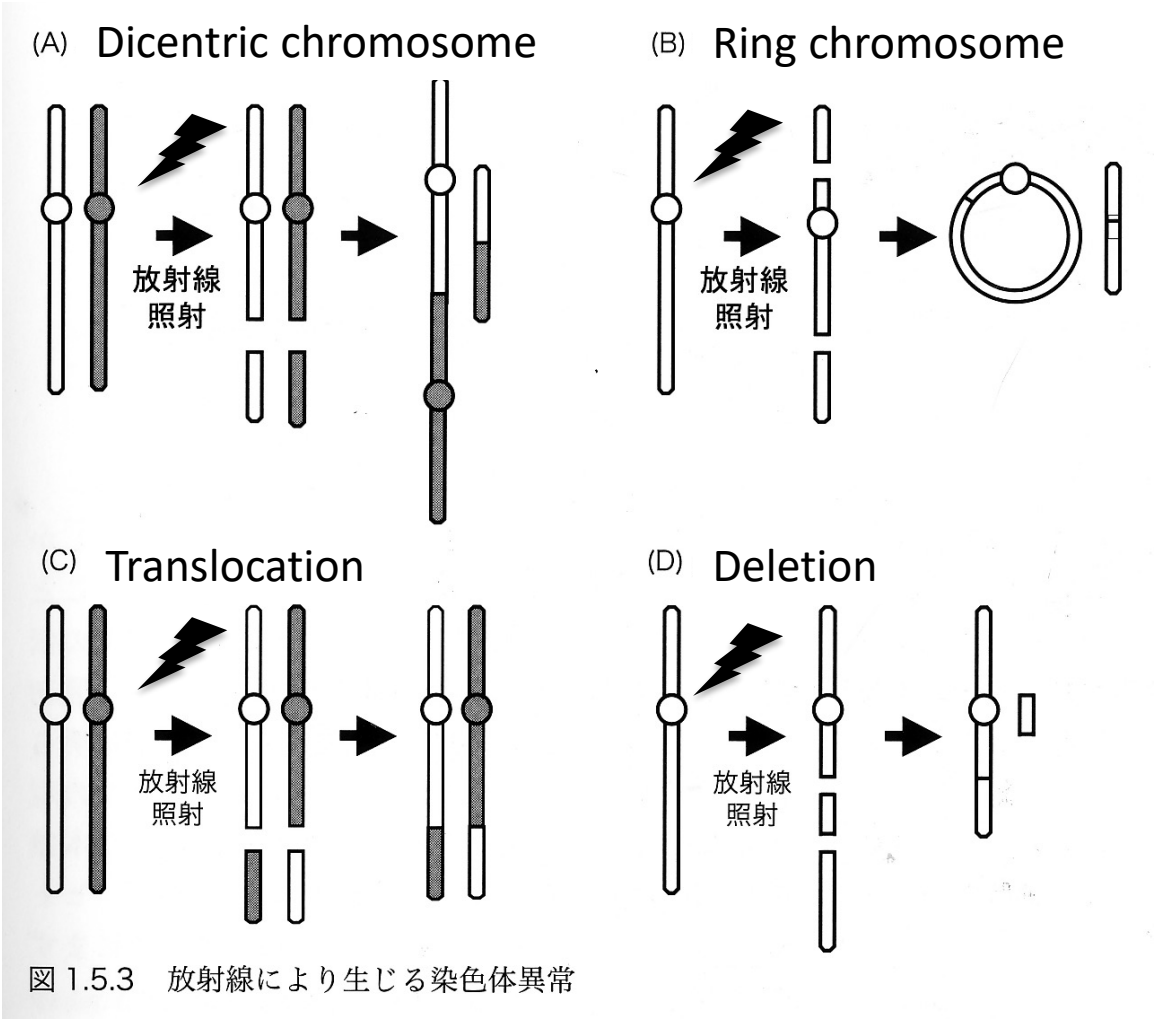


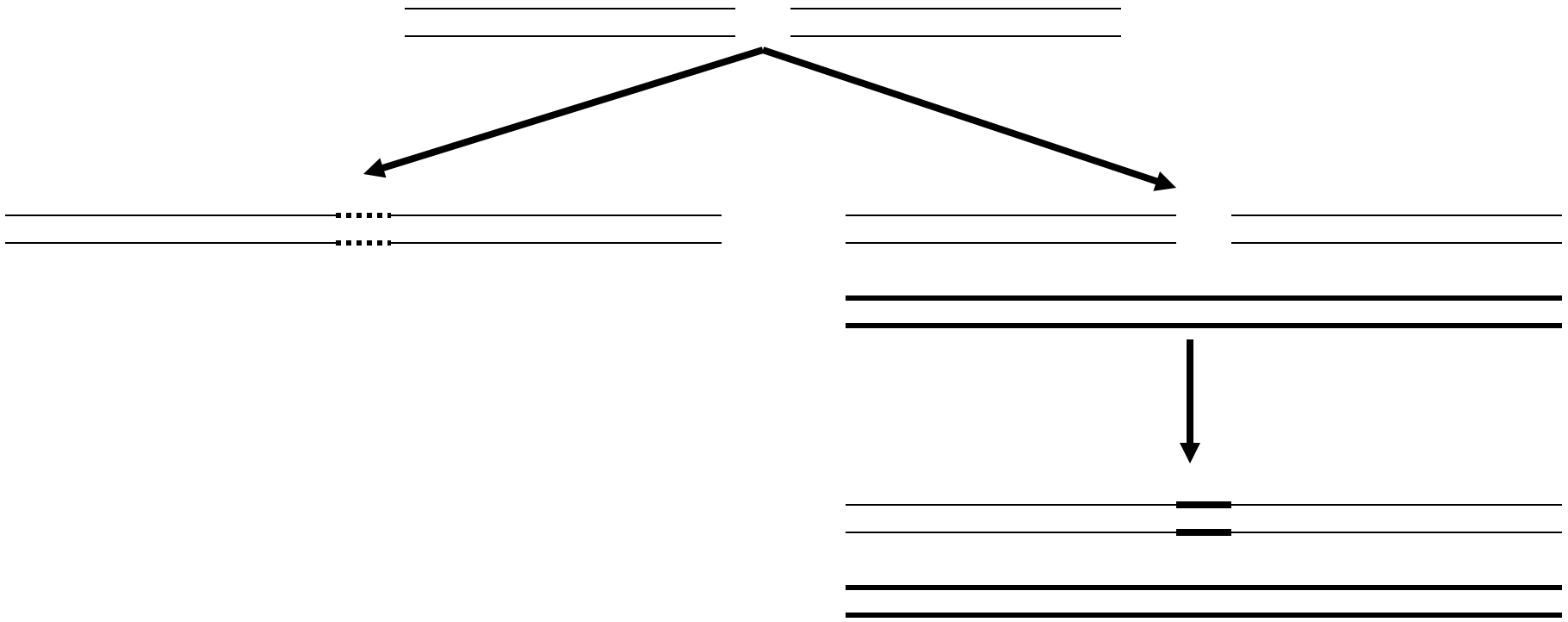
図 1.5.3　放射線により生じる染色体異常

→Unstable aberration
Easily lost in cell division

→Stable aberration
Not easily lost in cell division

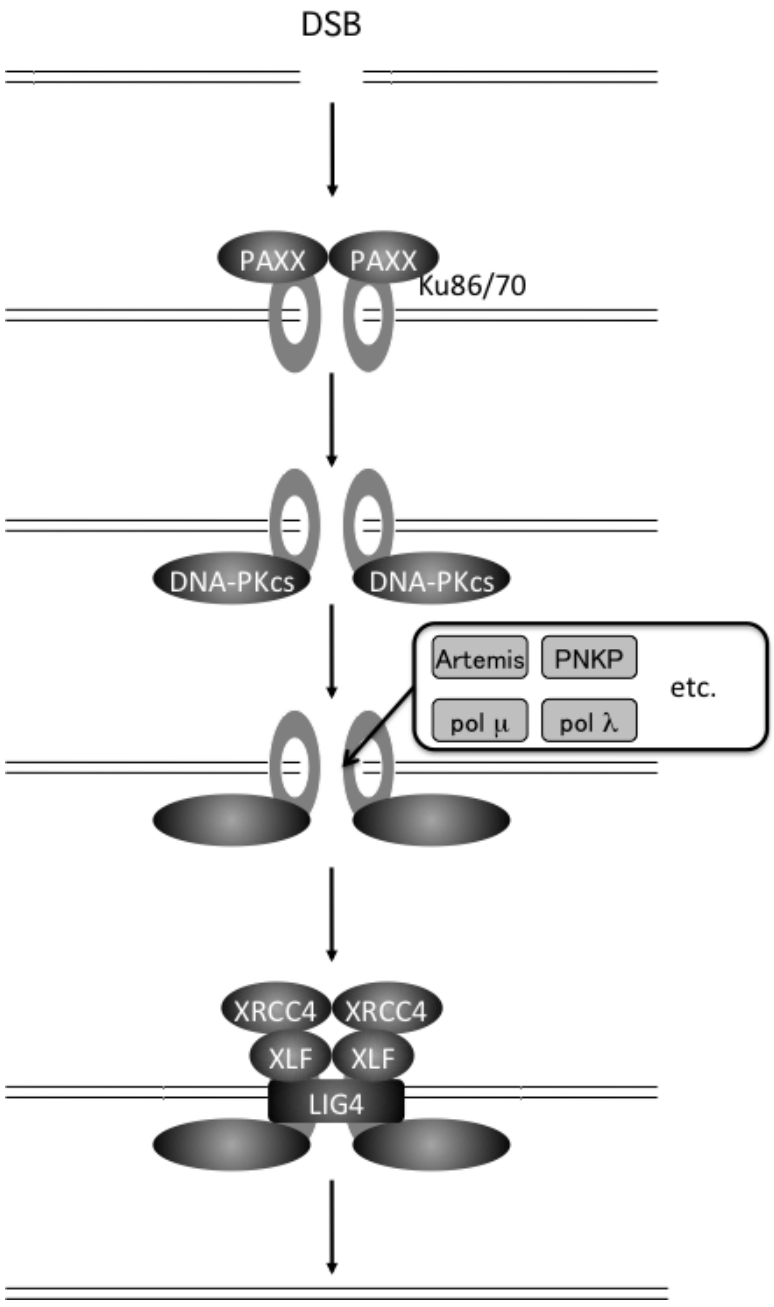
2. Mechanism of DNA repair

Repair of DNA Double-strand break



Non-homologous end-joining (NHEJ)

Homologous recombination (HR)



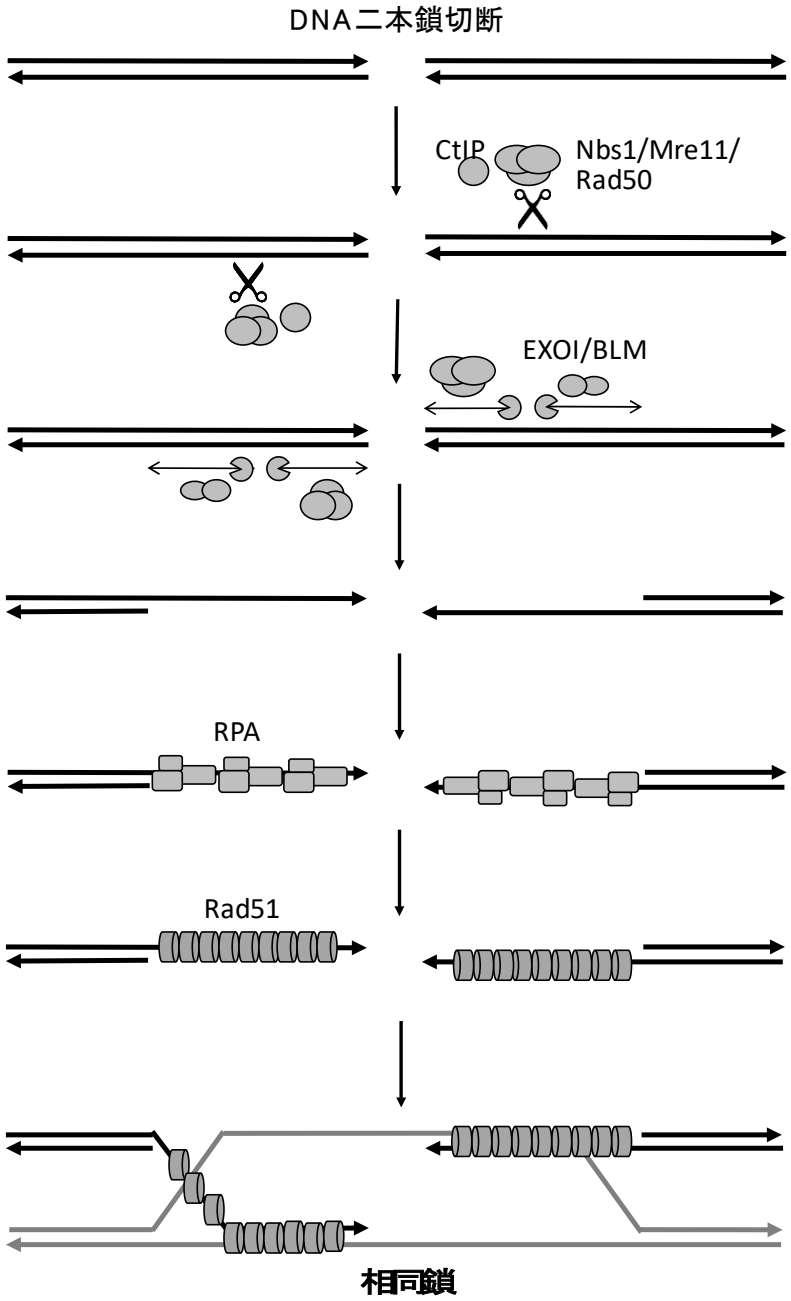
NHEJ Reaction

① Ku proteins (Ku86/70) binds to DSB.

② DNA-PKcs is recruited to DSB via Ku.

③ (When necessary) DSB is processed so that it can be ligated.

④ Two ends are ligated by DNA ligase IV (LIG4), where XRCC4 and XLF are thought to regulate LIG4.



Homologous strand (Sister chromatid)

HR Reaction (1)

① Complex of Nbs1/Mre11/Rad50 (MNR) and ExoI/BLM degrade one of the strands, generating single strand DNA (Resection).

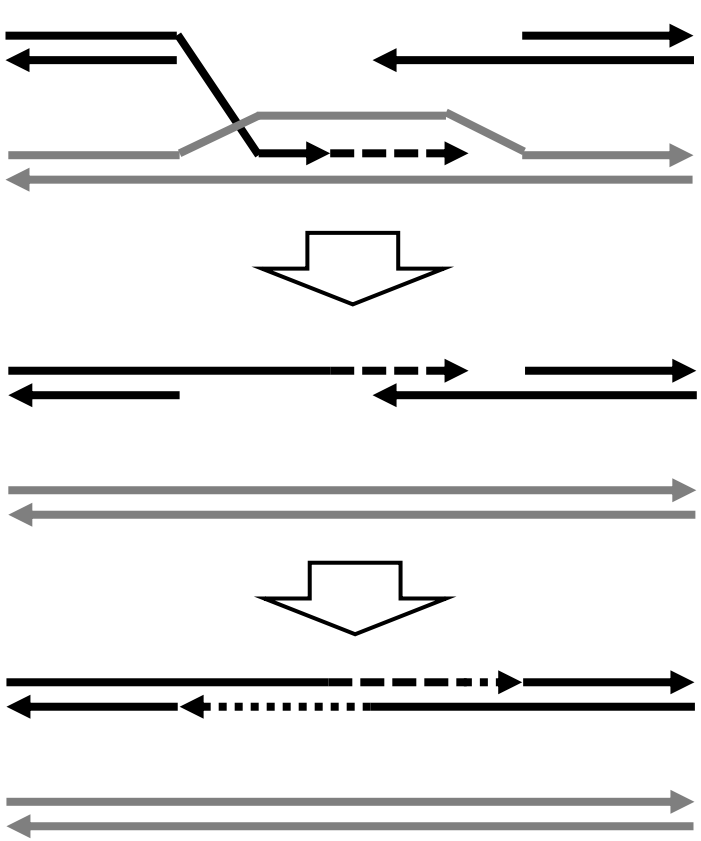
② RPA binds to single strand DNA.

③ RPA is replaced by Rad51, which is promoted by BRCA1, BRCA2, etc.

④ Rad51 promotes strand exchange to look for homologous strand.

HR Reaction (2)

SDSA (synthesis-dependent strand annealing) model

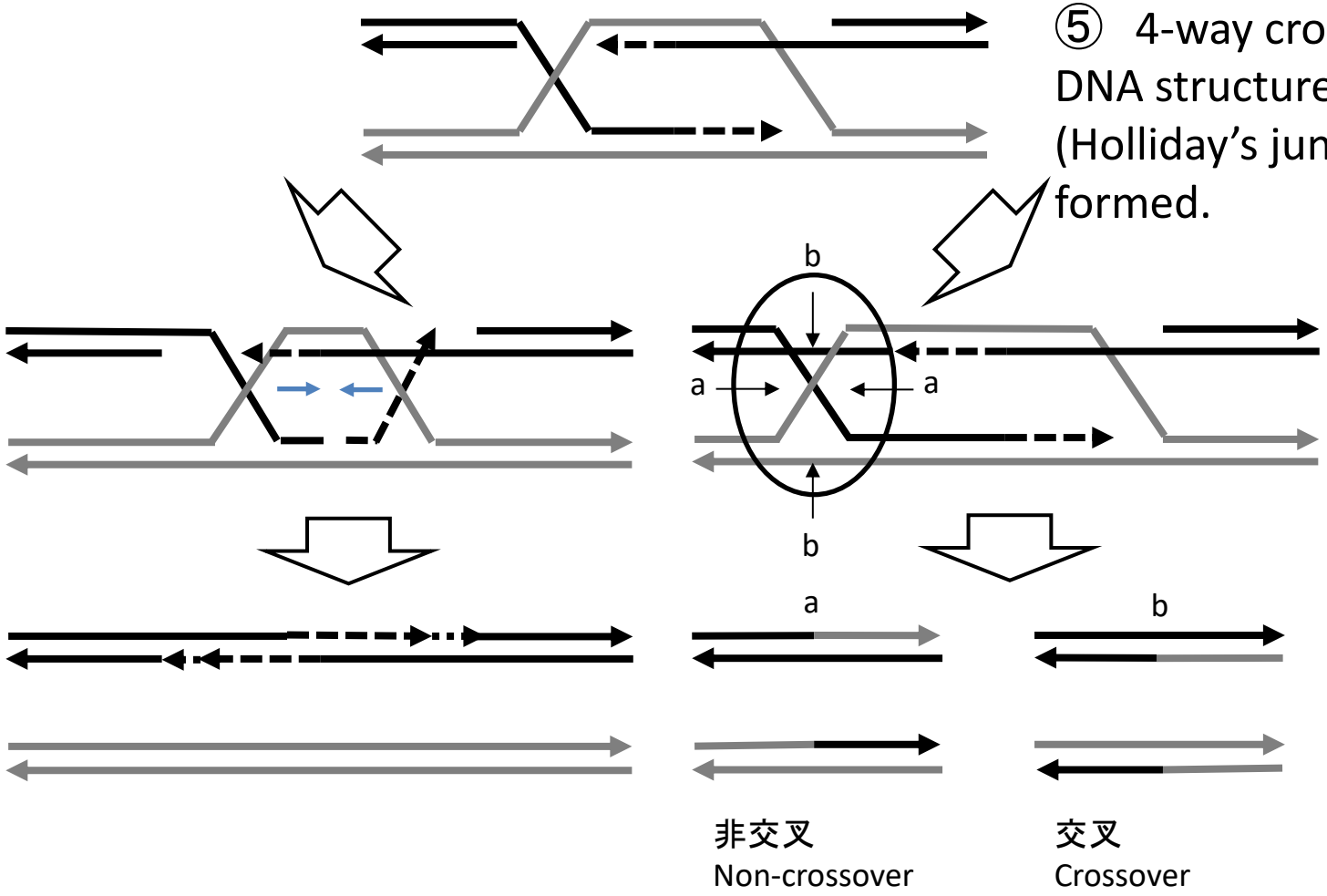


⑤ Strand synthesized along the template by DNA replication machinary, pol δ, PCNA etc.

⑥ Synthesized strand detach from the homologous strand and anneals with the opposite side of the broken strand.

⑦ Gaps are filled in by by DNA replication machinery, pol δ, PCNA etc.

HR Reaction (2') Holliday's junction model



⑤ 4-way crossed DNA structure (Holliday's junction) formed.

⑥ Two Holliday's junction move inward and eliminated

⑦ Two strands in Holliday's junction cut by enzymes, like Slx1-Slx4, Mus81-Eme1, Gen1 (Resolution).

Complementary plays of NHEJ and HR(1)

◆Weak point of NHEJ

NHEJ is the reaction to join two DNA ends
In the closest proximity
→Less accurate than HR

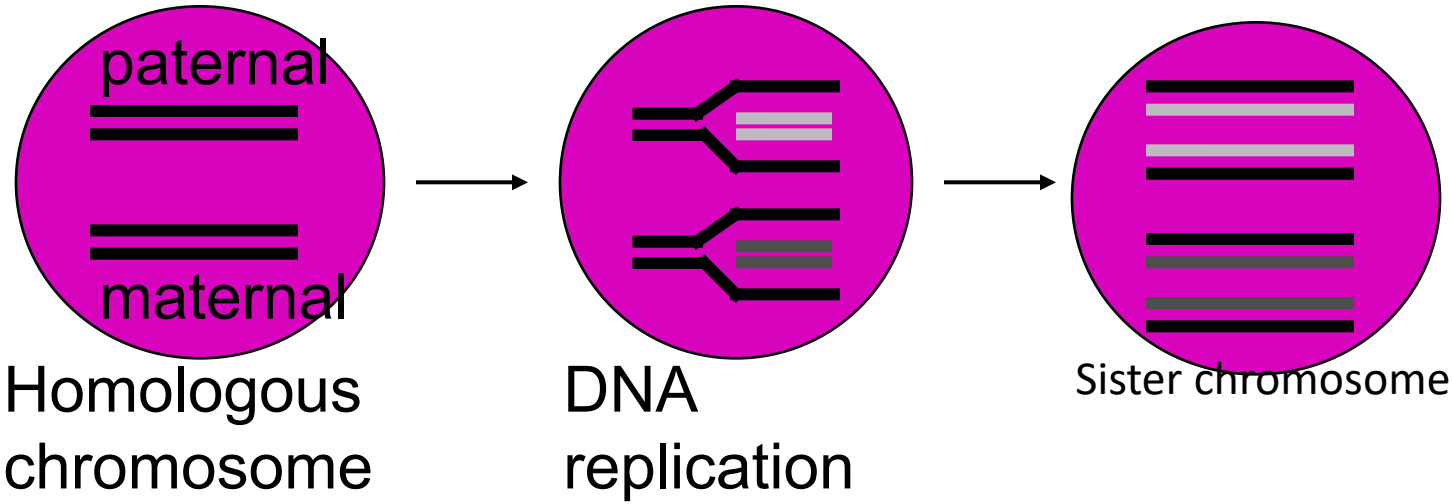
1. Possible insertion or deletion of nucleotides at the junction
2. Possible joining with different portion of the the same chromosome or with different chromosomes
   →Deletion, inversion or translocation

Complementary plays of NHEJ and HR(2)

◆Weak point of HR

Although the homologous sequence exsists on “homologous chromosome” and “sister chromosome”, only the latter is available as the template in vertebrate cells.

→HR is available only in late S and G2 phases.



Complementary plays of NHEJ and HR(3)

◆NHEJ is important in human and other vertebrates

Although it is thought less accurate than HR,

1. Most of the genome is non-coding region
   (Repeat sequence, intron, etc.)
   →Tolerate insertion or loss of few nucleotides.

2. Most of the cells are in G1 phase
   (Especially in tissue or organ)
   →G1 cells rely on NHEJ pathway to repair
   DSBs.

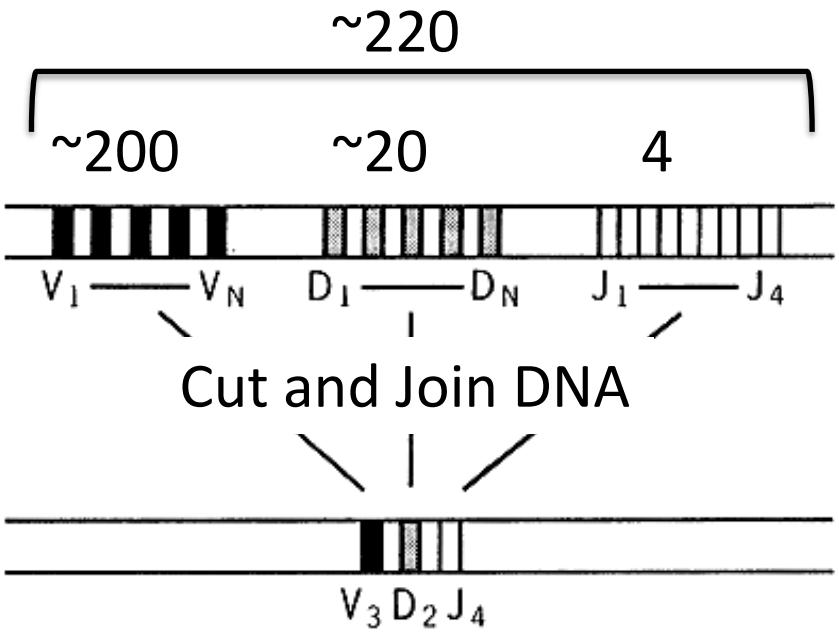
Phenotypes of mice lacking NHEJ factors

Name of genes	Phenotype
DNA-PKcs	Severe combined immunodeficiency (SCID, Leaky)
Ku70	SCID(Leaky) , Growth defect, Neural defect (mild)
Ku86	SCID, Growth defect, Neural defect (mild)
XRCC4	Embryonic lethal, SCID, Growth/Neural defect
DNA ligase IV	Embryonic lethal, SCID, Growth/Neural defect
XLF (Cernunnos)	- (Normal)

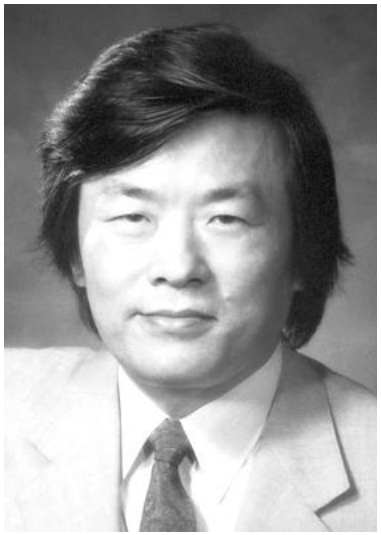
DNA repair factors play essential roles in the development of immune and neuronal systems.
There are also human patients who harbor mutation in NHEJ genes and show similar symptoms.

Mechanism to generate diverse antibodies

We have antibody preparation against infinite variety of bacteria and viruses. Antibodies are generated according to genetic information on DNA, which is finite …



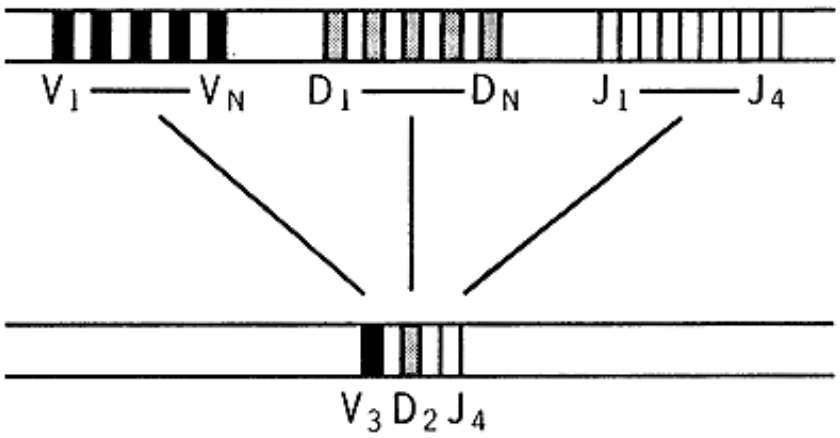
200 × 20 × 4=16,000 patterns!



(From nobelprize.org)

Nobel Prize awarded to Dr. Susumu Tonegawa in 1987

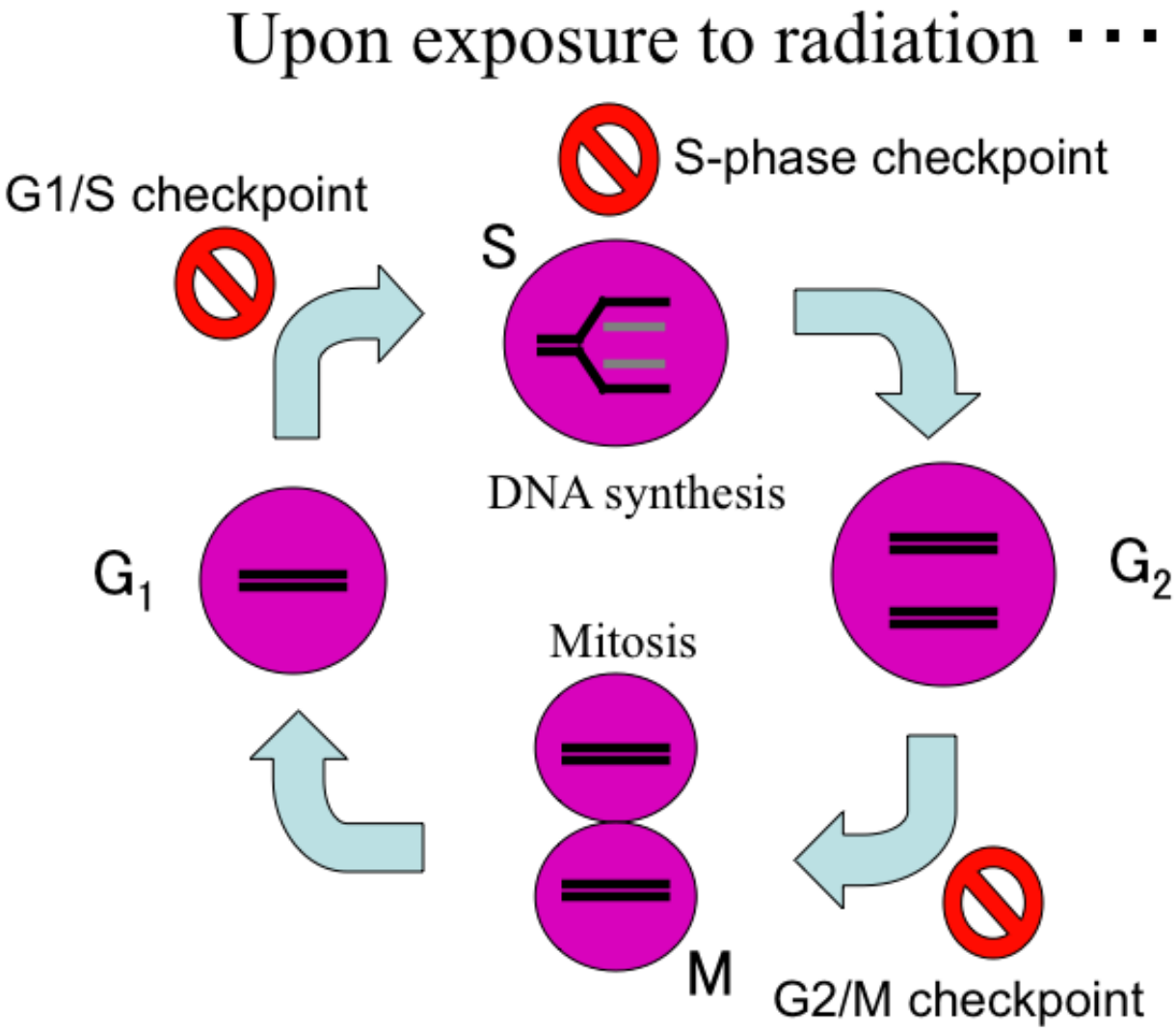
Mechanism to generate diverse antibodies



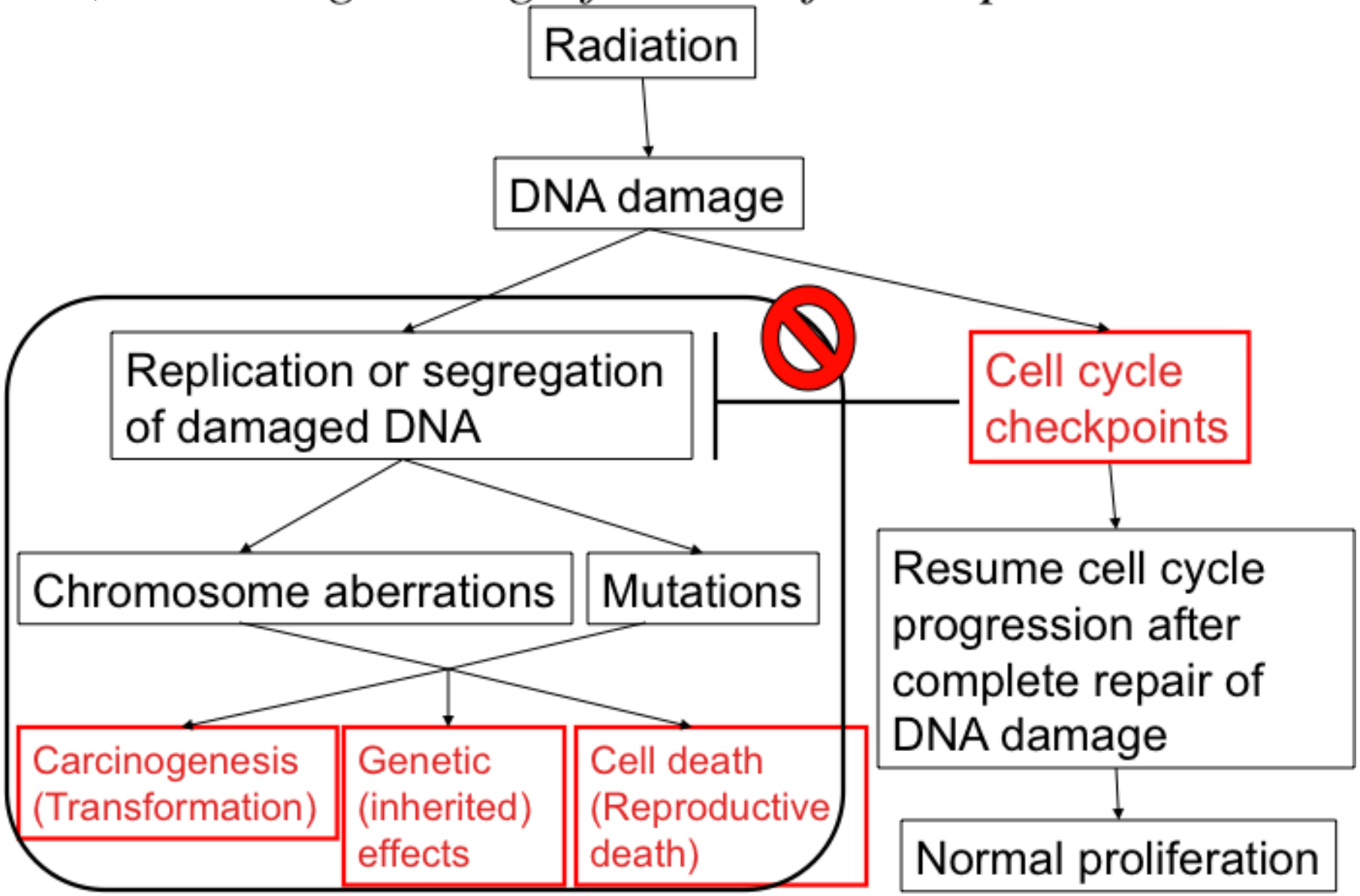
- How to cut ?
  →Enzyme Rag1/2
- How to join ?
  →Utilize NHEJ

3. Cell cycle checkpoint and apoptosis

Cell cycle checkpoints



Biological significance of cell cycle checkpoints



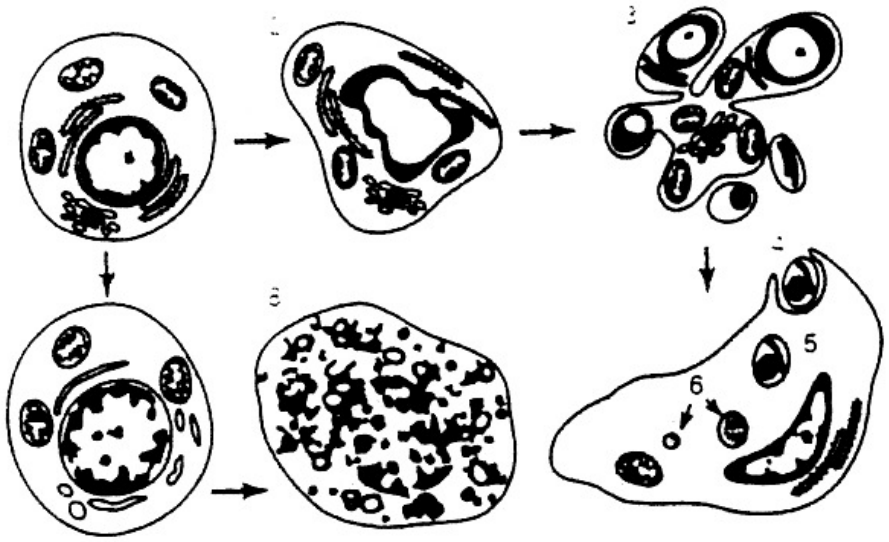
Apoptosis and programmed cell death

◆Apoptosis
(Kerr, Wyllie, Currie (Pathology), 1972)
A cell death process, which is distinct from necrosis in morphology and process.
Source : apo=away, ptosis=fall

◆Programmed cell death (Locksin and Williams (Developmental Biology),1965)
Cell death occurring at specific timing and position in development

Both of the concept foresaw that these are autonomous cell death, regulated by gene.

Apoptosis and necrosis



Apoptosis:
- Nuclear condensation and fragmentation
- Chromosome fragmentation (DNA ladder)
- Cell shrinkage
- Finally “eaten” by macrophage.

Necrosis:
- Enlargement, lysis and destruction of cell body

（実験医学別冊・Bio Science 用語ライブラリー「アポトーシス」より

Example of apoptosis and programmed cell death

1）Morphogenesis (between fingers)
2）Metamorphoses (tail of tadpole)
3）Formation of network in neural system
4）Generation of repertoire in immune system
(Removal of no antibody generating cells and autoimmune cells)
5）Turnover of cells in regenerating organ
(Skin, digestive tract, blood cells）

↓

Mechanisms to eliminate unnecessary or harmful cells in the development or homeostasis of multicellular organisms.

Biological significance of radiation-induced apoptosis