RNA Biology
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Lecture - 56
Telomere, Telomerase and Impact on Genomes: Cell Cycle Arrest

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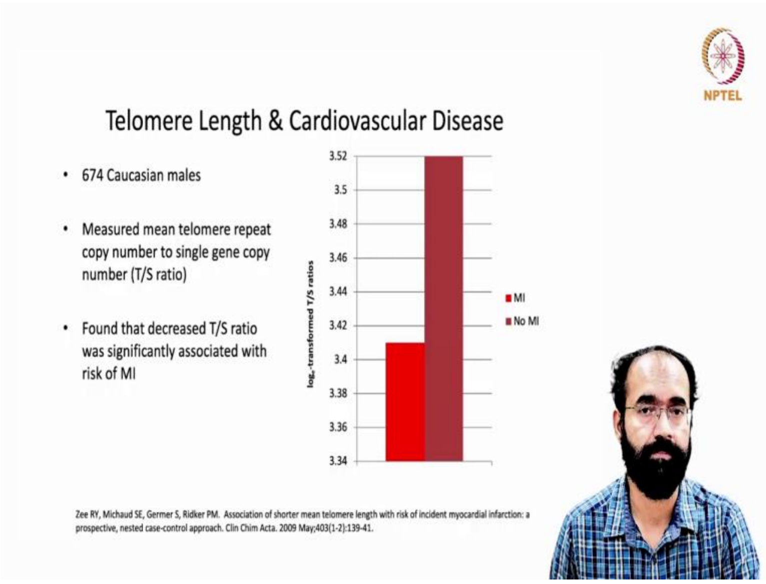

Hello everyone, welcome back to another session of RNA Biology. So, we were here learning the importance of telomere length and how the length of telomere is influencing or enhancing the propensity of getting certain disorders such as cancer, cardiovascular disease etcetera. So, we were here in the previous class the telomere length and cardiovascular disease.

So, they studied around 674 Caucasian males and measured the mean telomere repeat copy number to a single gene copy number. So, how it is compared this T S ratio is that we know that around 11 kb telomere length will be there per new chromosome in a given new chromosome average length.

So, we know 11 kb 11000 divided by T 2 A G 3 means 6 bases. So, 11000 divided by 6 will give you a number and that is the total number of repeats of telomeres. So, for convenience let us keep it as 500. It is definitely not 500, but at least some time point or maybe let us keep it 1000. So, 1000 into 6 is 6000. So, if you have 6000 is the length of the telomere full length, it is around 1000 copies of repeat will be there or let us keep one more example.

Say if it is 12 kb, 12 kb is the telomere length, 12000 divided by 6 is equal to 2000. So, the telomere copy number will be any time in an average number of telomere repeat will be less than 2000 repeats, ok. On an average because average length of telomere at start is 11000 or 11 KB and it comes down to 4000 or 4 kb the total length.

So, if it is 12000 is there you have around 2000 copies of telomere. So, total number of telomere divided by a number of genes in that chromosome. So, in that genome. So, this is basically you are referring to as a T S ratio. So, mean telomere repeat copy number to a single gene copy number.

So, you are bringing in a connection with the number of telomeric repeat per total gene that is available means a single copy gene. So, they have found that decreased TS ratio that means, decreased TS ratio means the numerator is getting shorter and shorter, denominator remains constant. So, a decrease in T S ratio was significantly associated with the risk of myocardial infarction or coronary heart problem.

So, you can see here as you get a healthy T S ratio like 3.5 that means the numerator T where the repeat is quite healthy and high. So, when that number is quite high you can see the chances of myocardial infarction is low as you can see here. But as the T S ratio decreases it comes up to around 3.4. Why it is coming to 3.4? Because the numerator is getting lower that is the T value, the repeats is getting lower and lower which brings down the T S ratio which enhances the rate of myocardial infarction.

So, message is clear that if the telomeric repeats are decreasing for whatsoever reason it can be due to aging, it can be due to stress, it can be due to you know various biological conditions, that can enhance the chances of getting myocardial infarction.

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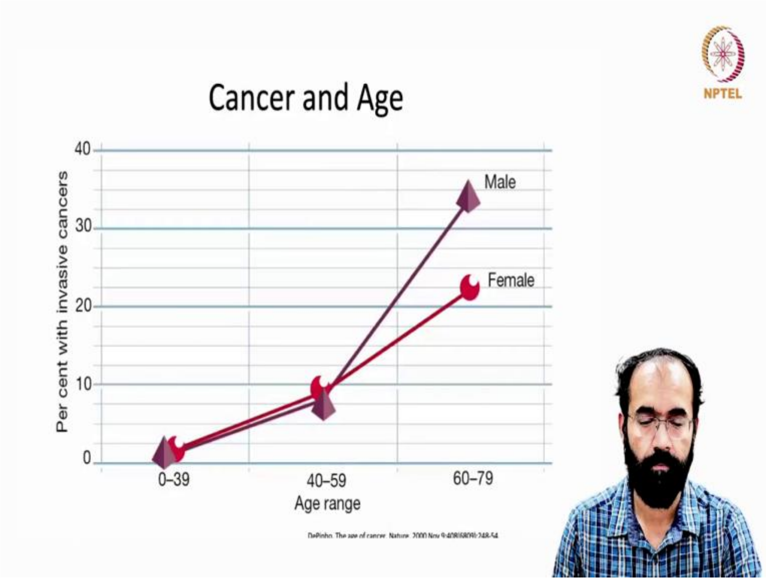

So, cancer and age. Cancer and age aging or the age calendar age have got a good connection. So, let us see a percentage with a invasive cancer no matter which cancer it is and you are having a in the y axis you have 10, 20, 30, 40 like that.

And in the x axis you have 3 age groups it is been put here 0 to 39 age group, 40 to 59 age group and 60 to 79 age group. So, this is the range of the age. So, you can see here as you grow old the chances of getting cancer go up quite exponentially like this is somewhat 39 that is the first group till second group there is a linear increase.

There is an increase there is no it is not going parallel to the x axis, there is a moderate increase is happening. But once from your 59th age onwards there is a exponential increase. Because your general bodies physiology lowers in its efficiency and this can allow the detection of a misbehaving or improper cell and that will allow the survival of this so-called problematic cell.

And it has a connection with the telomerase activity also because cancer in order to survive mere dividing or division of that cell is not enough. It has to have a proper support by the telomerase enzyme. Otherwise, it cannot function the way it is establishing cancer establishing in a host.

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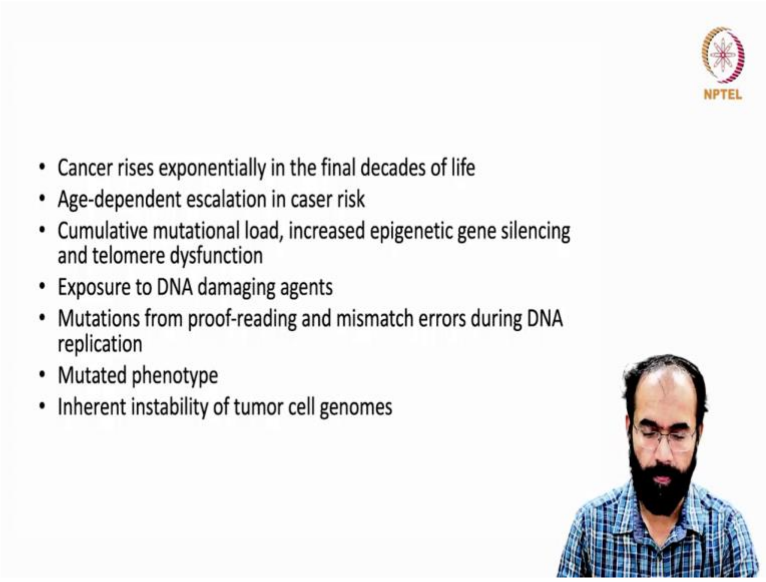

So, cancer rises exponentially in the final decades of life. This is a observed fact, age dependent escalation is always seen to be associated with high cancer risk. So, cumulative mutational load, increased epigenetic gene silencing and telomere dysfunction are the possible causes for it we will revisit them once again. So, exposure to DNA damaging agents is one of the important factor to be noted because if there is DNA damage then only all the other problems comes in line.

If there is a damage then it has to be repaired. And to repair first of all the damage should be sensed by the system and p53 comes into picture which is a tumor suppressor or guardian of the cell, it has to stop the cell cycle and allow the DNA repair genes to do their job. If DNA repair fails to fix it by HR or NHEJ as you saw in the previous classes if they fail to repair that p53 marks the cell for apoptosis.

If all these things fail when p53 is mutated all these things has to fail. Because p53 is not doing its duty or its not capable of doing its duty. Then it will automatically lead to cancer. However, cancer can establish as a disease, if the immune system fails to detect this damaged cell and this cancer cell is successfully turning on the telomerase activity.

If both of them are functional like immune system is strong, immune system is able to detect that cell and dismantle it or get rid of that. Then that cell disappeared mad cell disappeared then cancer cannot come. Or the telomerase activity is not there naturally that cell will not be able to make a proper survival.

Because telomere length is shortened and it will start showing senescence, it will reach the crisis and it will die or at least it will not propagate. Because crisis is helpful in many cases because it will not divide. So, cancer if it does not divide it is a good thing a cell is mad or it is a bad not working properly, but as long as it is not dividing it is, ok. So, this all are connected.

So, exposure to DNA damaging agents is one of the initial steps in getting cancer and then rest of the problems like short-end telomere length or reactivation of telomerase and various other factors contribute together to establish cancer. So, mutations from proof reading and mismatch errors during DNA replication.

So, normally when DNA is replicated there is always a possibility of having error. And our DNA polymerase have proofreading activity, RNA polymerase also have proofreading activity. Only the RNA dependent RNA polymerase from some viruses do not have proofreading activity.

So, what is proofreading activity? When a DNA synthesis is occurring or when an RNA synthesis is occurring it will have a degradation in the 3 prime to 5 prime direction. While synthesizing it is erasing also, means it is having a exonuclease activity, same enzyme can do a backward reaction. So, it is almost like you put 3 steps forward put 2 step backward, again put the 5 steps forward put 3 steps backward.

So, by doing this, chances of having a wrong base is prevented, it is just like you imagine a situation you want to say something. If you are saying spontaneously that will not be a perfect sentence, it may not be a meaningful loaded sentence. However, if you are writing it down then you will write something then you will cut it edit it and again you will make a better sentence and finally, you will read it and see is it conveying sufficiently.

So, with the minimum words you will be able to convey a strong meaningful sentence. So, that is nothing but proofreading. Same thing happens during proofreading activity. So, mutations if occur in the DNA or RNA in spite of having proofreading or there is error in proofreading and sometimes mismatch errors will be there that is done with the help of a DNA excision repair or mismatch excision repair.

If they fail then that can allow some mutation to persist in the system. So, mutated phenotype will be persistent, if this mutations are not detected in time you end up getting a phenotype and we call it as a mutant phenotype or mutation phenotype. So, inherent instability of tumor cell genomes.

Many a times if there is a tumor or if there is a trouble in a given cell. What will happen? They are not following any of the cell rules like anchorage dependence and not piling over another cell or do not switch to glycolysis alone, follow Krebs cycle, also for getting optimum use of um ATP production from glucose molecule.

So, cells cancer cells do not follow all these rules what normal cell is following. So, cancer cells end up in wasting glucose they make only 2 ATP from 1 glucose molecule instead of 38 ATP what a normal cell does. And they can grow anchorage independent manner means they can grow anyway and they lose cellular identity.

All these problems happen along with that you will end up having in unstable genomes also means like HeLa cells I mentioned in one of the earlier classes. If this is a very aggressive uterine cancer. This people done when they did the genome studies, they found too many pieces of chromosome chromosomes break randomly.

But still cell will find a way of surviving, even the DNA is broken there is lot of recombination, lot of joining here there. Because no proof reading, no repair nothing happens. Some cell may die in this process, but it is ok, if it is not, if it is having a very problematic mutation that particular cell will die, but another cell will continue.

So, it is a full chaos at genetic point of view cancer cell is full of chaos, there is no order, there is breakage joining here there everywhere. Cancer can afford to have that. Why because it do not work efficiently, it do not follow the rules what a normal cell is following and it can afford to waste energy and it divides very fast. Hence even if 10 cells are dying the remaining cells are, ok. And the cancer cell will be able to run the show.

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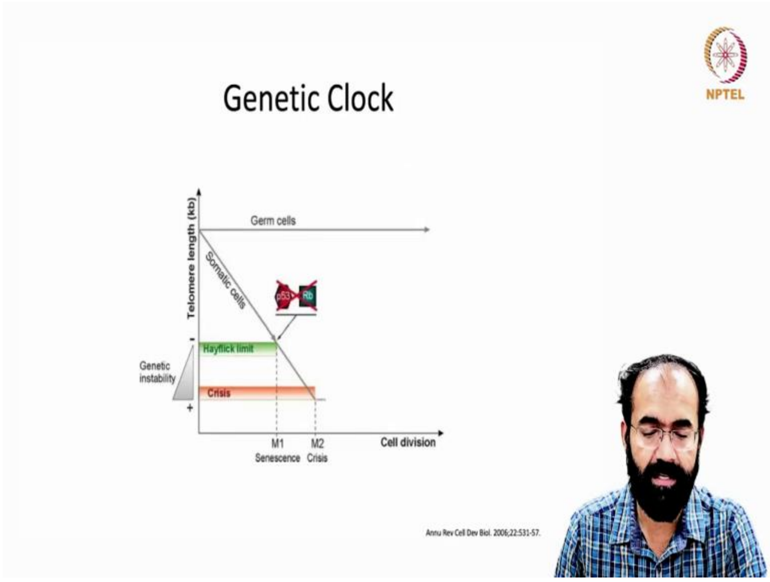

So, let us now see what is genetic clock. Genetic clock is a interrelationship between the length of telomere and the number of times the cell can divide further. So, some connection is there, it is just like you may have seen in some reality shows etcetera like they will say you have one lakh rupees you, how you want to spend it, you cannot put it in bank or invest you want to send in in a wise way, how effectively you will use it?

So, this is kind of a riddle like you can see in some games also children's games. So, you have given you are given a fixed amount. So, now, everyone is given one lakh rupee how will you utilize it? It depends with a lot of talent. Some people simply buy toys you know maybe wasted by food and some people use some other creative way which can you know give returns. So, there are different ways. Same way the telomere number also is fixed.

So, it has to be utilized by a cell how effectively it is preventing the shortening, everything depends on maintaining the genetic clock. So, telomere length is given in the y axis and you have two groups of cell germ cells and somatic cell. And cell division continues no matter which is cell it is.

Somatic cell also divides germ cells also divides as the time passes. Here technically you can say the cell division as the passage of time or age of the cell or the organism. If an organism is leaving its cells will be dividing. So, it will continue.

Now, you have something called Hayflick limit here. So, somatic cell the telomere length decreases as the cell division progress. As the cell division move from 0 to a fixed number here somewhere in the middle the length of the telomere comes shorter and shorter and shorter. Then it will reach a stage called Hayflick limit. Hayflick limit is a situation where the cell has to take the help of p53 and retinoblastoma proteins in order to make a living.

So, two scenario is possible. One is it will go through a phase of genetic instability that means; it has reached Hayflick limit. Now the question is should we go with this limitations or should we fix it somehow the problem can we fix it? So, the idea is simple, if a cell has reached a critical stage it has to make a call how are they going to proceed further. As it the telomere length once the telomere length reached starting from here very high telomere length reached up to here because of cell division that is Hayflick limit.

Then as the division continues further. So, Hayflick limit is reached at a stage where you have M1 senescence that is the first initiates first phase of senescence. And then division is continuing with lots of difficulty and it reached an M2 phase that is called crisis phase. Crisis phase you end up having a genetic instability.

So, once it reached genetic instability that is an alarm bell that is a real alarm bell. Because genetic instability means cells are having problem and cells will struggle and it will have real trauma present in the genome. If it is not contained then that all troubles will be passed down to the next generation; that means, next daughter cells.

So, we have to understand that this if it fails if it limit or the crisis stage is not handled properly this can go to if p53 and retinoblastoma are missing it can go to a cancerous phase.

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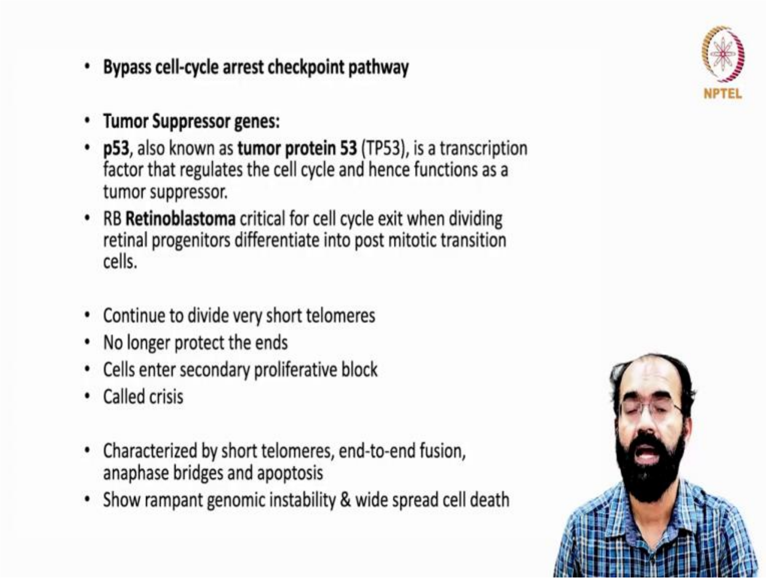

So, we should understand the normal point of a cancer progression or normal situation in which a cancer initiation can happen once it has reached Hayflick limit; that means, genetic instability comes and it can start showing the real signs of cancer.

So, let us see about the role of tumor suppressor genes. p53 also known as tumor protein 53 is a transcription factor that regulates cell cycle and hence functions as a tumor suppressor. RB that is Retinoblastoma is a critical protein required for cell cycle exit when dividing retinal progenitors differentiate into post mitotic transition phase or cells that is post mitotic transition. But RB protein can be seen in other cells also here we are saying as an example.

So, both are important for maintaining a constant phase of cell division. So, they normal situation they continue to divide at the cost of telomeres. Telomere becomes short and short. Once the telomere length becomes shorter the ends the tips of the chromosome are less protected.

They are protected, but their efficiency is coming down. Cells now enter secondary proliferative block. First proliferative block was in M1 phase where the Hayflick limit is reached and then you reach a crisis period that is M2 secondary and we call it as a crisis phase.

First crisis is Hayflick limit, once the telomere length reached a particular phase. Second is once the telomere length become further down. So, it is characterized by short telomeres and this can lead to end-to-end fusion. Chromosomes can fuse end to end resulting in bicentric chromosome. Chromosomes with two centromeres and it will lead to anaphase, bridges and apoptosis.

Anaphase is the final stage of the mitosis. It has got prophase, metaphase, anaphase and telophase. So, they reach the final stage of their cell cycle, they or the cell separation next is telophase prophase, metaphase, anaphase and telophase. Telophase they literally separate that is final stage.

So, they will have problem with anaphase and they show rampant genomic instability and widespread cell death will happen. So, this can lead to real complications eventually giving rise to a cancerous phenotype.

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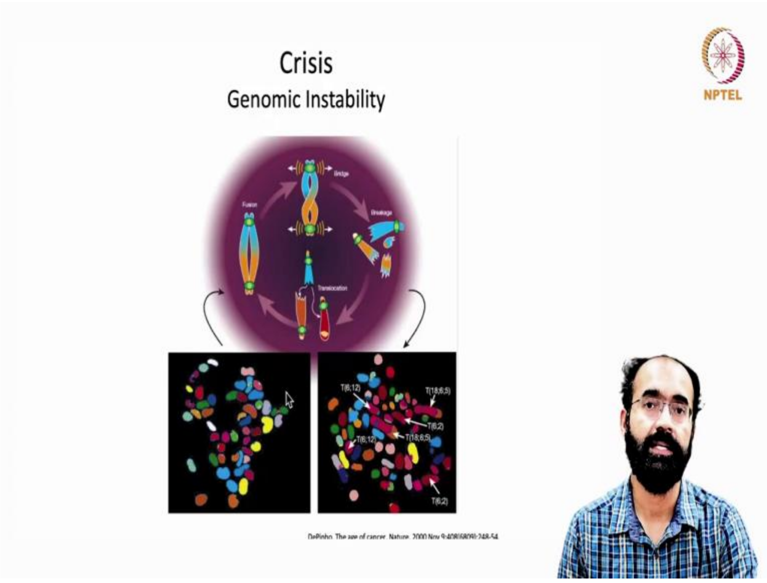

So, let us visit the genomic instability in a different angle as you see in this picture. So, here you have chromosomes which are fused because of which you are having two centromeres. And when the bridge is trying to pull them apart the chromosome will break. And this broken chromosome will enhance the fusion further, they can fuse again or they get attached or they get recombined elsewhere.

Three chromosomes are dangerous and you will end up getting even circular chromosome. So, in cancerous cell some chromosomes will appear circular. So, they can fuse in all possible ways as long as few genes are working. Like an organism will have say human require around 23,000 genes for the normal survival, but a cultural cell do not require that many genes as long as some genes are functional for the survival of the cell.

They will continue to survive in a very unstable manner. And since the cancer cells are blessed with fast division some mad cells mad cells here what I am saying cancer cell itself is mad cells. But, if some cells are so unstable, they cannot survive they will die because they cannot produce some enzymes, but that is, ok.

Because there is another cell which is not so bad will prevail. So, this will continue for longer time. So, this stage at crisis stage this will continue and you eventually end up in getting chromosomes or fragmented pieces here and there like you can see here they will go into pieces. And no two-cancer cell will have similar looking genome.

So, what we learn from here is that the chromosomes when they have some fusion that took place then this can lead to multicentric chromosome and in anaphase and telophase there can be serious problem with the breakage of the chromosome. Because the spindle point spindle fibers bind onto both the centromere just like I told you.

One bag has got two handles; two of you are holding it one pulling it towards the south another pulling towards the north the bag will tear into two pieces. Depending upon how strongly you are pulling like that is what is happening.

And that will lead to more broken chromosomes. And this broken chromosomes can now effectively fuse either fuse themselves and look like bangles circular chromosome and or it can recombine elsewhere some other part of the chromosome or it can look quite weird in shape. And this will continue this multicentric chromosomes will continue and every cycle they divide they can break.

So, this is a cartoon what has been shown here like bad or misbehaving chromosomes or genome will continue to prevail and persist and you end up getting a unstable situation. So, we will learn more in detail about the telomeres and how genetic crisis contribute to the instability of a cell in the next class.

Thank you.