Cell and Molecular Biology
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Genetic Material in Cells
Lecture - 24
Genome Damage and Repair Mechanism

Hello everyone, this is Dr. Vishal Trivedi from the Department of Biosensors and Biogenetics, IIT Guwahati. When DNA replication is happening, the cell is continuously exposed to different types of mutagenic molecules, and different types of mutations occur within the cell. Because when the cell is replicating, it has a proofreading activity; it utilizes that proofreading activity to correct the sequences, but even then, there are spontaneous mutations that are going to happen in the DNA. These mutations are actually going to be detected by a well-established machinery, and that's how it is going to participate; it will correct those mistakes. If these mistakes are not corrected, they will lead to the accumulation of mutations, and ultimately, it may cause the development of different types of cancers.

So DNA damage, as the name suggests, could occur in DNA due to errors in DNA replication. It could happen because it caused the spontaneous lesions, or it could be because of the transposable DNA, or it could be because of the physical mutagens, or the chemical mutagens. There are several examples of physical mutagens, and there are several samples of mutagens that we are going to discuss. And then errors in DNA replication are also very, very important in terms of DNA damage.

So what is meant by the DNA damage? It is known that the genome is not a static entity. The genome is present inside the nucleus or inside the cell in the case of the prokaryotic system. And it is whenever you are actually exposed to a particular type of physical or chemical environment. It is actually getting exposed as well, and you know that the importance of the genome, which is actually hereditary material, is that it follows the information to the next generation, so it is important that the genome should be intact and should not be damaged. So, hence it is highly subjected to a variety of heritable changes.

A sudden change in the sequence of an organism's genome that gives rise to an alternate form of any gene is called a mutation. As a result, the DNA is damaged. These mutations are mostly recessive and lethal. Mutations are random and can occur anytime in any of the cells of an organism. It is not as if the mutation occurs once; the same mutation can occur again.

Mutation is recurrent and can occur again and again, right? The question arises, how do the DNA damages happen? On a molecular basis, DNA can be damaged in two ways. Some mutations may occur spontaneously. Some mutations are induced by mutagens. Spontaneous damage occurs without the treatment of the organism with exogenous mutagens. It is mainly due to errors in replication, spontaneous lesions, and transposable elements.

Whereas the induced mutations arise when the mutagens react with the parent DNA, which causes structural alterations in base pairing. What is meant by the mutagens? Any agent that causes an increase in the frequency of mutations is called a mutagen. Now, as far as the DNA damage is concerned, you can have the two main categories. One is called spontaneous damage, the other is called induced mutations. So within this category, you have multiple components, and these components are important for causing DNA damage.

So agents causing the DNA damage, you have these agents that are causing the spontaneous mutations, and you also have the agents that are causing the induced mutations. Within the spontaneous mutations, you can have errors in the DNA applications. You can have the tautomeric shifts. And spontaneous lesions within the spontaneous lesion, you are going to have the deaminations, depurinations, depurinations, and the oxidative cleavage. Whereas the transposition is another phenomenon through which it is actually going to cause spontaneous mutations.

Whereas in the case of induced mutations, there are two different categories that can cause the induced mutations: one is called chemical mutagens, and the other is called physical mutagens. Within the chemical mutagens, there are different types of agents that can cause base analogs, so there are chemical agents that function as base analogs, and that's how they actually destroy the DNA. Then you can also have the deanimating agents; you are going to have alkylating agents. Most of the anti-cancer drugs or the majority of the anti-cancer drugs are alkylating agents. And then you are also going to have the intercalating agents because they are all actually going to interfere with the replication and interfere with the repair mechanism, and that is how they are actually going to cause mutations that will perpetuate from generation to generation.

Then you are also going to have the physical mutagens. Physical mutagens mean the physical parameters that you are going to use. So, in that case, you are going to have UV radiation, ionizing radiation, and you are also going to have heat. So, these are the physical parameters that are actually going to cause the mutations. Now, let us first start with the spontaneous mutations and then we will discuss the induced mutations.

So spontaneous mutations, the number one category, are the errors in the data applications. So, tautomeric shifts, right? For example, the shift of a proton from its nitrogenous base to its rare form is called tautomeric shifts. The stable keto form of thymine and adenine and the amino form of adenine and cytosine undergo tautomeric shifts to form the unstable enols and amines, respectively. For example, you have the stable form of adenine and guanine, which is the amine form, and once it undergoes tautomeric shifts, it will actually form the immuno forms, which are very rare. But they are actually going to be less unstable; these forms have very short lifespans.

If they are incorporated into nascent DNA, they may result in mutations if these bases are present in their unstable enol or immuno state. They tend to form the A-C and G-T base pairing. This AC and GT base pairing is not allowed, and that is how it is actually going to destroy or distort the DNA structures. And because of that, for example, this is C; it is actually going to form the interaction with the A form. A is always making a base pairing with T in the DNA, but in this case, A is actually going to make a pair with C, and that is actually going to cause an alteration in the sequences, and that is how it is actually going to go into the next generation.

So, imagine that you have a C. Instead of having a C in the template, ideally it should be a G in the replicated DNA, right? But since this kind of mutation is happening, or this kind of tautomeric shift is happening, what will happen is that C is actually going to give rise to a synthesis of A. So, instead of A, instead of G, you are going to have A in the DNA sequences, and that is how it is actually going to cause the mutations. The net effect of such an event and the subsequent replication required to segregate and mismatch bare fair, that is, the AT to GC or GC to AT based pairing substitutions, is how it is actually going to cause the mutations. Mutations occur via the tautomeric shift in the bases of DNA.

In the examples, guanine undergoes a tautomeric shift to a rare enol form at the time of replication. In its enol form, it is paired with thymine. So, this is exactly what is showing here: you are actually replicating a sequence where you have all sorts of nucleotides like G, C, T, and all that, and during the replication, if the G is actually getting converted or is shifting into another form, then G is actually going to start making a pair with T instead of starting to make a pair with C, and because it has altered the base pairing information. It is actually going to allow the formation of the T instead of G; it is actually going to give you the A right because it is actually going to give you the T instead of G, and as a result, it is going to replicate. So once the DNA replication of this particular sequence happens, it is actually going to give you the wild type, which should be G.

G is actually going to give you the C, but in this particular type of second generation,

instead of G and C, it is actually going to be AT. So this is exactly what happened when you were going to have the tautomeric shifts. So during the next generation, the joanine shifts back to its more stable keto form. The thymine incorporated opposite the enol form of the guanine directs the incorporation of the adenine during the subsequent replication. The net result is that the GC is going to be an AT mutation.

So G is making a base pairing with T. As a result, in the first generation, T is going to be synthesized. And then in the second generation, G is again reverting to the keto form. So because of that, it is actually going to start synthesizing the G to C. But here, instead of T, it is actually going to, since you have the T in the daughter, start synthesizing the A.

And as a result, what will happen is that wherever you have a G, it is going to be replaced by A. So, it is actually going to have G to A mutations. And if you have G-to-A mutations, then it is actually going to change many things. It is going to change the amino acid that corresponds to the G to A substitution and so on. And then you have substitution mutations.

So errors during replication result in substitution mutations or frameshift mutations. So the substitution of one base pair for another is called a substitution mutation. The swapping of the base pair may be a transition mutation or a transversion mutation. So what are the transition mutations? Substitution of one pyrimidine by another pyrimidine or one purine by another purine is called transition mutations. For example, G to C is going to be replaced by A and T, and vice versa.

So in that case, it is actually going to cause substitution mutations. Then you have the transversion mutations. So purine is replaced by pyrimidine or pyrimidine is replaced by purine. So subsequent transversion is a transition, for example, G to A. Or A to G or C to T or T to C, these are the transitions; if G is replaced by A, then it is going to be called a transition mutation, or if A is replaced by G, then it is also going to be called a transition because a pyrimidine is replaced by a pyrimidine and a purine is replaced by a purine.

But if it is the pyrimidine that is replaced by the purine, then it is going to be called transversin. So both of these kinds of substitutions are actually going to be very, very problematic because they are going to overall change the amino acids and cause mutations in the subsequent gene products. Then you have the frameshift mutations right. So sometimes it may happen that during replication some extra nucleotides may get inserted or may not get copied. So you can actually have either the addition of extra nucleotides or you can actually have the disappearance or deletion of some mutations.

And in both of these cases, it is actually going to cause frame mutation. This frame

information, anyway, you will be able to understand when we discuss the translation because you know that the protein is going to be synthesized in the form of codons. A codon is made up of three nucleotides. So, protein is synthesized in the form of the codon. So, for example, this is the codon ATG.

So these three nucleotides are going to be read together by the integron on what is present on the tRNA. But now imagine that if I add one more A into this, what will happen is it is going to be this sequence, right? Now, if I go by the three triplicates, then it is actually going to be like this. This means that earlier the codon was ATG; now the codon is going to be ATA, and the codon for ATG is going to code for X amino acid, whereas the codon for ATA could code for Y amino acid, and that's how there could be a change in the amino acid that is going to be incorporated into the protein. Another example is that, for instance, if I have A here and if I have C, for example. So if I have a sequence like A, T, G, C, A, and if I remove, actually, if I remove, for example, if I remove this, actually.

So if there will be a deletion, then what will happen is that it is going to have this. So, earlier you had this as a codon, now you are going to have this as a codon. So, this also is going to be cause the deletion. So, this is going to happen because of the deletion; this is going to happen because of the incorporations. So, if this happens in the axonic region of DNA, it may mainly change the translational reading frame, resulting in the production of a non-functional protein that can be observed in phenotypic characteristics.

So it is not only going to change the codon for this, it is actually going to change the codon for subsequent generations also. For example, it is going to change the rotation of the frame shape. So it is actually going to change the codon. For example, earlier you were having this. So this is the first codon; this is the second codon.

Now, if you remove this T, then you are going to have the first codon as AGC and the second codon as ATT, whereas earlier it was ATG and CAT. So, this was the codon, right? So, this is called not only going to change the frame shift only for the first codon, but also for all the codons, and because of that, it is actually going to cause a significant change in the amino acid composition of the product, and as a result, it is actually going to produce a protein that may not be functional and may actually cause problems for the cell. For example, this is the example that is being given. You have this as a standard for frames that are present. And when you have the mutations or the messenger RNA, what is going to be formed is actually going to form.

But if you have the addition of a T base pair, then it is actually going to change the frames, and that is how it is actually going to form the proteins; or if, suppose, you have

the deletion, then you are also going to change things. So these are some of the things that are very, very important, and the frameshift mutation is a very significant problem; as a result, this shift changes the translational reading frame, hence the name frameshift mutations. Then the second thing we have is spontaneous lesions. Naturally occurring damage to the DNA is called spontaneous lesions. Most common lesions are deaminations and depurinations.

So deaminations, the loss of an exocyclic amino acid group from cytosine, adenine, and guanine due to changes in pH and temperature, are spontaneously resulting in the formation of uracil, hypoxanthine, xanthine, and thymine, respectively. So, deamination is going to change the amino acids. For example, if there is deamination of these nucleotides, then it will actually be converted into uracil, hypoxanthine, xanthine, and thymine, and that will actually result in a change in the structure or a change in the nucleotide sequences. Then depurination and depyrimidination result in the loss of purines and pyrimidines by the breakdown of the glycosidic bond in nucleotides from the DNA due to damage caused by the change in pH. And then you are also going to have oxidative damage.

The damage in the DNA is due to the reactive species spontaneously. Radicals like peroxide, hydrogen peroxide, and toxic radicals attack the DNA product, reducing the variety of products. Attack at severe residual leads to fragments, base loss, and strand streaks. So all of these things can also lead to the frame shift mutations and the spontaneous mutations as well. So these are some of the examples; if you have deamination, the cytosol is going to be converted into uracil.

If there is a deamination of the adenine, it will actually be converted into hypoxanthine, and then if you have 5-methylcytosine and there is a deamination, it will be converted into thymine. Warning: it is actually going to get converted into xanthine, and some of these are non-natural amino nucleotides, so they will actually cause significant mutations in the DNA structures. Then we have transpositions; a transposon is a DNA segment that has the capacity to insert itself at any location in the genome without having any relation to the target sequence. Consequently, it causes loss of gene fraction or inappropriate overexpression of genes. So transposition is a very, very important and very, very significant topic that you should actually study, and transposons are also called jumping genes; they actually change their position from one locus of the genome to another locus, and as a result, they cause different types of artifacts and different types of problems in the genes.

So they are actually going to cause the loss of gene functions or inappropriate overexpression of genes. So transposons are a very important and broad topic, so if you

are interested, you can study this in any of the standard molecular biology books. And then we have the induced mutations. So, mutagens result in the induced mutations. Mutagens can be classified as physical mutagens and chemical mutagens.

So, these are the physical mutagens: UV radiation, ionizing radiation, and heat. The UV radiation is a potent physical agent that causes a number of photoproducts in the DNA. UV radiation of the wavelength 260 nanometers induced dimerization of the pyrimidine nucleotide bases, especially thymine, resulting in the formation of the cyclobutyl dimers. So this is exactly what happened: right when you have the two nucleotides, they will be exposed to the UV; they are actually going to dimerize, and they are going to form the cyclobutane rings. Adjacent pyrimidines are covalently linked to form a four-member ring structure, and this structure is called the pyrimidine dimers.

Then ionizing radiation mainly causes DNA strand breakage, and you also have heat stimulating the wave-induced cleavage of the N-glycosidic bond, which results in apurinic or apyrimidinic sites, or the baseless sites. So in this particular case, what will happen is that there will be a cleavage of the glycosidic bond, and you know that the glycosidic bond is holding the sugar to the base; because of that, there will be no base present on these particular nucleotides. Then we have chemical mutagens. So in chemical mutagens, you can have four categories: base analogs, deaminating agents, alkylating agents, and intercalating agents. Base analogs are certain bases that are not normally present in DNA but resemble the normal nitrogenous bases that can be incorporated during DNA synthesis; for example, 5-bromouracil is a base analog of thymine, and 2-aminopurine is an analog of adenine.

So these base analogs are going to induce mutations because they mimic the natural bases, but they are not natural, and they will be incorporated into the DNA during DNA synthesis. Then we have the deaminating agents which cause point mutations by the removal of the amino group from the nitrogenous bases. Nitrous acid deaminates adenine, cytosine, and guanine, while sodium bisulfite deaminates only cytosine. The deamination of adenine gives rise to hypoxanthine, which pairs with cytosine instead of thymine. Deamination of cytosine gives rise to uracil, which pairs with A instead of G, and this actually is going to cause problems in the first generation as well as in subsequent generations because of the C to T mutations and the A to G mutations.

Then we have the alkylating agents. So some examples of alkylating agents are ethylene, methane, sulfone, nitrogen mustard, and dimethylnitrosamine. These agents actually add the alkyl group to a certain position in the nucleotide, and these alkylating agents are actually going to cause the mutation, and that's how it's actually going to kill the cells. Many of the anti-cancer drugs are alkylating agents as well. So they alkylate the DNA,

and that is how they are actually activating the machinery to kill these cells. Then we have intercalating agents usually associated with simple single mutation pair insertions or deletions.

Intercalating agents are flat molecules that flip between the base pairs in the double helix, resulting in the unbinding of the DNA helix and therefore increasing the distance between the adjacent base pairs. Some examples are proflavin, acridine orange, ethidium bromide, and the ICR compounds. Intercalating agents are also very problematic because they interfere with DNA synthesis and change the normal DNA structures, and that's how they actually cause mutations. So, these are one of the effects. So, for example, if this is the DNA, how is the base analog actually causing the problem? So, for example, this is the normal DNA and you have the A, which is in the corresponding template, you are going to have T.

Now, if there is a base mutation, so, for example, the fibroma uracil is going to be present instead of A. So, if there is a BU that undergoes a tautomeric shift, then BU is actually going to get converted into this. And that is how it is actually going to have the affinity for C rather than G, because this is going to have the affinity for G rather than C, but rather than A, because you should have an intra-affinity for A. However, it does not have the intra-affinity for A; it has affinity for G.

So, what will happen is when the replication occurs. In the wild type, the A is going to form, and A is going to be synthesized in front of T. But in this one, instead of this, you are going to have the G. Now, once you do another round of applications A, this wild type will not actually have any problem because it is still going to have the A to T. But here, Now the G is first mutated, and now the second strand is also going to be mutated, and that's how it is actually going to have the C. So this is actually going to be a mutated DNA that is going to be formed, and this mutated DNA, if you do the subsequent replications, will proliferate, and it will continue into the subsequent cells, actually, or neutral cells.

Similarly, we have deaminating agents. For example, adenine, when it's going to be attached to nitrous acid, is going to get converted into hypoxanthine, or cytosine when it's going to get converted into AT. So once you have the adenine to the hypoxanthine, hypoxanthine will not form the interaction with T. Instead, it is actually going to have the interaction with C, and because of this, the AT is actually going to be replaced by GC, exactly with the same mechanism that in the first generation the A will actually recognize the D, but in the subsequent generation, when the A gets converted to hypoxanthine. The daughter strand is going to have the cytosine, and cytosine is actually going to incorporate the C. So that is exactly what is going to happen in the subsequent generation

with the deaminating agents.

And then you are also going to have the alkylating agent. For example, gonine is going to be converted into ethylene gonine. And ethylene guanine is going to have an affinity for thymine instead of the interaction with cytosine. And because of that, there will be a reverse. In this case, the AT is being replaced by GC.

In this case, the GC is going to be replaced by AT. And the same is true for thymine when it is being alkylated. It is going to form ethylene thymine. And ethylene thymine has an interaction or is going to make the base pairing with guanine rather than adenine. As a result, the TA is going to be replaced by the CG, so these are some of the mechanisms through which the DNA is going to be mutated. Now, how is the DNA going to be damaged? Whether it is going to be damaged by spontaneous mutations or by induced mutations, you are supposed to repair these changes, right? We are supposed to have the machinery to detect, and then, if possible, you can actually be able to have these things repaired.

So, systems for repairing the numerous unintended lesions that frequently occur in DNA are also required for maintaining genetic stability in addition to the extremely precise DNA replication mechanisms. The vast majority of these unintentional DNA replications are temporary because the DNA repair system, a group of connected systems, immediately corrects them. Without repair processes, a genome cannot maintain its essential biological functions. These DNA repair mechanisms fall into two broad categories. Direct reversal of the chemical process that causes the DNA damage, and the damaged bases are removed and then replaced with freshly synthesized DNA.

So, you have two choices for reversing these damages. First, you can actually be able to reverse the process. You can actually reverse the reaction. For example, if you have the alkylating agents, you can actually reverse the alkylating agent and reverse these reactions so that guanine is converted back to adenine and so on. Another thing is that you can just replace these damaged bases and replace them with the normal bases, and that is also going to be another base, so additional mechanisms have developed to help the cell deal with the damage where the DNA repair fails. DNA repair mechanisms include the single strand break repair mechanism and the double strand break mechanisms.

In the single-strand break mechanism, you can have direct reversal, excision, mismatch repair, and within excision repair, you can have nucleotide excision repair or base excision repair. Whereas in double strand breaks, you can have homologous recombination or non-homologous DNA recombination. So directly acting on the

damaged nucleotide converts it back to the original structure. So pyrimidine dimers are usually repaired by a light-dependent direct reversal process called photoreactivation.

DNA photolysis enzymes participate in the mechanism that is found in E. coli. These enzymes get activated at wavelengths of 300 nanometers and 500 nanometers. The enzyme binds to the pyrimidine dimer and converts it back to the original monomeric nucleotides. So this is exactly what happens when you have the thymine dimers that are going to be formed and when you expose this particular DNA to visible light. It is actually going to lead to the photolysis of these particular strands, where you are having the nucleotide dimer being formed. And then, with the help of the enzyme called DNA photolysis, it will replace and remove these nucleotides and form normal DNA.

So these are going to reverse, and that is how it is actually going to recover the DNA. Then we also have the excision repairs, so excision reports involve the excision of the damaged segment of DNA followed by the resynthesis of the current nucleotide sequence by an enzyme called DNA polymerase. So, base excision repairs can actually involve the removal of the damaged base used to repair minor damages like alkylation and deamination, which are consequences of exposure to mutagens. It is initiated by an enzyme called DNA glycosylase. And the DNA glycosylase cleaved at the glycosidic linkage, hence detaching the altered base.

As a result, apyrenic or apyrimidinic sites are generated. Final ligation of the nucleotide takes place by DNA polymerase and DNA ligase. So, this is the mechanism where you are actually having the UDG role of the UDG, uracil DNA glycosylase. So, if you have the deaminated cytosine, which is actually going to be uracil, that is actually going to first form the epigenic sites, and then these epigenic sites are actually going to refill back, and that's how you're going to have the repaired DNA at the end of this particular repairing mechanism. Then you can also have nucleotide excision repair. So similar to base excision repair, it acts on a more substantially damaged area of the DNA.

It includes the following steps. So damaged DNA, first you are going to have the damaged DNA, the breakage of the phosphodiester bond on either side of the damaged portion. For example, this is damaged DNA. So on both sides, you are going to have the breakage of the phosphodiester bond, and then you are going to have the excision leaf gap. So you are going to have a gap that is going to be created, and this gap is going to be filled by the DNA polymerase, while ligase seals the breaks.

The best study mechanism for the nanoplane is the UVR system in the E. coli. A key enzyme involved is called ABC exonuclease, which is made up of the three subunits UVR A, UVR B, and UVR C genes. The ABCXC nucleus binds to the damaged site on

the DNA and cuts the phosphodiester bond in both the 5' and 3' regions. UVRD is acting as a helicase and helps to unwind the DNA at the site of the cut. The gap is filled by DNA polymerase I and sealed by ligase.

And then we have the third mechanism. The third mechanism is called as the mismatch repair. It detects the mismatch that occurs during renal replication. The mismatch repair occurs in the daughter strand and it is highly prone to mismatches during replication. How can you distinguish between the parent strand and the daughter strands? Immediately after the replication, the parent strand will contain a methyl group, whereas the daughter strand awaits the introduction of the methyl group. In this way, the two strands can be distinguished, and this is the best time period for the repair mechanism to scan the lesion like the correction.

So it is very important to see that the damage will only occur in the daughter cells rather than the parent cells. So, parent cell, you are just going to remain intact. In the daughter cells, you are going to have these kinds of repair mechanisms, and how you are going to recognize the daughter cell is that the daughter DNA is going to be unmethylated because the methylation has still not been done for all the adenine groups. How does methylation occur? In E. coli, methylation is executed by an enzyme called DNA adenine methylase, which converts adenosine to 6-methyl adenosine in sequences like GATC, and by DNA cytosine methylase, which converts cytosine into 5-methyl cytosine in the 5' sequences.

It should be noted that these methylations are not mutagenic. The modified version has the same basic property as the unmodified one. And then equalize the mechanism is completed by the mute protein. There is an involvement of three mute proteins: mute H, mute L, and mute S. Mute H and mute L recognize the sequence GATC and mismatch, respectively.

And then we also have the SOS response. So, sometimes DNA damage is so dangerous that it stimulates the cells to produce a DNA repair enzyme that allows an immediate reaction to the specific DNA damage. SOS response in bacteria is the most researched illustration. When the bacterial chromosome is severely damaged, the SOS response genes are activated. Many of these genes are involved in DNA repair and mutagenesis.

Requioprotein and LexA repressors are the main players in the SOS response. Lexa is a repressor that binds to the 20-base pair segment of DNA known as the SOS box to prevent the activation of the SOS response genes. As a result, Lexa governs the transcription of each SOS response gene. So this is just a mechanism through which the SOS response is happening. So you are going to have the SOS box where the LXA gene binds, and that is how it will initiate the SOS response gene transcription. And there will

be no transcription of the SOS response, so there will be no damage to the chromosomal DNA.

But if there is damage to the chromosomal DNA, then you will have the recruitment of RecA, and that is how it will actually cause the cleavage of LexA. Once there is cleavage of LexA, then this inhibition or attenuation will be removed, and that is how the SOS box is free, which is how it will actually cause the production of the SOS response gene. That's actually going to cause damage to the bacterial chromosome repair. And then we also have the double-strand breaks.

So far, what we have been discussing is the single standard brake repair mechanisms. In the double standard break mechanisms, you have two mechanisms: homologous recombination and other kinds of mechanisms. So, these are some of the steps that you are supposed to follow when you are going to have the homologous combinations, and these steps are very, very important. We are going to discuss in detail all these steps when we discuss genome editing and other kinds of phenomena in subsequent lectures. Then we are going to discuss non-homologous DNA repair and end joining, because this process repairs double-strand breaks in the DNA, and it is known as homologous because the broken DNAs are directly ligated without any homologous template. The term was pointed out by Morey and Haber in the year 1996, and double standard breaks are recognized by a protein called Ku 70/80, which recruits the DNA PKs or the kinases, and then recruits Artemis, which removes the damaged ends.

So in conclusion, DNA damage is inevitable due to various factors. Cells have evolved repair mechanisms to counteract DNA damage. Types of DNA damage include breaks, base modifications, and cross-links. Repair pathways like the burner, MMR, and HR fix different types of DNA damage. Accumulated unrepaired DNA damage can lead to mutations and diseases, including cancers. Defective repair mechanisms contribute to cancer development; some cancer therapies exploit the DNA repair mechanisms, and that's how they can actually cause mutations in the cancer cells.

Since you are going to have several mutations, the cancer cell will have no option but to die. Aging is linked to the declining efficiency of DNA repair. The environmental factor can overwhelm the DNA repair mechanisms, and ongoing research seeks to improve the understanding and develop the therapies. So there are many mechanisms. Once the DNA is damaged, there will be many mechanisms through which the DNA is repaired in the eukaryotic cell or the prokaryotic cell. So this is all about the DNA damage and repair mechanisms, and we have discussed various mutagenic molecules that are actually causing the induced mutations.

We have also discussed spontaneous mutations and how spontaneous mutations occur due to errors in DNA replication and other phenomena. So, with this, I would like to conclude my lecture here. Thank you.