What is mutation?
Components of DNA have unique structures

DNA, as genetic materials, can be modified.

Why mutation?
-- to gain chance for surviving
-- spontaneous vs. induced/forced

Mutation is involved in evolution
- Adaptation
- Genetic drift
- Gene flow
- Mutations
- Natural selection
- Speciation

Gene function may be altered by mutation
*e.g.*, embryonic/pre-mature death, cancer

1. DNA mutation
2. DNA repair mechanism
3. Transcription-coupled DNA repair
4. DNA damage response and human diseases
If mutation occurs in a germ line cell that will eventually produce a gamete, the mutation has the potential to be passed on to the organism's offspring.

The rate of evolution in a particular species (or, more narrowly, in a particular gene) is a function of the rate of mutation. Consequently, the rate and accuracy of DNA repair mechanisms have an influence over the process of evolutionary change.

How mutation?

DNA is a chemical compound, its structure change and biological consequences can be interpreted by comprehensive chemical terms......

1. DNA Mutation

-- mutation frequency

*spontaneous mutation: $10^{-5} \sim 10^{-6}$ events/locus/generation for a 1200-bp gene, mutation at individual nt = $10^{-9} \sim 10^{-10}$

*hotspot

Transition vs. transversion

In genetics, a transition is a mutation changing a purine to another purine nucleotide (A <-> G) or a pyrimidine to another pyrimidine nucleotide (C <-> T). Approximately two out of every three single nucleotide polymorphisms (SNPs) are transitions.

In molecular biology, transversion refers to the substitution of a purine for a pyrimidine or vice versa. It can only be reverted by a spontaneous reversion. Because this type of mutation changes the chemical structure dramatically, the consequences of this change tend to be more severe and less common than that of transitions.

1. DNA Mutation

-- terminology

*transition vs. transversion
*insertion, deletion, suppression
*forward vs. back mutation, silent mutation
*induced vs. spontaneous
The triplet, nonoverlapping code

Insertion or deletion mutations alter the sequence of triplets. Adding/subtracting 3 nt leaves the remaining triplet intact, providing evidence that a codon has 3 nt.

A point mutation, or substitution, is a type of mutation that causes the replacement of a single base nucleotide with another nucleotide. Often the term point mutation also includes insertions or deletions of a single base pair (which have more of an adverse effect on the synthesized protein due to codons no longer being read in triplets, but in different orders—a mutation called a frameshift mutation).

For coding sequences one can categorize such point mutations as follows:

- **nonsense mutations**: code for a stop, which can truncate the protein.
- **missense mutations**: code for a different amino acid.
- **silent mutations**: code for the same amino acid.

For example, sickle-cell disease is caused by a single point mutation (a missense mutation) in the beta hemoglobin gene that converts a GAG codon into GTG, which encodes the amino acid valine rather than glutamic acid.

A single amino acid change causes hemoglobin proteins to form fibers.

**Will the mutation sites matter?**

Point mutations that occur in non-coding sequences are most often without consequences, although there are exceptions.

If the mutated base pair is in the promoter sequence of a gene, then the expression of the gene may change.

Also, if the mutation occurs in the splicing seat of an intron, then this may interfere with correct splicing of the transcribed pre-mRNA.

**1. DNA Mutation**

-- terminology

*transition vs. transversion
*insertion, deletion, suppression
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*induced vs. spontaneous
Spontaneous mutations on the molecular level include:

- **Tautomerism** - A base is changed by the repositioning of a hydrogen atom.
- **Depurination** - Loss of a purine base (A or G).
- **Deamination** - Changes a normal base to an atypical base; C → U (which can be corrected by DNA repair mechanisms), or A → HX (hypoxanthine).
- **Transition** - A purine changes to another purine, or a pyrimidine to a pyrimidine.
- **Transversion** - A purine becomes a pyrimidine, or vice versa.

Induced mutations on the molecular level can be caused by:

**Chemicals**
- Nitrosoguanidine (NTG)
- Base analogs (e.g. BrdU)
- Simple chemicals (e.g. acids)
- Alkylating agents (e.g. N-ethyl-N-nitrosoure (ENU))
  - These agents can mutate both replicating and non-replicating DNA. In contrast, a base analog can only mutate the DNA when the analog is incorporated in replicating the DNA.
  - Each of these classes of chemical mutagens has certain effects that then lead to transitions, transversions, or deletions.
- Methylation agents (e.g. ethane methyl sulfonate (EMS))
- Polycyclic hydrocarbons (e.g. benzpyrenes)
  - found in internal combustion engine exhaust
- DNA intercalating agents (e.g. ethidium bromide)
- DNA crosslinker (e.g. platinum)
- Oxidative damage caused by oxygen radicals

Sources of damage

1. **Endogenous damage** such as attack by reactive oxygen species produced from normal metabolic byproducts (spontaneous mutation), especially the process of oxidative deamination.
2. **Exogenous damage** caused by external agents such as ultraviolet radiation from the sun; other radiation frequencies, including x-rays and gamma rays; hydrolysis or thermal disruption certain plant toxins; human-made mutagenic chemicals, especially aromatic compounds that act as DNA intercalating agents; cancer chemotherapy and radiotherapy

Induced mutations on the molecular level can be caused by:

**Radiation**
- Ultraviolet radiation (nonionizing radiation) — excites electrons to a higher energy level. DNA absorbs one form, ultraviolet light.
  - Two nucleotide bases in DNA - cytosine and thymine-are most vulnerable to excitation that can change base-pairing properties. UV light can induce adjacent thymine bases in a DNA strand to pair with each other, as a bulky dimer.
- Ionizing radiation

Hermann J. Muller — 1946 Nobel Prize in Physiol./Medicine
"for the discovery of the production of mutations by means of X-ray irradiation"

**Alkylating agents**
- Alkyls are radicals;
- Unbonded alkyls are free radicals.

- **Busulfan**
  - (crosslink DND-DNA or DNA-protein)
- **Cyclophosphamide**
  - (formation of 7-methylguanine)
By effect on function:

**Loss-of-function mutations** are the result of gene product having less or no function. When the allele has a complete loss of function (null allele) it is often called an **amorphic mutation**. Phenotypes associated with such mutations are most often recessive. Exceptions are when the organism is haploid, or when the reduced dosage of a normal gene product is not enough for a normal phenotype (this is called haploinsufficiency).

**Gain-of-function mutations** change the gene product such that it gains a new and abnormal function. These mutations usually have dominant phenotypes. Often called a neomorphic mutation.

**Dominant negative mutations** (also called **antimorphic mutations**) have an altered gene product that acts antagonistically to the wild-type allele. These mutations usually result in an altered molecular function (often inactive) and are characterized by a dominant or semi-dominant phenotype.

In humans, **Marfan syndrome** is an example of a dominant negative mutation occurring in an autosomal dominant disease. In this condition, the defective glycoprotein product of the fibrillin gene (FBN1) antagonizes the product of the normal allele. The genetic disorder of the connective tissue characterized by disproportionately long limbs, long thin fingers, a typically tall stature, and a predisposition to cardiovascular abnormalities, specifically those affecting the heart valves and aorta.

**Lethal mutations** are mutations that lead to a phenotype incapable of effective reproduction.

By aspect of phenotype affected:

**Morphological mutations** usually affect the outward appearance of an individual. Mutations can change the height of a plant or change it from smooth to rough seeds.

**Biochemical mutations** result in lesions stopping the enzymatic pathway. Often, morphological mutants are the direct result of a mutation due to the enzymatic pathway.

1. **DNA Mutation**
   -- screening of mutagens
   *DNA repair test
   *prophage induction
   *Salmonella (Ames) test
   *sister chromatid exchange (SCE) test

**Ames test**

**General procedure**

In the test several strains of *Salmonella typhimurium* that carry mutations in genes involved in histidine synthesis are used. The bacteria require histidine for growth. The variable being tested is the mutagen's ability to cause a reversion to growth on a histidine-free medium. The tester strains are specially constructed to have both frameshift and point mutations in the genes required to synthesize histidine, which allows for the detection of mutagens acting via different mechanisms. Some compounds are quite specific, causing reversions in just one or two strains.

**Ames test**

**General procedure (cont’d)**

[The tester strains also carry mutations in the genes responsible for lipopolysaccharide synthesis, making the cell wall of the bacteria more permeable, and in the excision repair system to make the test more sensitive.]

[Rat liver extract is added to simulate the effect of the metabolism, as some compounds, like benzopyrene, are not mutagenic themselves but their metabolic products are.]

The bacteria are spread on a histidine-free agar plate in the middle of which the mutagen to be tested is added. The plates are then incubated for 48 hours. The mutagenicity of a substance is proportional to the number of colonies observed.
Salmonella enterica is a flagellated, Gram-negative bacterium.

**Ames test**

with mutation in histidine synthesis

Salmonella enterica 

filter-paper containing mutagen histidine-free medium 

(bacterial colonies)

1. DNA Mutation

-- mutagenesis

* chemical modification of a base
* incorporation of base analogs
* deamination of 5-methylcytosine
* activation of ras protooncogene by point mutation

**Mutation by chemical modification of a base: cytosine > uracil**

**Mutation by the incorporation of base analogs into DNA: thymine ~ BrdU T > C**

Tautomerism - A base is changed by the repositioning of a hydrogen atom.

“Tautomeric shift”
Changes in DNA caused by mutation can cause errors in protein sequence, creating partially or completely non-functional proteins. To function correctly, each cell depends on thousands of proteins to function in the right places at the right times. When a mutation alters a protein that plays a critical role in the body, a medical condition can result. A condition caused by mutations in one or more genes is called a genetic disorder. However, only a small percentage of mutations cause genetic disorders, most have no impact on health. For example, some mutations alter a gene's DNA base sequence but don’t change the function of the protein made by the gene.

Often, gene mutations that could cause a genetic disorder are repaired by the DNA repair system of the cell. Each cell has a number of pathways through which enzymes recognize and repair mistakes in DNA. Because DNA can be damaged or mutated in many ways, the process of DNA repair is an important way in which the body protects itself from disease. A very small percentage of all mutations actually have a positive effect. These mutations lead to new versions of proteins that help an organism and its future generations better adapt to changes in their environment.

If a mutation is present in a germ cell, this can give rise to offspring that carries the mutation in all of its cells. This is the case in hereditary diseases. On the other hand, a mutation can occur in a somatic cell of an organism. Such mutations will be present in all descendants of this cell, and certain mutations can cause the cell to become malignant, and thus cause cancer.

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**DNA repair mechanism**

--- Direct reversal
- photolyase & AG alkyltransferase
--- Base excision repair & SSB repair
- glycosylases & AP endonucleases

**Direct reversal:** Photoreactivation by photoreactivating enzyme (photolyase)

1. Native DNA
2. Pyrimidine dimer in UV DNA
3. Complex of DNA with photoreactivating enzyme
4. Absorption of light (>360nm) by enzyme
5. Release of enzyme to restore native DNA

*Bacterial photolyase
* (Deisenhofer J., Maier, R., 860: 143, 2000)
Direct reversal: by O^6-alkylguanine-DNA alkyltransferase

Base excision repair & SSB repair
*glycosylases & AP endonucleases

The DNA glycosylase is used to break the $\beta$-N glycosidic bond to create an AP site (apurinic/apyrimidinic). AP endonuclease recognizes this site and nicks the damaged DNA on the 5' side (upstream) of the AP site creating a free 3'-OH.

DDNA repair mechanism (cont’d)
--- Bulky nucleotide excision repair (NER)
*damage recognition: DDB & HMG
*incision: endonuclease
*postincision: exonuclease, polymerase & ligase
-- Recombination repair

-- Bulky nucleotide excision repair (NER)
*damage recognition: DDB & HMG
DDB, damaged-DNA binding proteins (e.g., DDB1)
HMG, high-mobility group proteins (e.g., HMG1)
*incision: endonuclease
*postincision: exonuclease, polymerase & ligase

What are the signals? Anticancer Agents

Damaged-DNA recognition proteins (DRPs)
e.g., HMG-1, DDBs & p53

Nucleotide excision repair
Mismatch repair

Some mutant bacteria cell lines exhibit high frequencies of spontaneous mutation.

In *E. coli*, the mutability-causing mutations are *mutS*, *mutL* and *mutH*. The *mutS* protein recognizes and binds to mismatches in DNA duplexes. The *mutL* protein binds to *mutS*. The *mutH* protein binds to hemimethylated *dam* methylation sites.

The *mutS*-*mutL*-DNA complex stimulates *mutH* to cleave unmethylated DNA strand at the GATC sequence.

The GATC site can be either 5' or 3' of the recognized mismatch. One of two exonucleases (depending on whether cleavage was 5' or 3') chews away at the DNA to beyond the mismatch site. Long patch repair synthesis follows.

Mismatch repair

Some mutant yeast and mammalian cell lines also exhibit high frequencies of spontaneous mutation.

Eucaryotes have proteins with sequence similarity to *mutS* and *mutL* that are involved in a similar repair pathway.

The eucaryotic *mutS* is a dimer of *MSH2* and GTBP (now known as MSH3 or MSH6) proteins. Eucaryotic *mutL* also consists of two polypeptides, MLH1 and PMS2. The *PMS2* gene was originally identified in yeast where its mutation causes abnormalities in post-meiotic segregation.

Mismatch repair synthesis follows.

The systems primarily repair undamaged, but mismatched base pairs and small insertions or deletions. Some modified bases, such as O-methylguanine are also recognized.

Mismatches resulting from damaged base may lead to mutations if recognized by the mismatch repair system instead of BER or NER. This may account for the effectiveness of MNU and MNNG as mutagens.
3. Transcription-coupled DNA repair

“Several types of helix-distorting DNA lesions block the passage of elongating RNA polymerase II. Surprisingly, such transcription-blocking lesions are usually repaired considerably faster than non-obstructive lesions in the non-transcribed strand or in the genome overall.”


**Mechanism of TCR:**

Genes are copied from DNA to make messenger RNA to instruct protein synthesis by RNA polymerase II. When RNA polymerase finds a lesion in the DNA, like those caused by UV light it stops and the gene is not transcribed. TCR is associated with RNA polymerase II and removes lesions before the polymerase reaches them. The CSB protein, which is mutated in patients with Cockayne syndrome, is associated with XPG (another protein associated with the syndrome). RNA polymerase II is stalled during transcription, XPG and CSB respond to the stalled transcription bubble. They then recruit transcription factor II H and other proteins and protein complexes to remodel RNA polymerase, gain access to the bubble, and repair the lesion while leaving polymerase in place.

**Mechanism of TCR: (cont’d)**

The fast, preferential repair of the transcribed strand of an active gene — occurs in both prokaryotes and eukaryotes. This kind of repair is performed by the nucleotide excision repair (NER) or the base excision repair (BER) pathways.

TCR is triggered by the stalled polymerase itself. In the promoter of an active gene, repair is slow. TCR is extra fast immediately downstream from the transcription initiation site, presumably because TFIIH is still associated with the polymerase at this point.

**Mechanism of TCR: (cont’d)**

Different factors allow the TCR repair machinery to be specifically targeted to the transcribed strand and the global genome, respectively.

The best-studied TCR factors are CSA and CSB (yeast Rad26), but factors such as XPG and TFIIH also have a role.

In the transcribed strand, RNA polymerase II (RNAPII) is an obstacle to TCR and CSB/Rad26 is required to overcome this obstacle to fast repair.
TCR also exists in bacteria, and is mediated by the TRCF (Mfd) protein. TRCF is an SF2 ATPase that uses ATP hydrolysis to translocate on dsDNA upstream of the transcription bubble and forward translocate RNA Polymerase, thus initiating dissociation of the RNA Polymerase ternary elongation complex. TRCF also recruits the Uvr(A)BC nucleotide excision repair machinery by direct physical interaction with the UvrA subunit.

### DNA damage response signal-transduction pathway

![DNA damage response signal-transduction pathway](image)

### Mammalian DNA damage response pathway

![Mammalian DNA damage response pathway](image)

### Table 1: Conserved DNA damage response genes

<table>
<thead>
<tr>
<th>Functional class</th>
<th>Mammals</th>
<th>S. cerevisiae</th>
<th>S. pombe</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCNA-like proteins</td>
<td>Rad1</td>
<td>Rad17</td>
<td>Rad1</td>
</tr>
<tr>
<td></td>
<td>Rad9</td>
<td>Cdc1</td>
<td>Cdc9</td>
</tr>
<tr>
<td></td>
<td>Hus1</td>
<td>Nmc3</td>
<td>Hus1</td>
</tr>
<tr>
<td>RFC-like proteins</td>
<td>Rad1</td>
<td>Rad24</td>
<td>Rad17</td>
</tr>
<tr>
<td>RFCX</td>
<td>Rad52</td>
<td>Rad52</td>
<td></td>
</tr>
<tr>
<td>RFC3X</td>
<td>Rad51</td>
<td>Rad51</td>
<td></td>
</tr>
<tr>
<td>BRCT proteins</td>
<td>BRCA1, SSBP1</td>
<td>Rad3</td>
<td>CK2/Hsp90</td>
</tr>
<tr>
<td></td>
<td>CKM1</td>
<td>CKM1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>ATM</td>
<td>Tel1</td>
<td>Tel1</td>
</tr>
<tr>
<td>E3-like kinases</td>
<td>Chk1</td>
<td>Chk1</td>
<td>Chk1</td>
</tr>
<tr>
<td></td>
<td>Chk2</td>
<td>Rad53</td>
<td>Cdc1</td>
</tr>
<tr>
<td>Coiled-coil proteins</td>
<td>7</td>
<td>Cdc2/Lod1</td>
<td>Rad21</td>
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</table>

### Table 2: Targets of damage response kinase-dependent phosphorylation

<table>
<thead>
<tr>
<th>Kinase class</th>
<th>Mammals</th>
<th>S. cerevisiae</th>
<th>S. pombe</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATM, ATR (Mammalian)</td>
<td>p53</td>
<td>ATM</td>
<td>p53</td>
</tr>
<tr>
<td>Rad3, Tel1 (S. pombe)</td>
<td>p53</td>
<td>ATM</td>
<td>p53</td>
</tr>
<tr>
<td>Chk1 (Mammalian)</td>
<td>p53</td>
<td>Chk1</td>
<td>p53</td>
</tr>
<tr>
<td>Chk1 (S. pombe)</td>
<td>p53</td>
<td>Chk1</td>
<td>p53</td>
</tr>
<tr>
<td>Chk2 (Mammalian)</td>
<td>p53</td>
<td>Chk2</td>
<td>p53</td>
</tr>
<tr>
<td>Rad53 (S. cerevisiae)</td>
<td>p53</td>
<td>Rad53</td>
<td>p53</td>
</tr>
<tr>
<td>Cdc1 (S. pombe)</td>
<td>p53</td>
<td>Cdc1</td>
<td>p53</td>
</tr>
</tbody>
</table>

* In vitro phosphorylation and in vivo dependency. ** In vivo dependency.
H4.2 -- Hereditary DNA repair disorders
Defects in the NER mechanism:
d xeroderma pigmentosum: hypersensitivity to sunlight/UV, resulting in increased skin cancer incidence and premature aging
Cockayne syndrome: hypersensitivity to UV and chemical agents
trichothiodystrophy: sensitive skin, brittle hair and nails

[Mental retardation often accompanies the latter two disorders, suggesting increased vulnerability of developmental neurons.]

Cockayne syndrome, autosomal recessive disorder characterized by growth failure, impaired development of the nervous system, abnormal sensitivity to sunlight (photosensitivity), and premature aging. Hearing loss and eye abnormalities (pigmentary retinopathy) are other common features, but problems with any or all of the internal organs are possible. It is named after English physician Edward Alfred Cockayne (1880-1956).

Trichothiodystrophy (TTD) sensitive skin, brittle hair and nails; TCR defect associated.

Ataxia telangiectasia sensitive to ionizing radiation and some chemical agents

H4.2 -- Hereditary DNA repair disorders
Other DNA repair disorders:
d ataxia telangiectasia: sensitivity to ionizing radiation and some chemical agents.
Bloom's syndrome: sunlight hypersensitivity, high incidence of malignancies (especially leukemias).
Werner's syndrome: premature aging and retarded growth.

[All of the above diseases are often called "segmental progerias" ("accelerated aging diseases") because their victims appear elderly and suffer from aging-related diseases at an abnormally young age.]

Xeroderma pigmentosum (XP)
Hypersensitive to sunlight/UV induced pyrimidine dimers, namely CPDs (Cyclobutane-Pyrimidine-Dimers) and 6-4PP (pyrimidine-6-4-pyrimidone photoproducts), resulting in increased skin cancer incidence and premature aging. There are seven complementation groups (A, B, C, D, E, F, G), plus one variant form (XPV).

Ataxia telangiectasia sensitive to ionizing radiation and some chemical agents
Bloom’s syndrome (BS)
Sunlight hypersensitivity, high incidence of malignancies (especially leukemias).

4.2 -- Hereditary DNA repair disorders
Diseases associated with reduced DNA repair:

Fanconi’s anemia:
Hereditary breast cancer:
Hereditary colon cancer:

Fanconi’s anemia (FA) is a genetic disease that affects children and adults from all ethnic backgrounds. The disease is named after the Swiss pediatrician who originally described this disorder, Guido Fanconi. FA is characterized by short stature, skeletal anomalies, increased incidence of solid tumors and leukemias, bone marrow failure (aplastic anemia), and cellular sensitivity to DNA damaging agents such as mitomycin C.
FA is primarily an autosomal recessive genetic condition. There are at least 13 genes of which mutations are known to cause FA: A, B, C, D1, D2, E, F, G, I, J, L, M and N.
Eight of these proteins, FANCA, -B, -C, -E, -F, -G, -L and –M assemble to form a core protein complex in the nucleus.
Assembly is thought to be activated by DNA damage due to cross-linking agents or reactive oxygen species (ROS).

Repair defect and breast cancer
BRCA1 and BRCA2, two famous mutations conferring a hugely increased risk of breast cancer on carriers, are both associated with a large number of DNA repair pathways, especially NHEJ and homologous recombination.
The BRCA1 protein is directly involved in the repair of damaged DNA. In the nucleus of many types of normal cells, the BRCA1 protein is thought to interact with RAD51 to mend breaks in DNA. The BRCA2 protein, which has a function similar to that of BRCA1, also interacts with the RAD51 protein.

Mismatch repair defect and colon cancer:
Individuals with hMSH2 deficient CRC in the general population exhibit a family history and other characteristics suggestive of hereditary nonpolyposis colorectal cancer (HNPCC), and may carry germline MMR mutations.
Loss of hMLH1 is only associated with a strong family history of extracolonic cancer at older ages, suggesting a novel mechanism of susceptibility.

HNPCC is inherited in an autosomal dominant fashion.

Some repair-associated proteins are also known as BBASC (BRCA1-associated genome surveillance complex):

*ATM: ataxia telangiectasia mutated gene
*BLM: Bloom’s helicase
*BRCA1: NHEJ and homologous recombination
*MLH1/2, MSH2/6: mismatch proteins
*4.2 -- Hereditary DNA repair disorders

**Other damage-responsive proteins:**
- *p48/DDB2: Xeroderma pigmentosum* group E (XPE)
- *Nbs1: Nijmegen breakage syndrome* (NBS)
- Defect in rejoining double-stranded DNA breaks

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**Interactions between the DNA damage response pathway and DNA repair networks**

**DNA repair rate is a determinant of cell pathology**

**DNA repair and aging**

Most lifespan influencing genes affect the rate of DNA repair.

---

**Wrong DNA damage response can cause human diseases including cancer!**

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**Quiz:**

Briefing a best described mechanism for \textit{getting a gene mutation} in a population of growing cells repeatedly exposed to nitrous acid.

[\textbf{Hint}: \textit{e.g.}, CG to UA mutation]

Describe a repair mechanism in cells to avoid the mutation.

[\textbf{Hint}: \textit{e.g.}, NER (enzymes)]