Medicinal Chemistry
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Anti-Cancer Agents Part – 1

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Ok so in today's lecture we will look at a very important dieses called cancer and this is under the umbrella of anticancer agents so before we go into the anticancer agents let us try and understand the disease itself.

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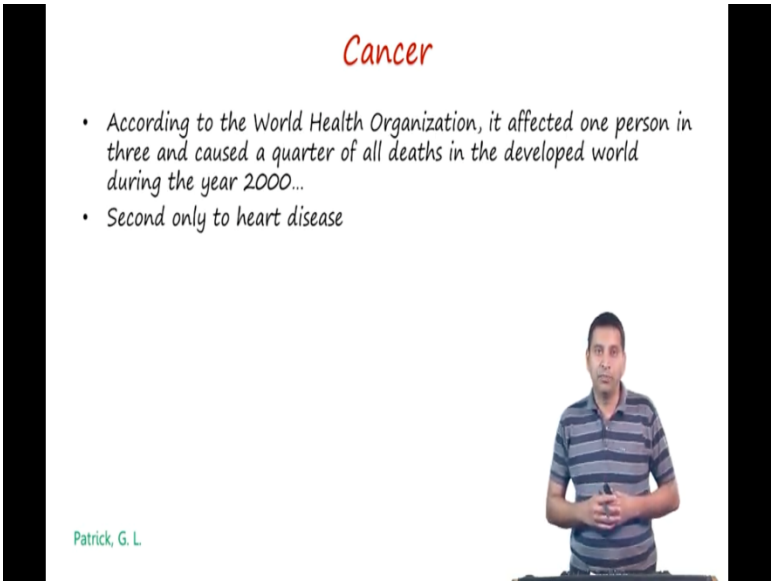

So cancer is one of the most you know devastating diseases in the worldwide according to the World Health Organization a 1 in 3 actually affected by this and it's also form that about a quarter that is 25 percent of all deaths in the developed world during the your 2000 is due to cancer And India as well cancer is becoming a huge problem and the number of deaths due to cancer is actually going up Of course infectious diseases still take a large toll on people but as time has progressed cancer is also becoming important disease to tackle And worldwide it is only second to heart disease in terms of the cause of death.

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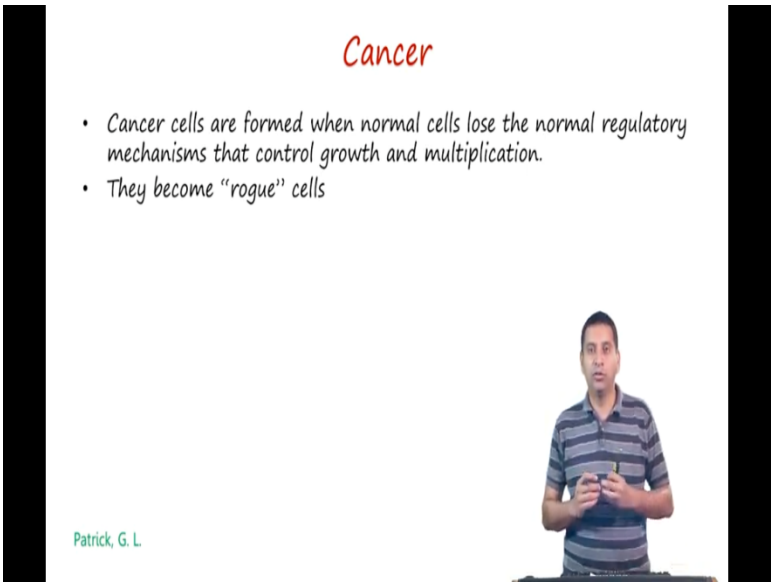

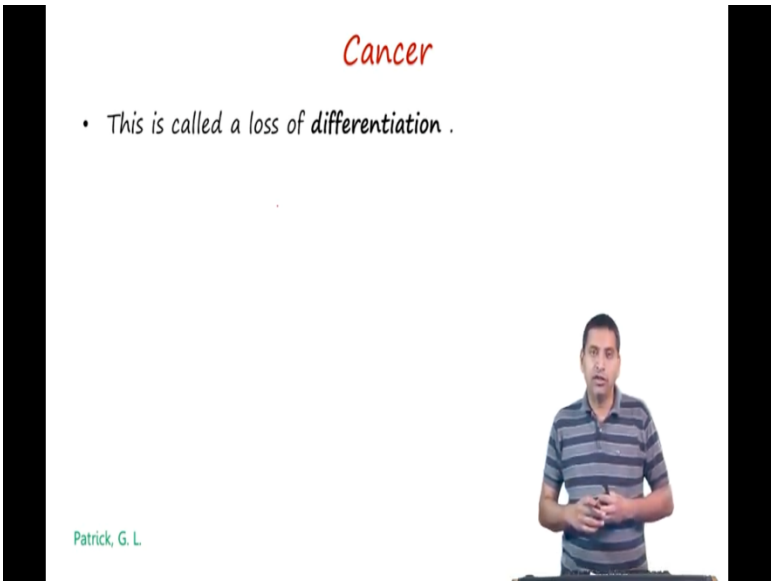

So cancer cells are formed when normal cells lose though normal regulatory mechanisms that control the Growth and multiplication So these cells become what are known as Rouge cells so rouge cells are nothing but cells which are not going to follow the rules ok so This process is called as loss of differentiation So typically when a cell divides and then what happens is that it goes through a process called as differentiations so Differentiation means from the stem cells what happens is that let's say all our cells are derived from germ cells stem cells and so at some point there these cells differentiate and become bone says or on muscle cells and so on so in cancer this process is accompanied by a loss of differentiation.

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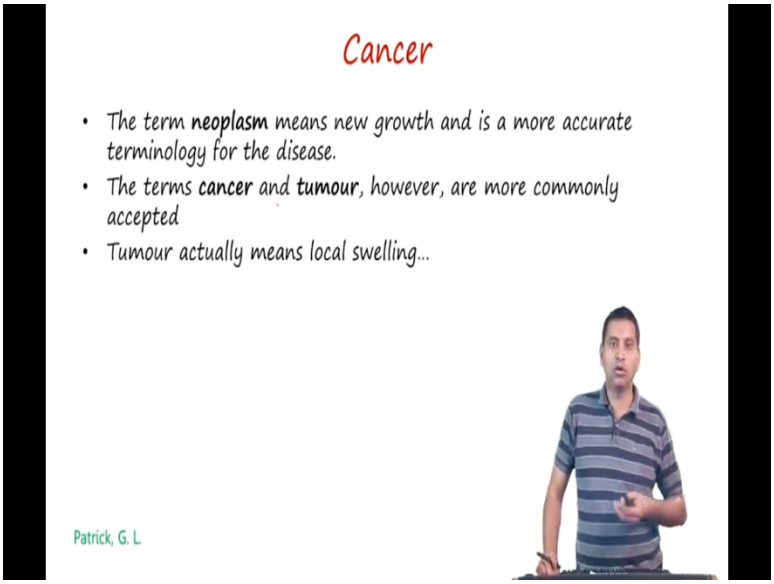

So the term neoplasm is actually used to indicate new growth and is actually a more accurate terminology for the disease the more common name that are used are cancer and Tumor and tumor in reality actually just means a local swelling.

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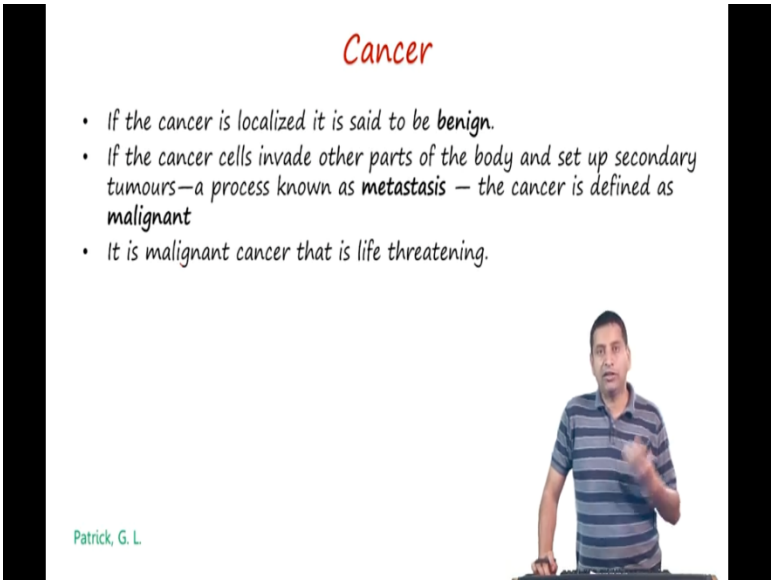

So if the cancer is localized it is said to be benign and if it invades other parts of the body and said support on a secondary cancers secondary tumor this process is called us metastasis And such cancers are defined as malignant So the benign cancers a benign tumors are actually in order major problem the malignant and ones are the ones that become life threatening.

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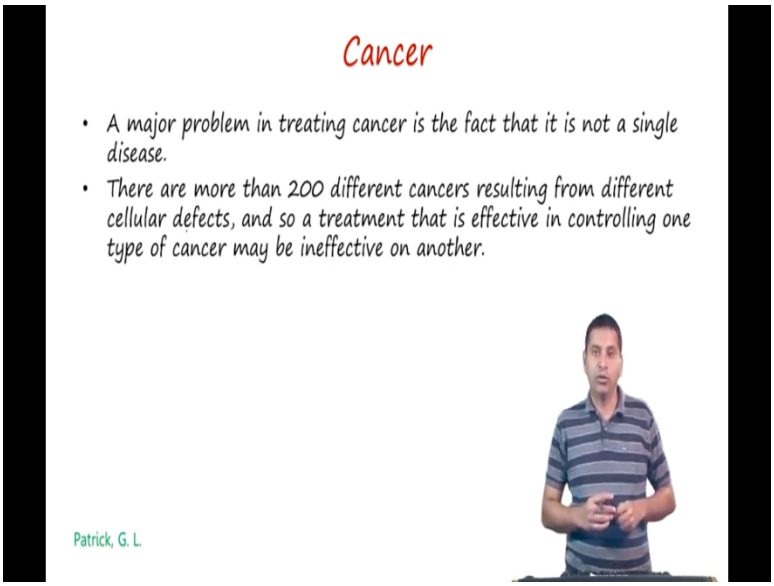

So a major problem in treating cancer is that it's not a single disease there are over 200 different types of cancers is resulting from various cellular defects And so a treatment that is effective in

controlling one type of cancer is completely ineffective on the other Therefore we need to evolve multiple strategies to address this disease.

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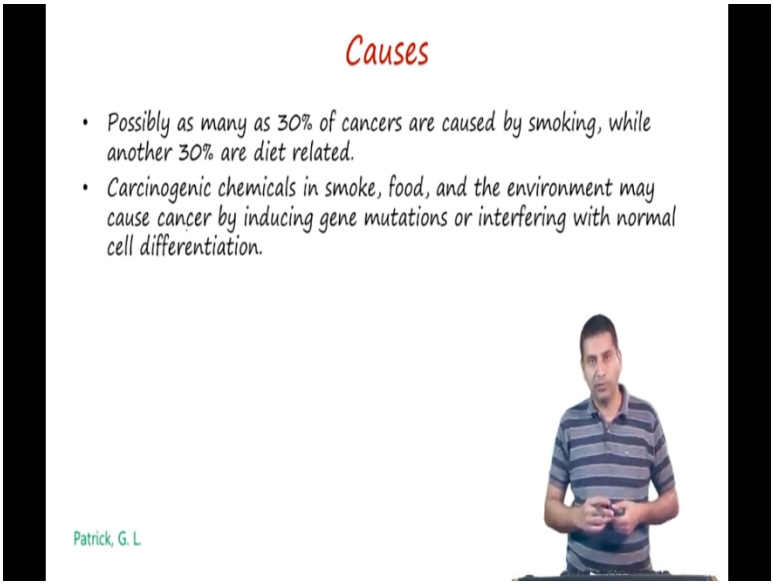

So as many as 30 percent of cancers actually cause by smoking while another 30 percent pretty much diet related so there are a number of molecules which are known carcinogenic molecules so what this means is that these are Cancer causing chemicals and these can be in the smoke or the food and of course the environment. And what this can do is they can induce gene mutations or interfere with normal cell differentiation So once one of these 2 mechanisms happen then it's likely that cancer can develop.

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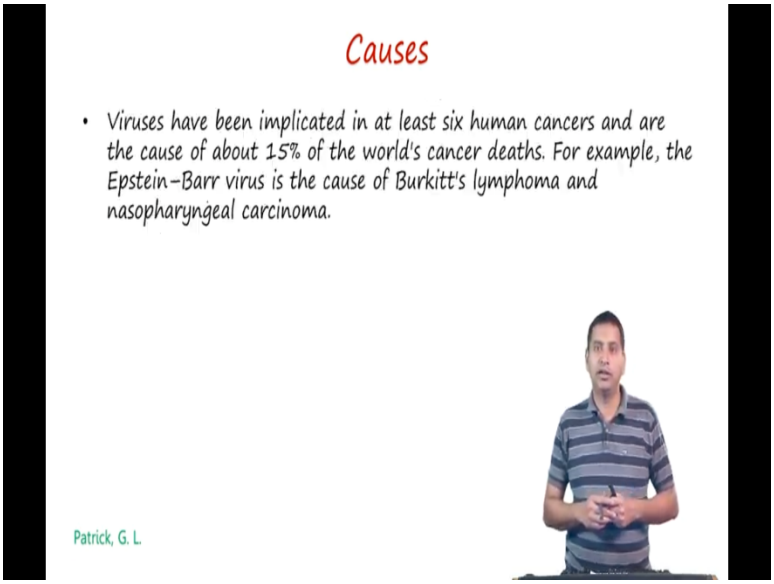

So the process off the both of the cancer is called as carcinogenesis and it's initiated by a chemical known as a mutagen But other triggering events such as exposure to further mutagens for example you know smoke from a cigarette for example are also required for the cancer to develop There are some white assist which have been implicated in at least six human cancers and this cause about 15 percent of the world's cancer deaths ok for example the Epstein Barr virus is the cause of Burkitt's it is lymphoma and nasopharyngeal carcinoma.

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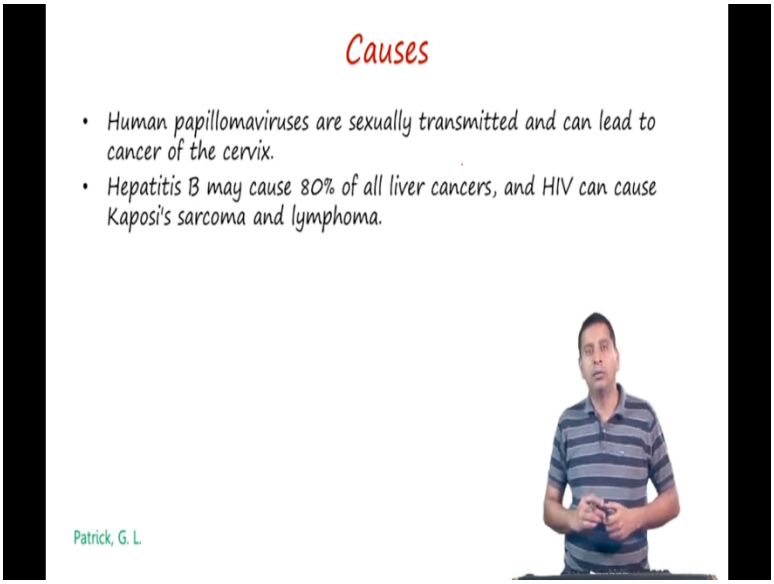

There's another kind of virus known as human papillomaviruses which is sexually transmitted and can lead to cervical cancer there is another virus causing the hepatitis B which cause which leads to 80 percent of all liver cancer and of cause HIV can cause Kaposi's sarcoma and lymphoma One major way which cancer can be can be initiated is through the presence of mutagens and these mutagen can cause in genetic defects which can be further accentuated by a you know continued exposure to the particular mutagen the other way in which cancers can be initiated is through viruses.

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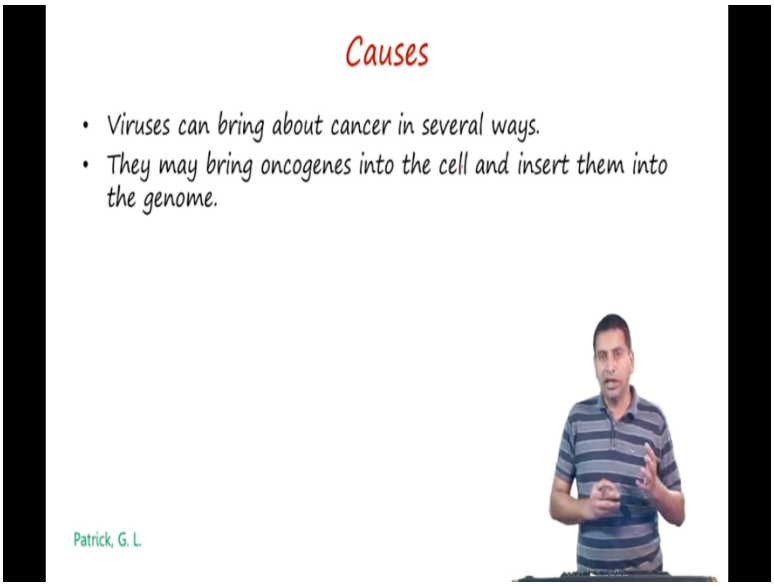

Now virus can actually bring about cancer in several ways so they may bring what are known as oncogenes oncogene's will look at it later but these are genes that are important in cancer and these oncogenes can be brought into the cell and they can insert themselves into the genome just a couple of lectures back we look that how the virus integrates its own nucleic acids it could be aroma which then further up is converted to DNA or DNA based way virus is can actually going inside themselves into the genome.

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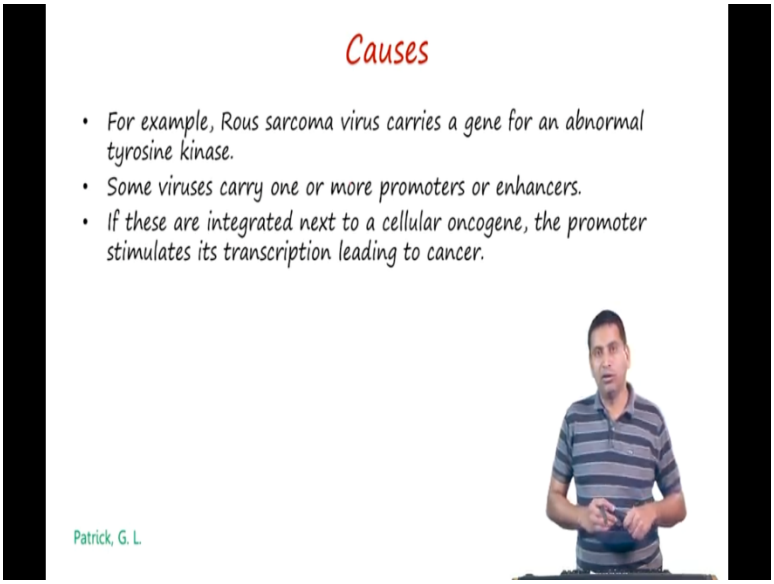

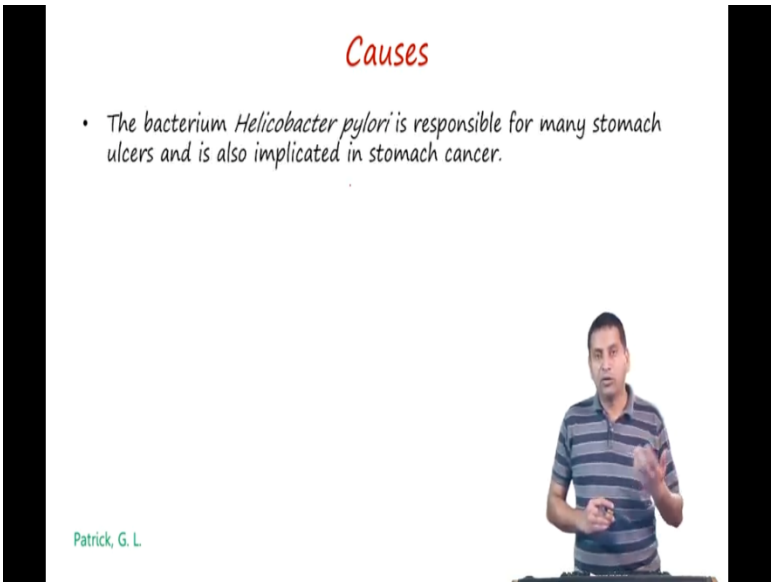

So for example the Rous Sarcoma virus carries the gene for abnormal tyrosine kinase the some viruses carry one or more promoters and enhancers ok if these are integrated into the cellar genome then the promoters stimulates its transcription leading to cancer a Cancer can also be In a sort of initiated by a bacteria so the famous case is the Helicobacter pylori which is responsible for many of the stomach ulcers and is implicated and stomach cancers.

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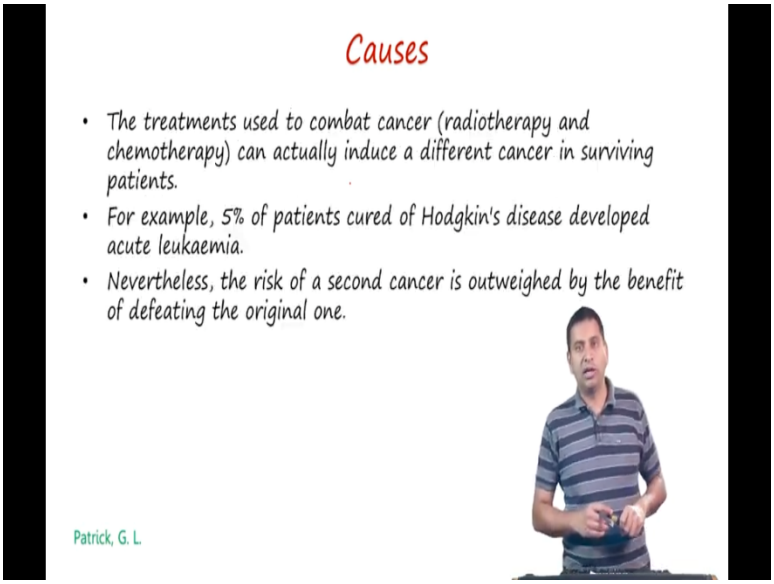

So the treatments used to combat cancer which are typically radiotherapy were high intensity radiation is used or chemotherapy when variant drugs given can actually induce a different cancer surviving patients so that's one of the problems in using these types of therapies however this methods can also be used to treat cancers For example 5 percent of patients cured of Hodgkin's disease developed acute leukemia Nevertheless the risk of a second cancer is outweighed by the benefit of defeating the original one.

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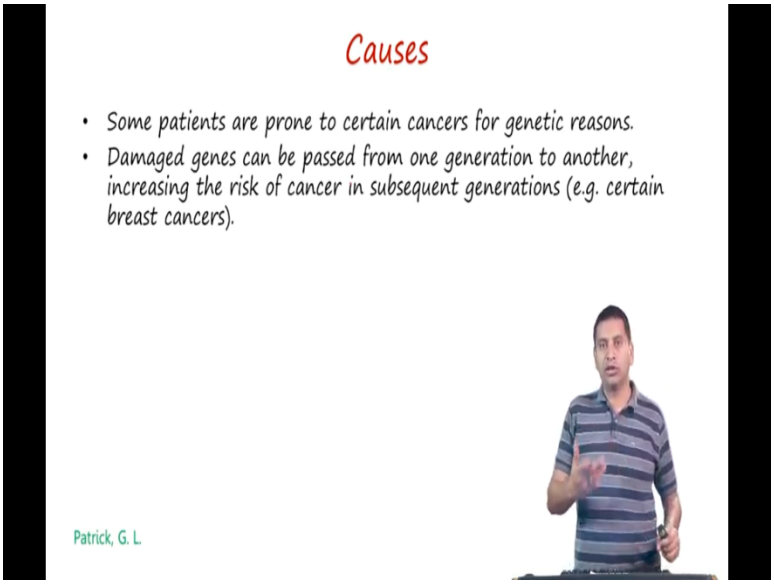

so some patients are prone to certain cancers for genetic reasons so it's possible that certain damage genes can be passed on from one generation to another ok so the most common example is in the case of breast cancers and so these are the prisons of these genes can lead to an increased risk off or development of cancers in subsequent generations.

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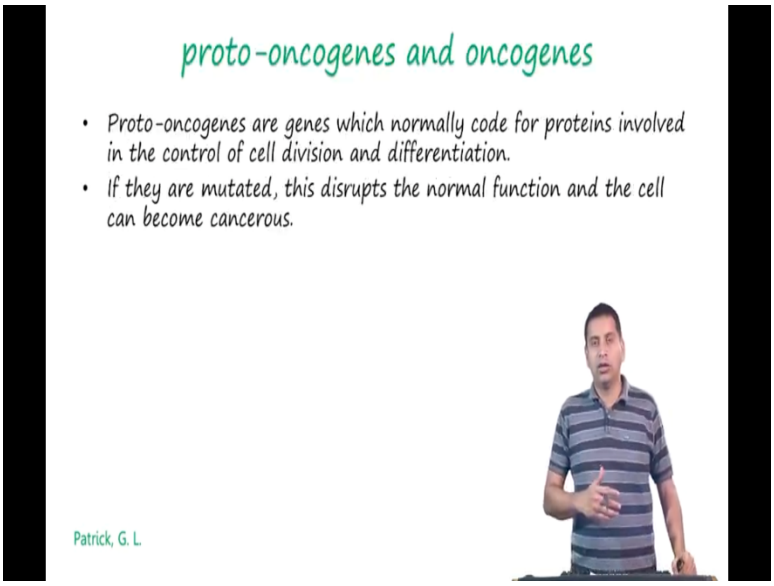

So now we look at the concepts of proto oncogenes and oncogenes we already look at being exposed to the terms oncogenes so proto oncogenes are genes which normally code for proteins involved in the control off cell division and differentiation ok so these normally code for proteins which are involved in the control of cell division and differentiation just to remind you cell division is the process by which cells divide and differentiation is the process by which a stem cell gets converted to A cell with a function for example of muscles Now with these proto oncogenes are mutated does disrupt the normal function of the cell and the cell can potentially become cancerous.

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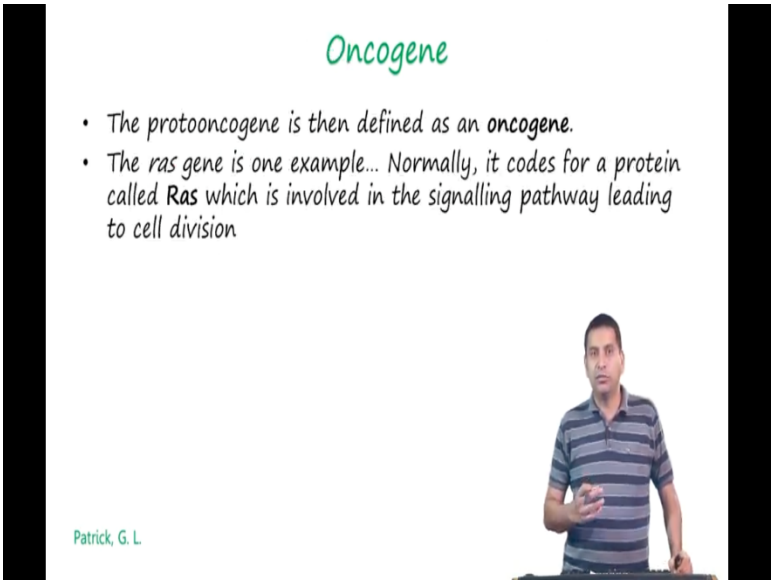

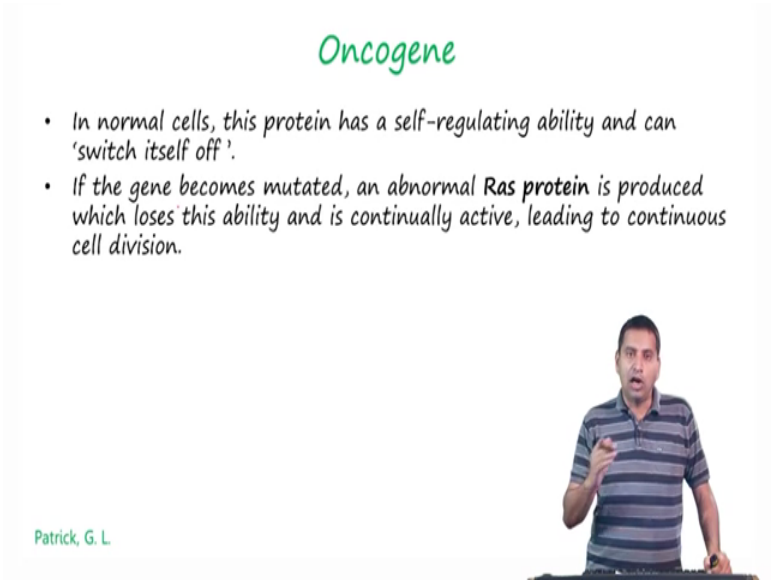

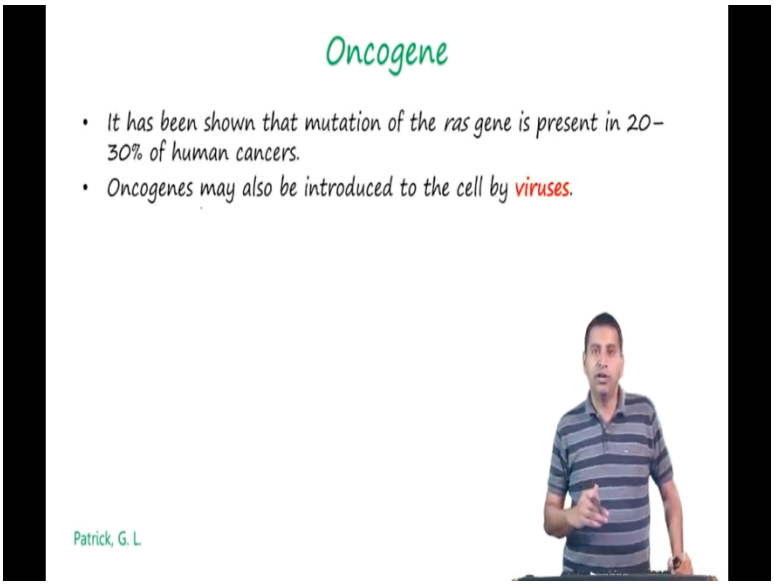

So then the storm of this so proto oncogene is defined as a as actually an oncogene So one example is the ras class off the oncogene so this is gene code for proteins known us ras ok which is involved in the signaling pathway leading to cell division. In normal cells this protein has a self-regulating ability and can switch itself off However if the gene becomes mutated an abnormal ras protine is produced which then loses his ability and is continuously active leading to continuous cell division so when you have an abnormal ras protein then what happens is that you would have the cell dividing continuously or it becomes immortal It has been shown the mutation of ras gene is present in about 20 to 30 percent of human cancers So these oncogenes as I discussed earlier can also be introduced by viruses.

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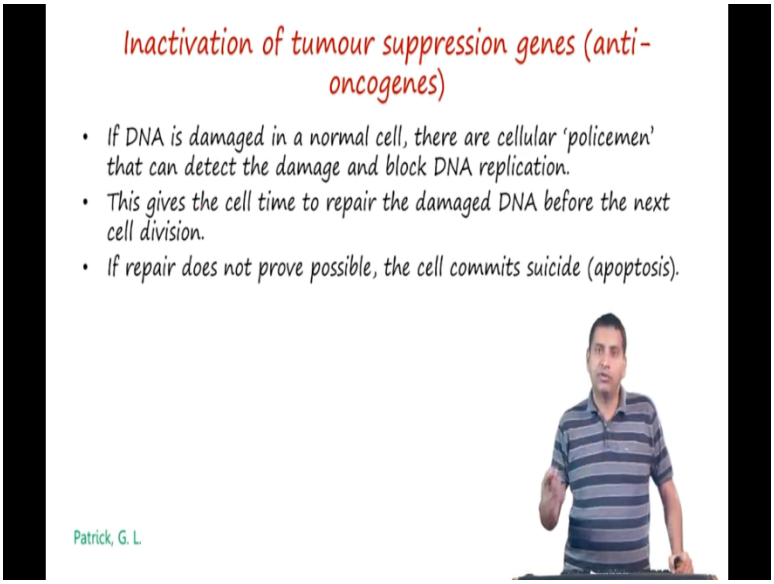

Now there is also another concept which is anti-oncogenes so these are nothing but tumor suppression genes so here in a normal cell if you think about the how during normal metabolism it is possible the DNA is damaged for example the go out in the sunlight and some of our DNA gets damaged ok but there are policemen in the cell of which can actually detect these damages and then blocked the DNA replication so that you don't have you know faulty a division happening So what is the block the DNA replication it gives the cell enough time to repair the damage DNA before the next solution However if the cell repair is not possible then there is this series of events that is through good in which the cell actually commit suicide and this process is called as apoptosis.

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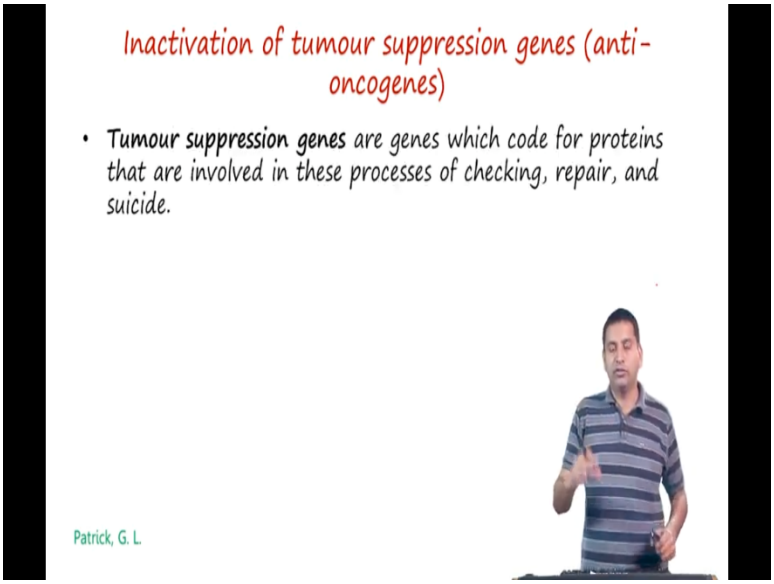

So there are genes which are known as tumor suppression genes. And these actually code for proteins that are involved in the process off checking whether there's enough there's damage in the cell or not the repaired in in the case of DNA damage and suicide so this is a very intricately regulated process and tumor suppression genes are forming an important part of this.

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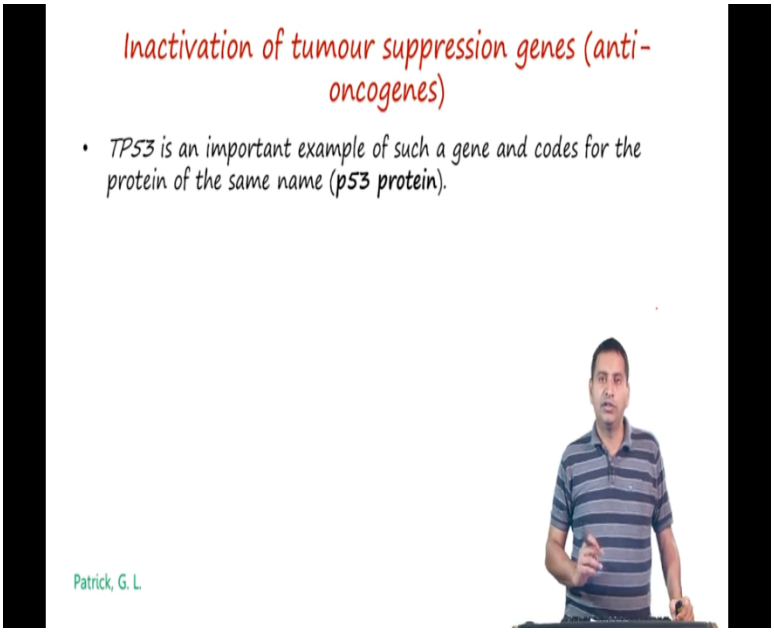

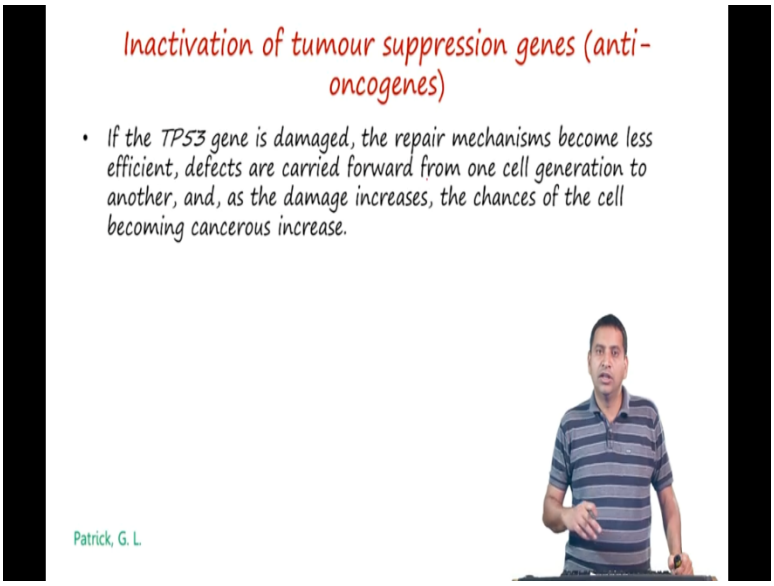

For example is this TP 53 which is a gene which codes for the protein by the name P53 Ok so P 53 protein is very intimately linked with several cancers so If the TP 53 gene is damaged then the repair mechanisms become less efficient so once the repair mechanisms inside the cell become less efficient the defects carry forward from one cell to the other and one generation cell to another and during this process because of the damaged repair process. The level of damage actually increases and now because there is a lot of DNA damage inside the cell the chances of cell becoming cancerous will increase.

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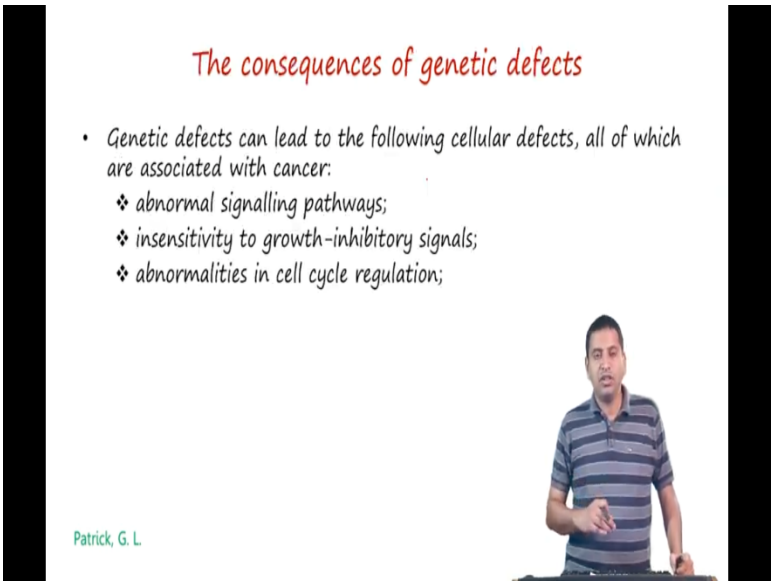

So these genetic defects have many consequences so some of them are listed below So some of the genetic defects which are associated with cancer can lead to abnormal signaling pathways so here because your DNA is damaged no you're going to code for a protein which is again going to have a slightly different Structure and so this could lead to a abnormal signaling pathways but it can also lead to insensitivity to growth inhibitory signals so as we discussed earlier a intricate process off cell growth occurs where there are signals sent out to slow down growth there are signals send out to differentiate that a signal sent out for apoptosis.

So when there is a signal given to inhibit Growth These genetic defects can actually make this cell insensitive There's also another possibility that it leads to abnormality be in cell cycle regulation we look at it look out later about What cell cycle is and how it can be how it can be a abnormal.

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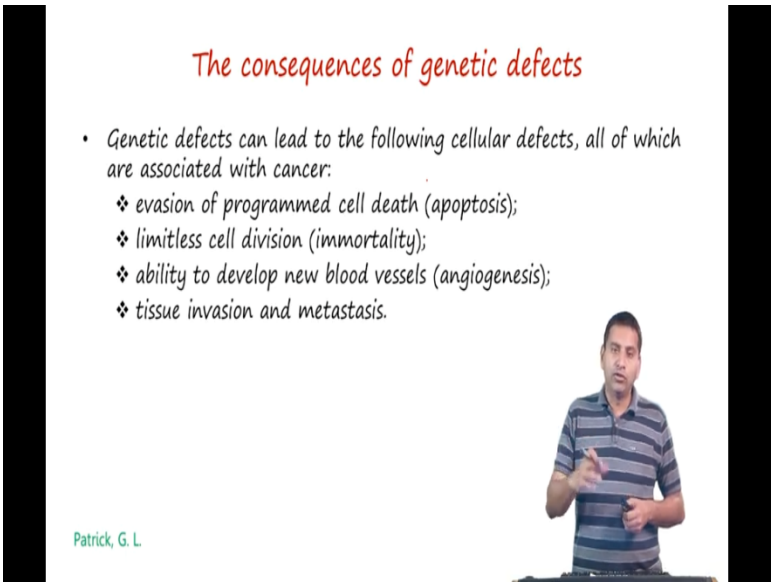

Genetic defects can also cause invasion off programmed cell death which also called as apoptosis so here when the cell in such a damage condition it should normally trigger apoptosis but now because of some of these defects that are present it can be evade this program cell death and become cancerous And this essentially leads to limitless cell division or what is known as immortality but this cells cannot grow without the supply of nutrients.

So major process in the growth of cancer this is a process known as angiogenesis so here in angiogenesis you need blood vessels since you need blood vessels to develop in the proximity of these tumors so that you can have a constant supply of nutrients Lastly these genetic defects can also cause what are known tissue invasion and metastasis we've already looked at previously that there are two types of cancers what is a benign cancer and the other one this metastasis cancers.

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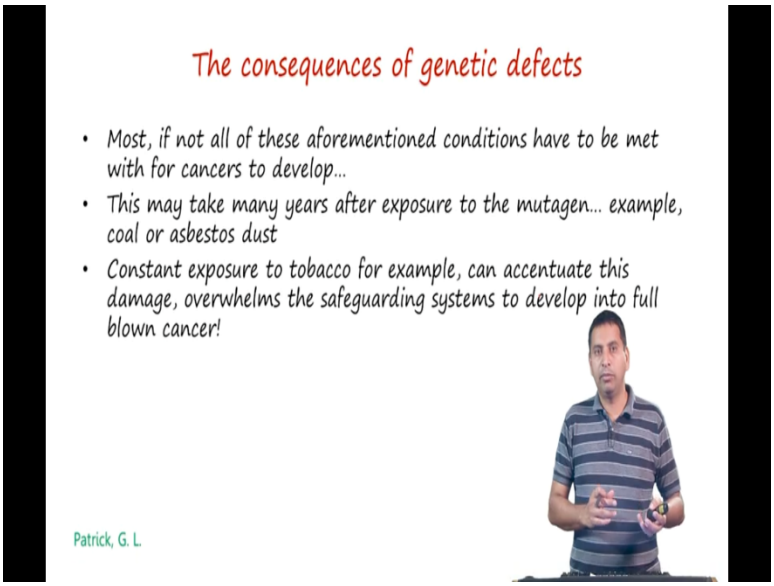

So most if not all of these aforementioned conditions have to be met for cancer to develop So therefore it's a fairly complicated disease where a number of things in a coordinated manner have to go Wrong However it is quite common. So for example one of the mechanisms proposed is exposure to mutagenic carbon and coal is suggested as a mutagen there's also asbestos dust which is quite harmful.

So it may take many years of exposure to the mutagens for example coal or asbestos can may take several years for you to develop cancers. It's also possible under a large number of smokers and tobacco consumer worldwide and constant exposure to tobacco can accentuate does damage right So once it accentuates it what happens is that it overwhelms the safeguarding systems and develop up into full blood cancer.

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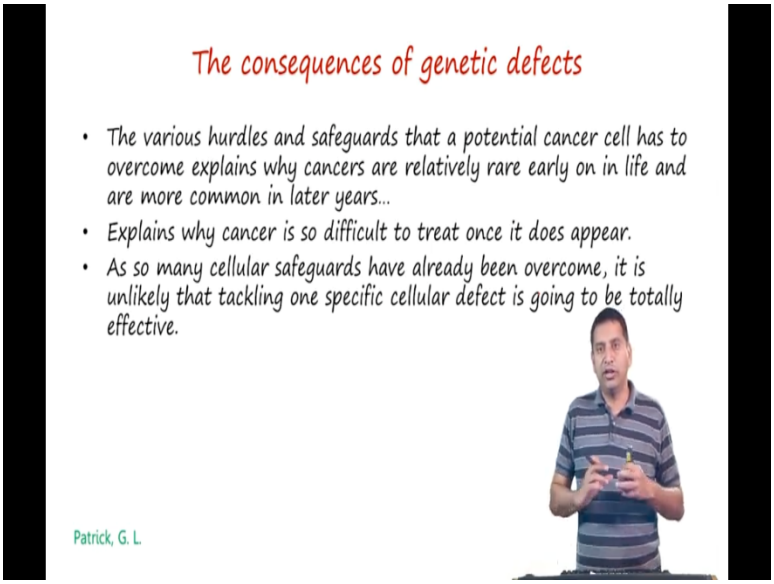

So the various hurdles and safeguards at a potential cancer cell has to overcome explains why cancers is a relatively very rare in early life ok and so it becomes more common as we get older. It also explains why it is so difficult to treat once it appears so as there are so many self-cellular safeguards have already been overcome it's unlikely that the tackling one specific cellular defect is going to be effective.

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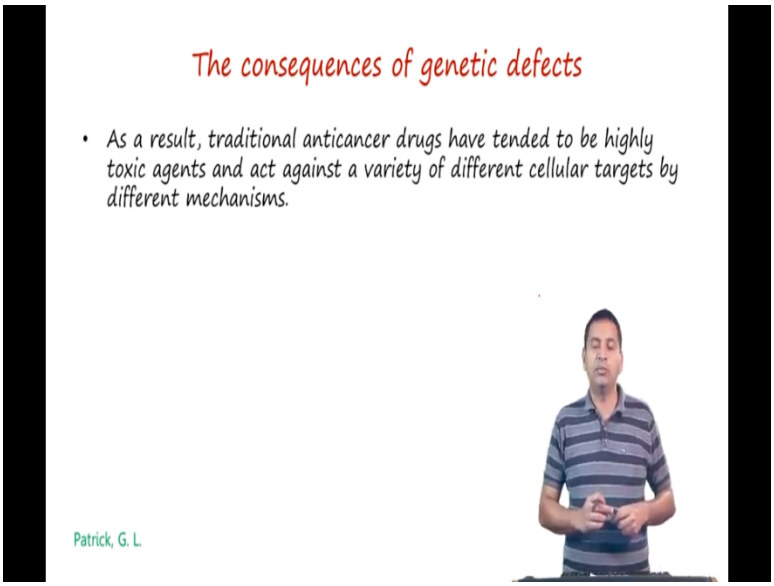

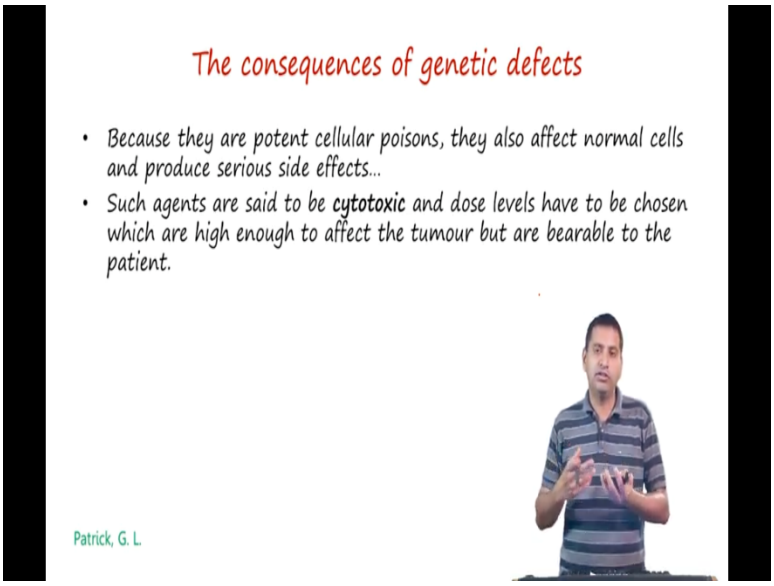

So as a result many anticancer drug have tended to be highly toxic agents And they act against a variety of different cellular targets by different mechanisms so but being toxic one of the problems is that they are quite poisonous to normal cells as well and these end up causing a number of serious side effects and these agents which are anticancer agents are said to be cytotoxic cyto means cells toxic means bad or potentially killing and the dose levels of the cytotoxic agents have to be chosen in such a way that get high enough to affect the tumor but quite safe for the patient so that many of the side effects associated with the these anticancer agents on because these agents are quite cytotoxic.

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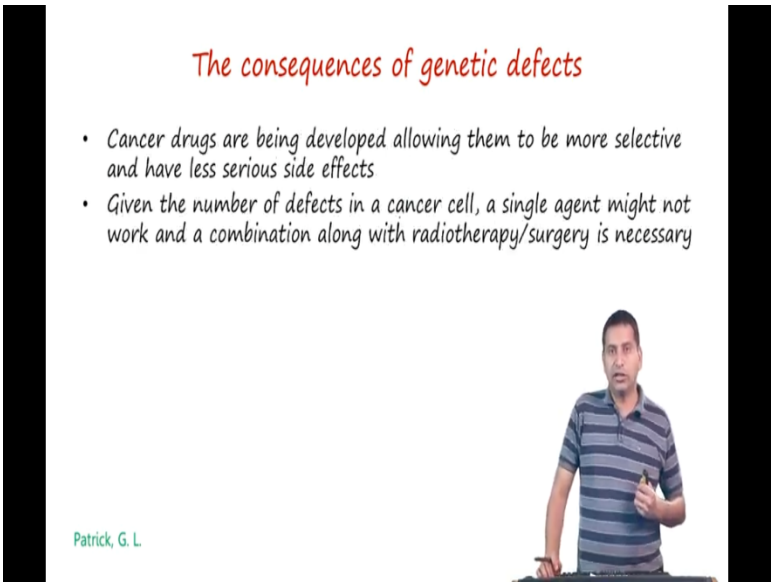

So cancer drugs are now being developed so that you can have them to be more selective and these highly selective agents have a potentially less serious side effects so given the number of defects in a cancer cell a single agent might not work and therefore a combination of radiotherapy surgery along with chemotherapy is what is typically necessary.

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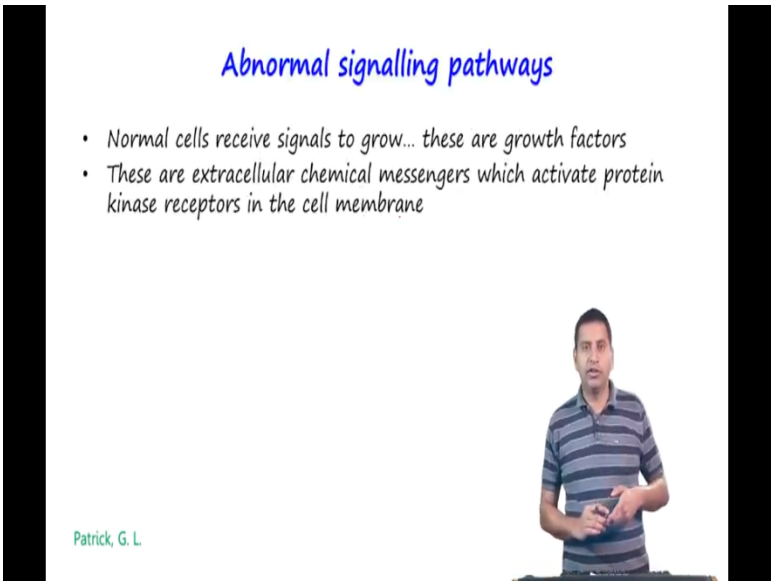

So let's look at some of abnormal signaling pathway is done so like I mentioned earlier normal cells receive signals to grow they receive signals to divide and they receive signals to differentiate wherever the case might be So these signals that allow them to grow or propelled them to grow are known as growth factors and these are in many cases external cell chemical messengers which activated kinase receptors so you have a cells which with a kinase receptors and so this lagan binds and it activate the growth ok.

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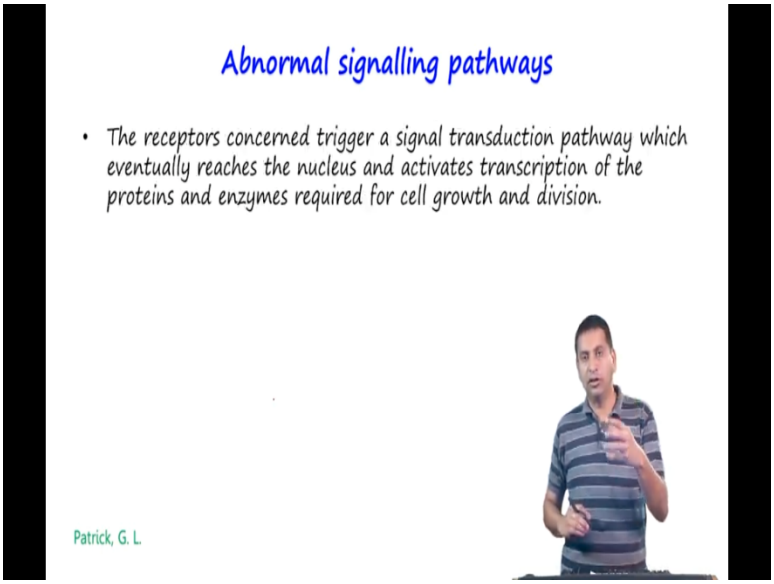

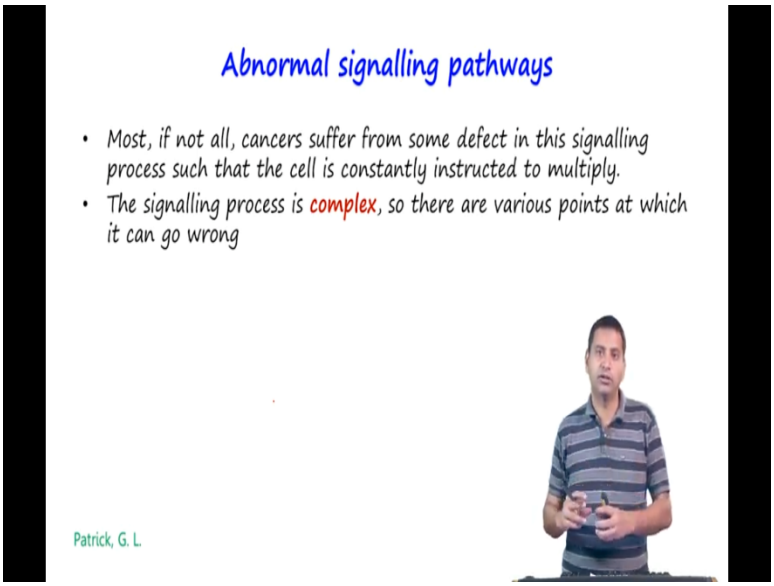

Now these receptors will trigger a signal transduction pathway which eventually leads the nucleus to activate transcription of the protein which are required for cell growth and division most if not all cancers suffered suffer from some defect or the other in this signaling process So therefore the cell instead off invasion and growth after some time it actually is instructed to multiply constantly and as you can imagine the signaling process is quite complex and there are various pointed which it can go wrong.

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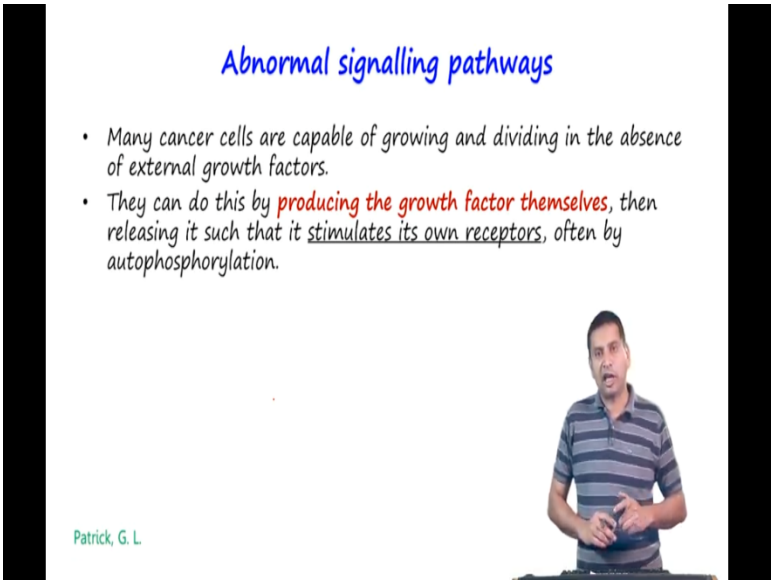

So many cancers are capable of growing and dividing in the absence of external growth factors so once cancer develops it doesn't need any external growth factors it just goes on its own They can also do keep indefinitely going by producing the growth factors themselves ok so therefore you can have a series of cancer cells which are growing which do not need any growth factor at this time but then they can stimulate these so they can produce these growth factors which then further allows other cancers cells to grow So therefore this is up a process which can often by auto phosphorylation. So through this mechanism these cancers become a mortal.

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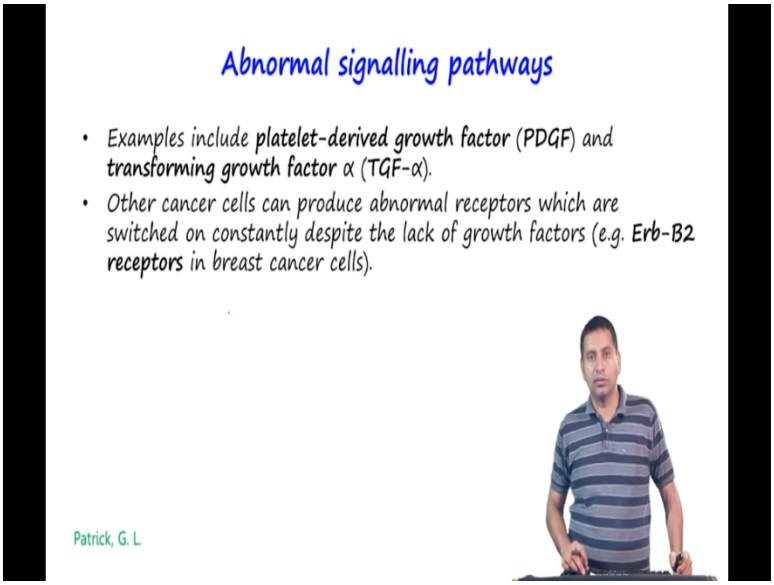

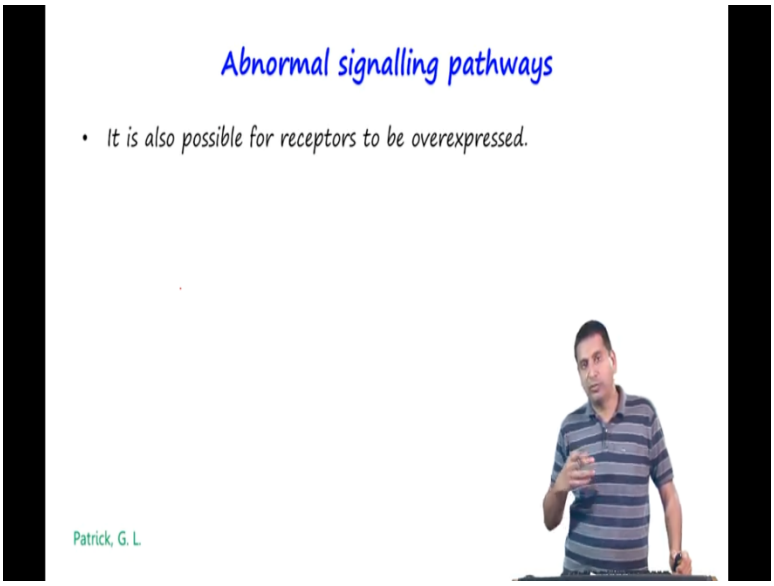

So the example hear are platelet derived growth factors which is called as PDGF as well as transforming growth factor as TGF Alpha Other cancers can produce abnormal receptor which are switched on constantly despite the lack of growth factors so for example this ERB B2 receptors in breast cancer cells right so these are always on and therefore you don't need an externally lagan to activated It's also possible for the receptors to be over expressed and so you don't need a whole lot of the of the growth factor to be activating it a small amount is sufficient for to trigger growth.

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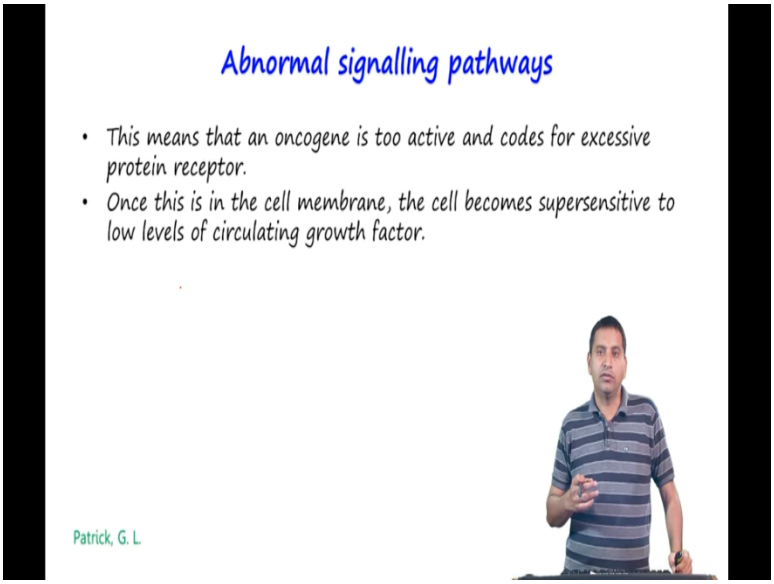

So what it means is that the oncogene is to active and codes for excessive amount of this protein receptors So once it is in the cell membrane the cell become super sensitive to even extremely low levels of the circulating growth factor.

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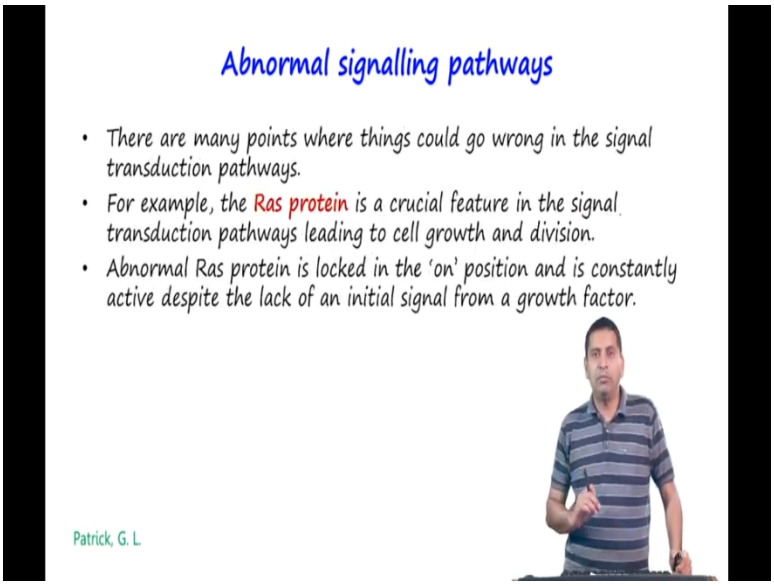

So there are many points where things could go wrong with the signal transduction pathways so for example the ras protein which where looked back is a very crucial feature in the signal transaction pathways which leads to cell growth and division abnormal ras protein is locked in the on position and is constantly active despite the lack of an initial signals from a growth factor.

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So there are several external hormones which are used to contact the the effects of the stability symmetry to the growth factors So these are what are known as growth inhibitory signals So one example here is the transforming growth factor beta which is known as TGF beta and these actually prevent the growth of cells and prevent them from dividing However cancers can become insensitive to these growth inhibitory signals so this is another way in which you can head over the cell becomes immortal.

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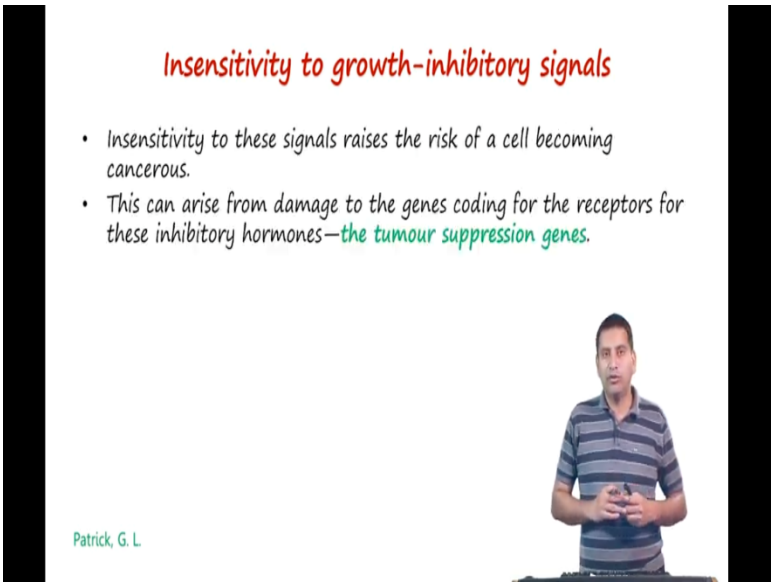

So what happens is that when it becomes insensitive then the risk of the cell becoming cancerous is quite high so this can arrays from damage to the genes coding for the receptors for these inhibitory hormones which are known as the tumor separation genes.

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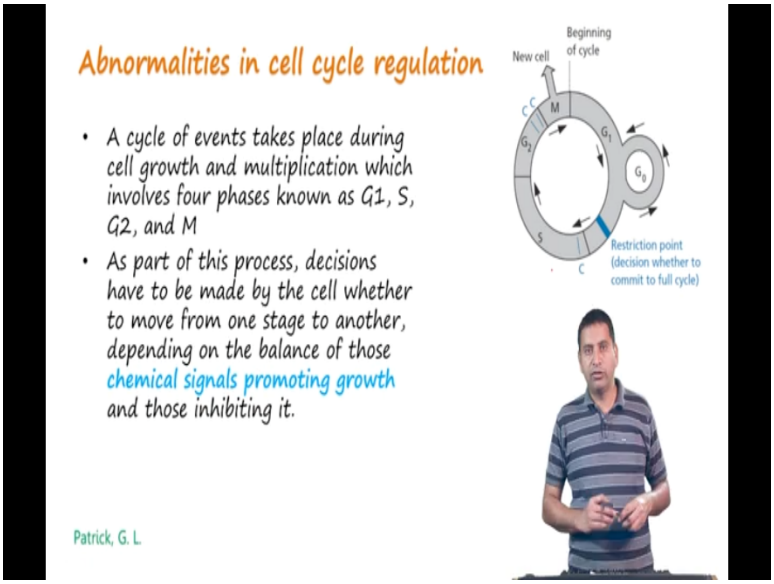

So let's look at some of the cell cycle regulation methods and how it occurs so during a cell division there are several phases which are involved the first one is called the G1 phase followed by an S phase subsequently there is a G2 phase and that M phase Now these are highly coordinated events ok and they occurs with great level off synergy Now During this process a number of decisions have to be made by the cells So for example when the G1 phases initiated So here is the G1 phase Now it has to decide at some point to Go into S phase right so there are chemical signals which are secreted to promote the growth and it also helps there are some other signals which are produced inhibited.

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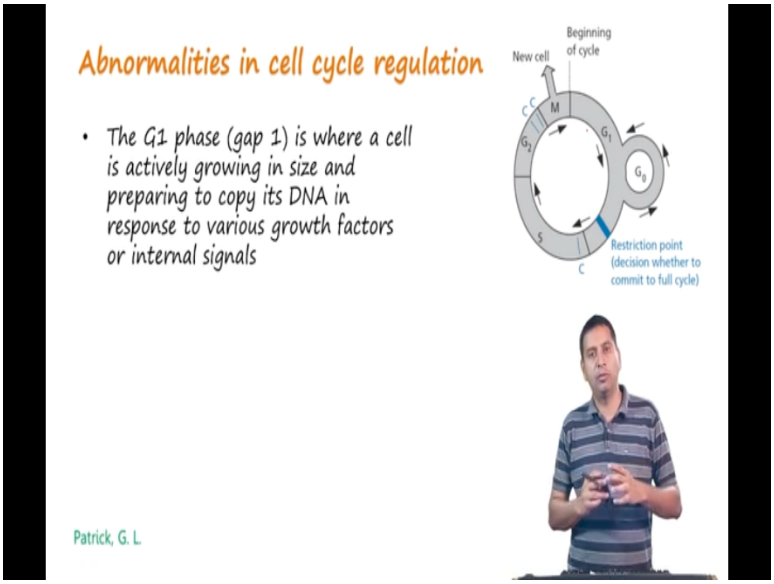

So the G1 phase is where cell is a growing in size ok and prepared starting to prepare to grow to copy its DNA in response to various growth factors or internal signals so this is considered as the beginning of the cycle.

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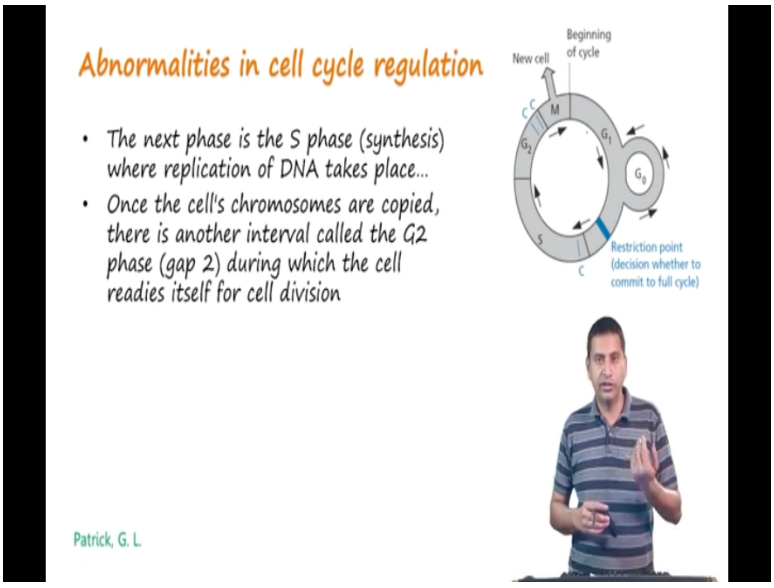

Now in the next phase which is called as the synthesis phase or the S phase is where DNA replication takes place one the cells chromosomes are copied then there's another interval which is called as the G2 phase on the gap to phase In this phase cell readies itself for cell division ok

so this gap or interval is very crucial because it gives a time the cell time to check if the copy DNA is as good and if there's any repair DNA damage that occurs then it's repaired ok.

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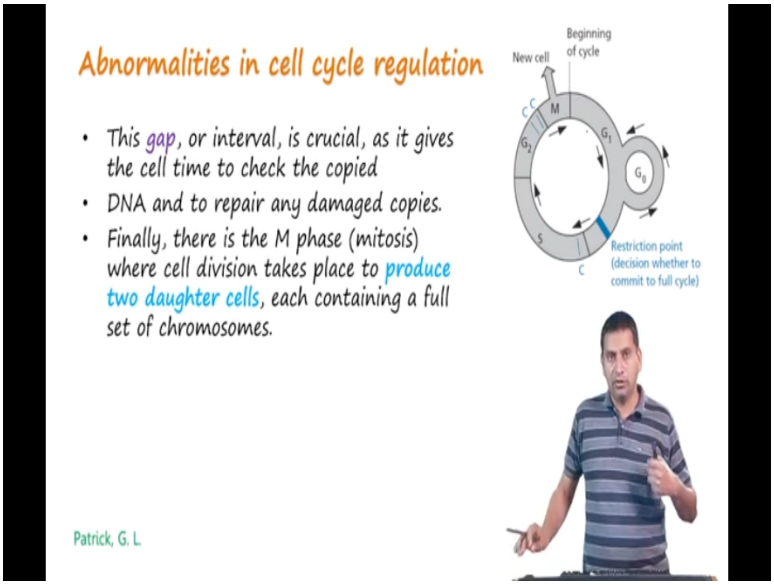

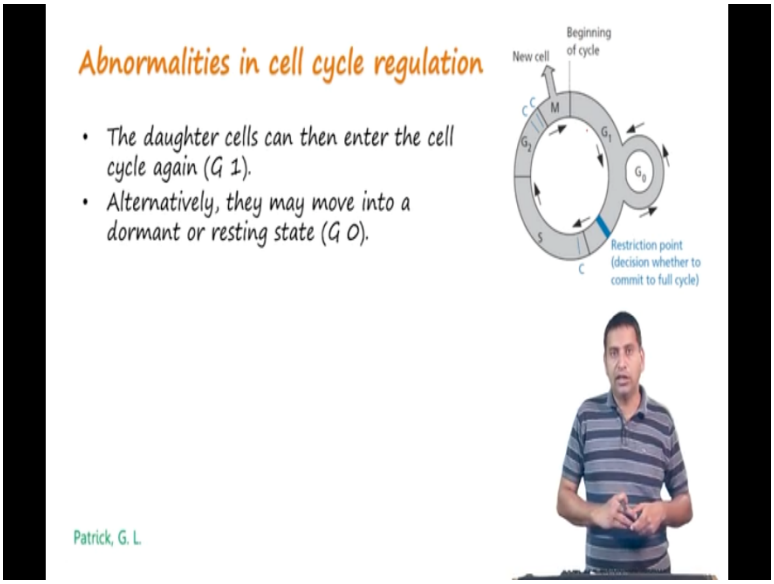

Now finally there is a M phase which is also called mitosis phase where the actual cells divides and producers to daughter cells each containing a full set of chromosomes so the daughter cells can then enter the cell cycle again or alternatively they may move what is known as a resting state G zero states.

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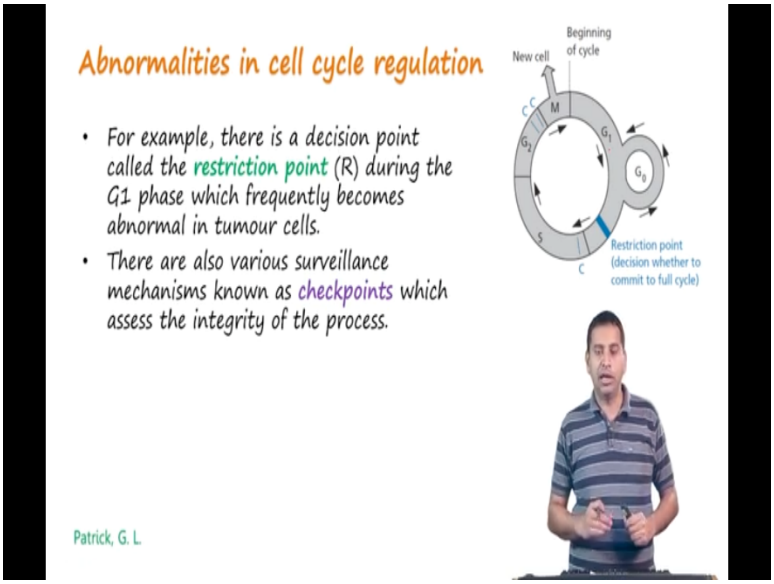

So there is a decision point here during the cell cycle which is called the restriction point I just denoted by R ok so here this becomes this phase becomes abnormal in many cases of tumors So there are also various surveillance mechanisms or checking mechanisms which an known as checkpoints Which allow for checking of whether gene integrity still happening or not a is good or not.

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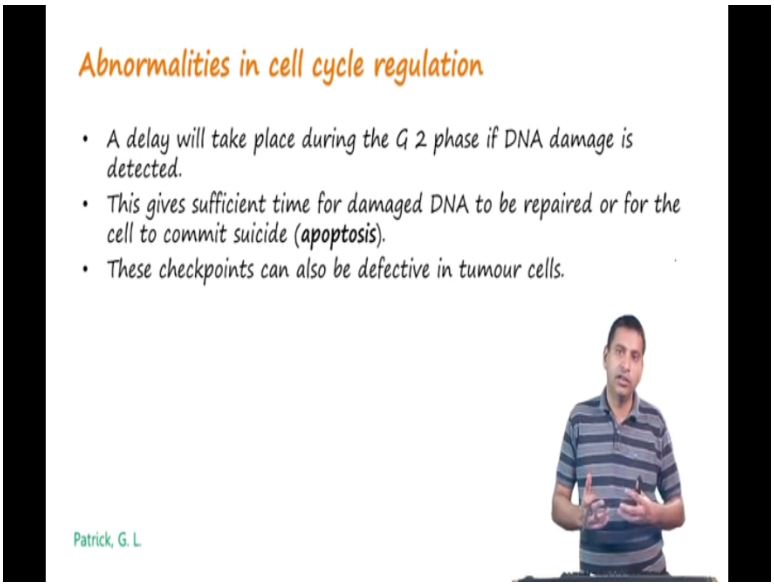

So a delay will take place during the G2 phase as we have discussed earlier in gives DNA damages detected and as we have discussed previously cancers are frequently associated with

damage DNA and therefore one would argue that the G2 phase there should be an arrest because there's going to be significant amount of DNA damage in the cell So now in this time that is given for a repair if you know if the DNA damage the repair is not possible then there is another signal which is given for the cell to commit suicide So these checkpoints also become defective in tumor cells.

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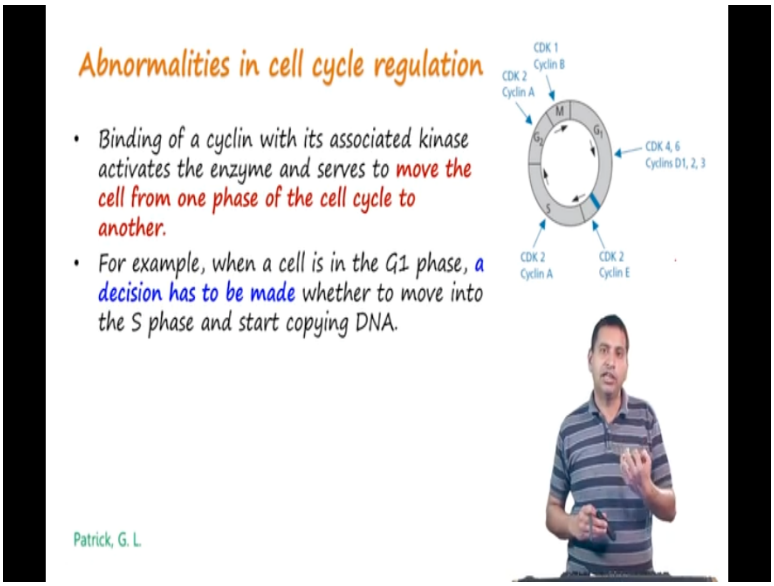

So for example are in this process there is a binding offer cyclin ok which is associated kinase which activates the enzymes and serves to move the cell from one phase of the cell cycle to the another. For example when a cell is in the G1 phase a division has to be made whether to move into S phase and start copping DNA.

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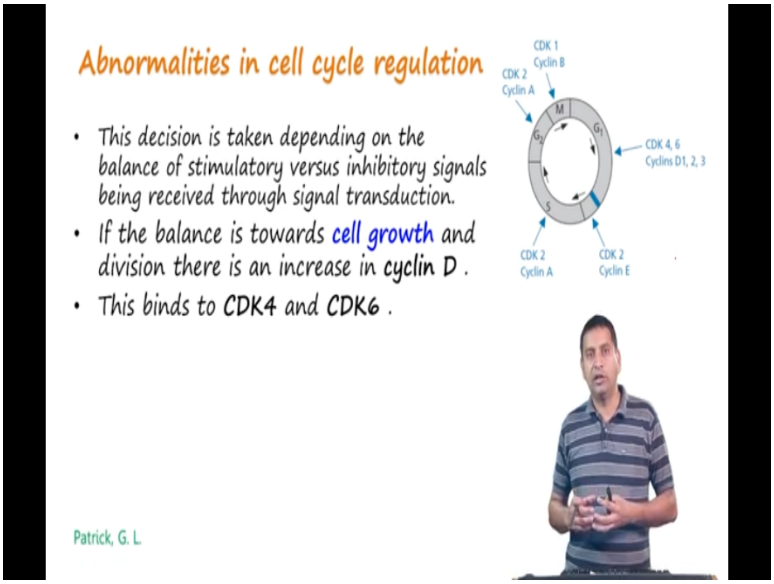

So this decision is taken depending on the balance of the you know various grow process inhibitory signals that have been received through signal transduction so if the balance is towards the cell growth then there is an increase in cyclin D ok and this binds to the corresponding kinases to CDK 4 and CDK 6 so this happens in this phase right.

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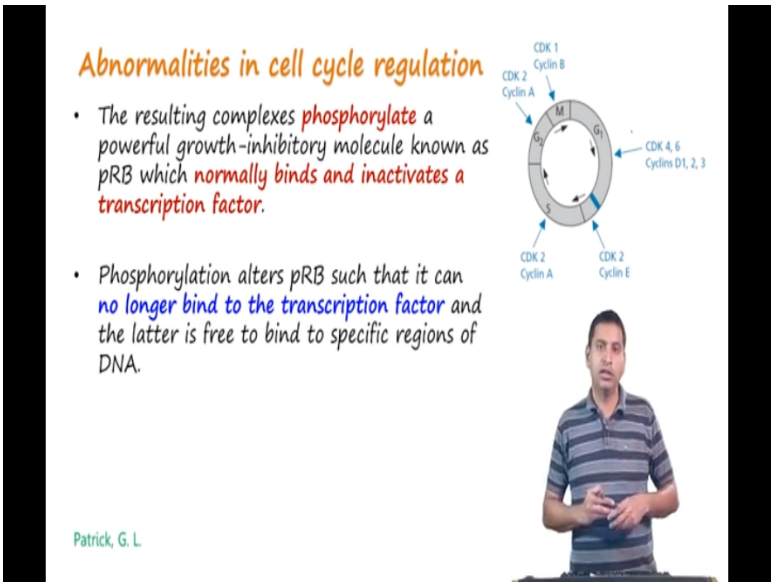

Now so the resulting complexes of phosphorylate is powerful growth inhibitory molecule known as PRB and this PRB which normally is normally binds and inactivates a transcription factor

Phosphorylation alters PRB such that it can no longer binds to the transcription factor and then the latter is free to bind to specific regions of DNA ok.

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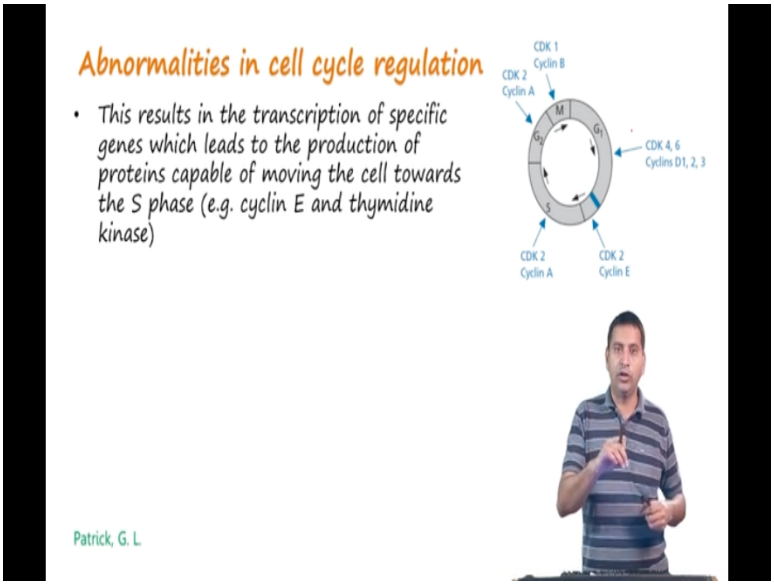

So this results in the transcription of specific genes which lead to the production of proteins capable of moving the cell towards S phase so therefore the cascade is initiated by cyclin which Go and binds the CDK which leads to phosphorylation which then leads to transcription of which of the specific genes which lead to the production of proteins and a cable of moving the cell towards S phase so examples here are cyclin E easy and thymidine kinase.

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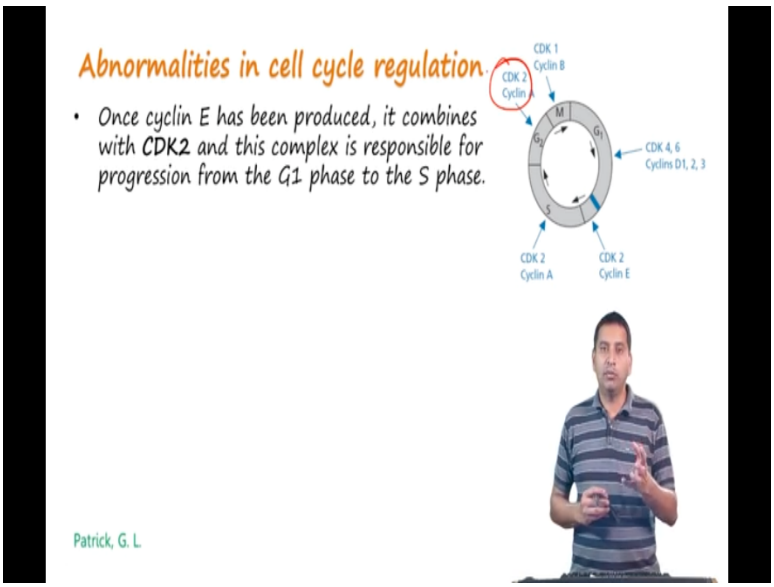

So once cyclin E the has been produced it combines with CDK 2 and that shown here right and what happens is that this complex is no responsible for the progression of the of the cell from the G1 phase to the S phase.

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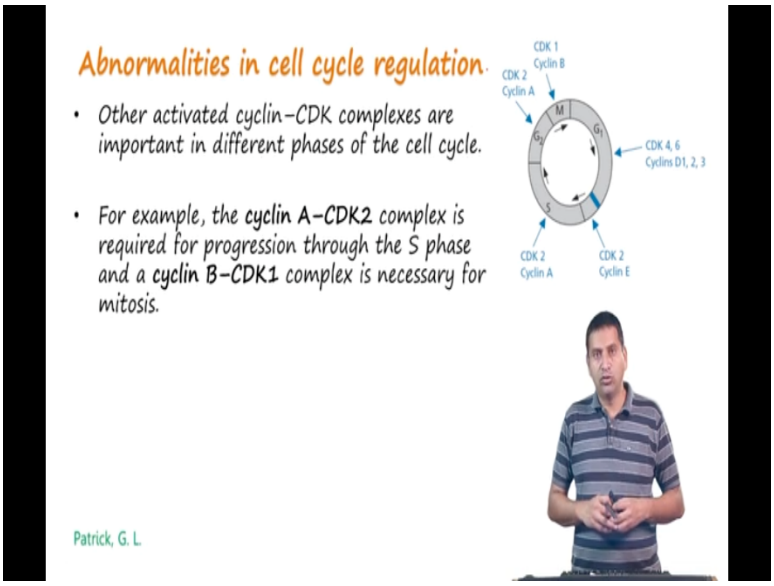

So once other activated cyclin of the CDK get complexes are important different phases of the cell cycle so for example the CDK 2 cyclin a complex which is shown here is very important to the S phase whereas cyclin B CDK 1 complex is responsible with the M phase or the Mitosis phase ok.

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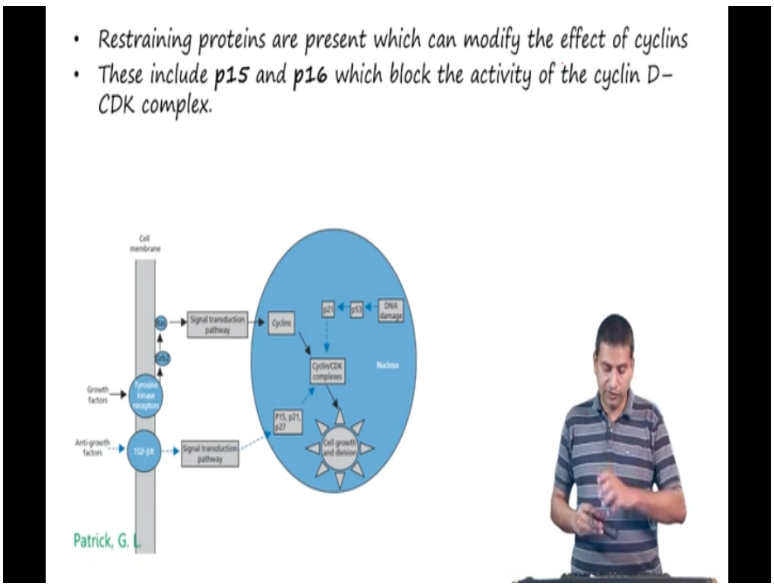

So restraining proteins are present which can modify the effects of Cyclin so these include example such as P15 and P16 ok so what these do is that the block the activity cyclin B CDK complex So another example of inhibitory protein is P 21 which is a which is again control by P53 which where looked at previously So P53 is an important protein that monitors the health of the cell and the integrity of DNA So here is 53 in this process.

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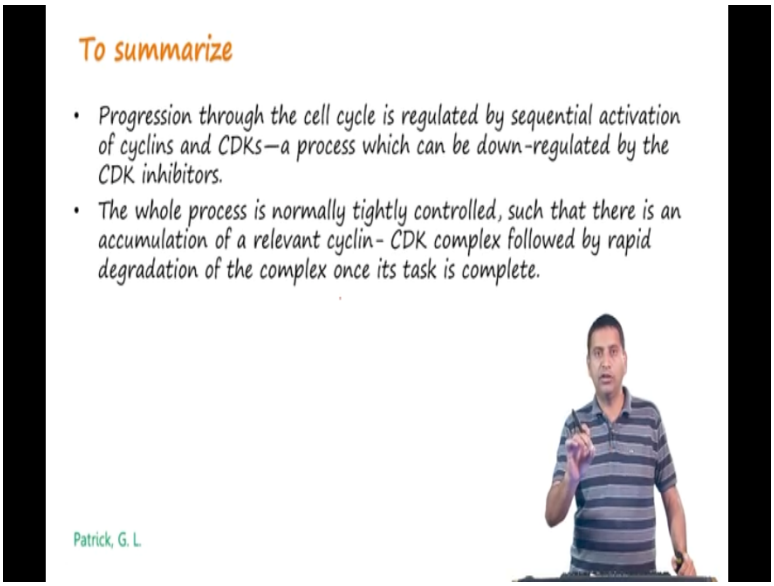

So to summarize progression through the cell cycle is regulated by sequential activation of cyclin and CDKs A and this process can be down regulated by the CDK inhibitors and the whole process is tightly regulated such that there is an accumulation of the relevant cycling CDK complex followed by a rapid degradation of the complex ones the task is complete.

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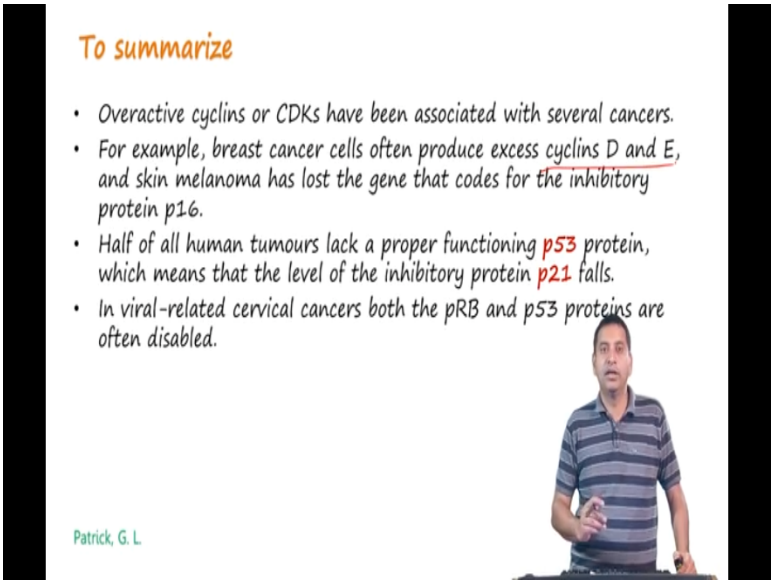

So overactive cyclins or CDK have been associated with several cancers so for example breast cancers often but produce excess of cyclin D and E And skin melanoma which is a case where a one develops a cancer on the skin has lost the gene that codes for the inhibitory protein P16 So keep in mind you can have excess of the growth factors or you can have separation of inhibitory proteins Half of all human tumor lack a proper functioning P53 protein people so P53 protein is the one that monitors the health of the cell Which means that the level of the inhibitory protein P 21 also falls down so in viral related cervical cancers the PRB and P53 protein are often disabled.

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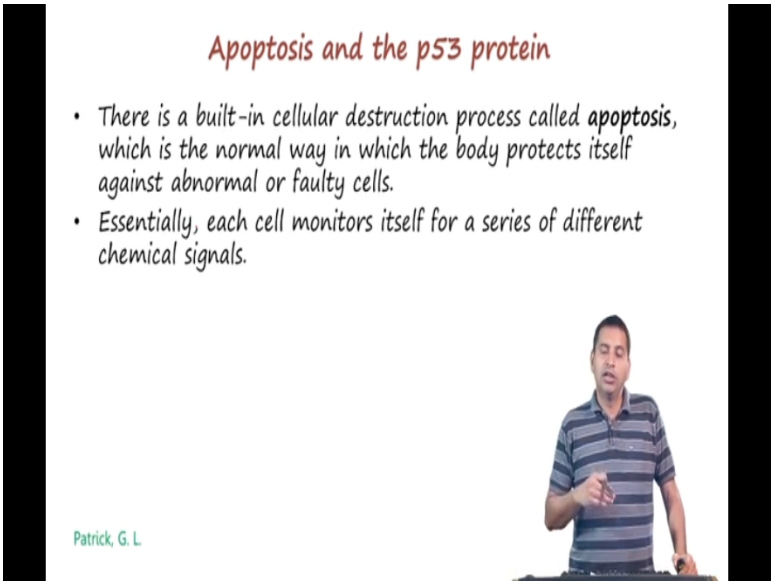

Now with this let's look at the induction of apoptosis So like I mentioned earlier there is a self-destruction process or suicide process that is programmed into each cell So once there is enough DNA damage that occurs and there is a huge problem with the genome integrity Usually apoptosis struggle this is the normal way in which the body protects itself So and this again is coordinated by all serious of chemical signals.

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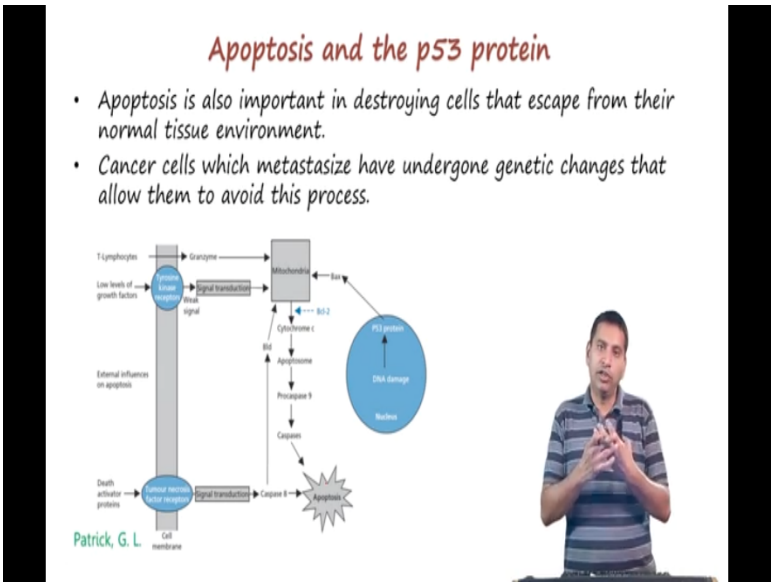

So should there be any of these chemical signals that are absent A self-destruct mechanism is automatically initiated a shown here ok So apoptosis is also important in destroying cell that escape from their normal tissue environment so for example if in the case of an a muscle cell let’s say if one of the cell going to detach itself an go into the lung the functional for muscle cell inside the lung it is not probably useful therefore what happens is that it is detected by immune system and it is destroyed through the induction of apoptosis So cancer cells which metastasize have undergone a long number of genetic changes that allows them to avoid this process ok.

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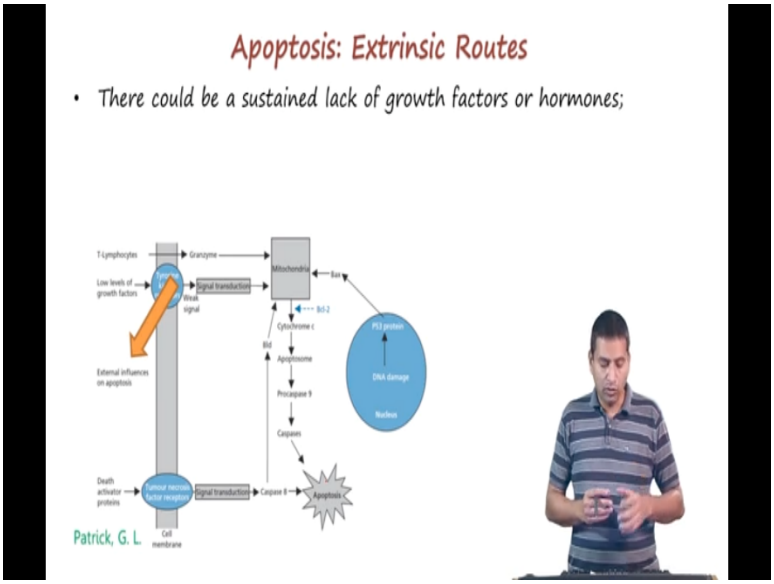

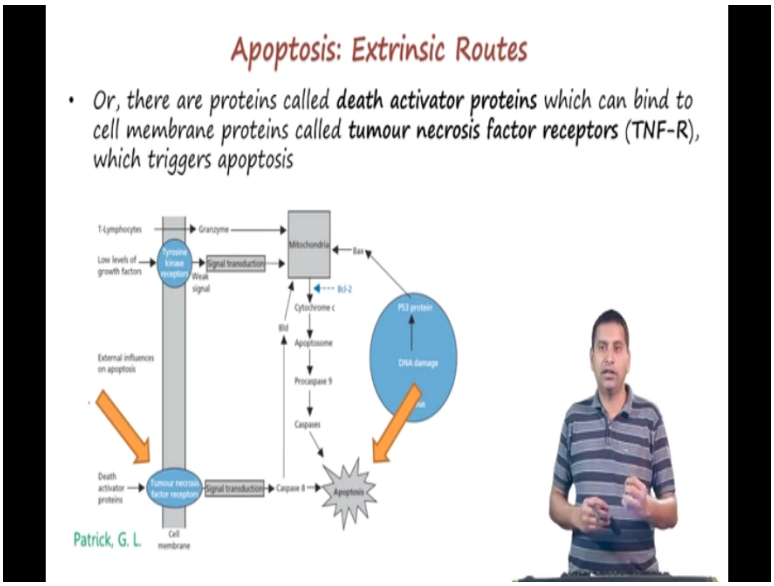

So this could be a sustained lack of growth factors or hormones so you have these external influences that can clearly influence the growth and so it by having this lack of growth factors one could induce apoptosis or there are proteins which are known as death activator protein which can bind to the cell membrane called us tumor necrosis factor receptor or TNFR So ones these binds then what happens is that it triggers apoptosis.

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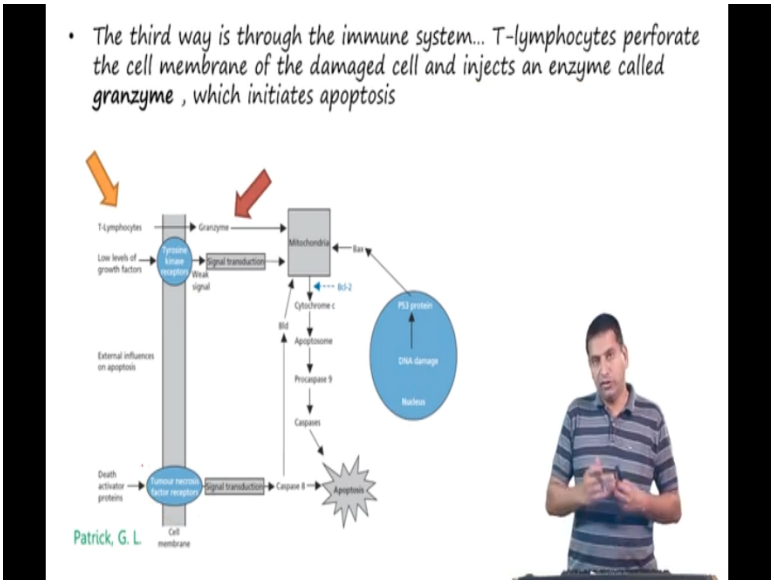

The third way is as I mentioned earlier is to the immune system so once your muscles cell which has escaped goes into the lungs the immune system recognizes this as something that is not supposed to be there and then the T lymphocytes perforate the cell membrane of the damage cell and injects an enzyme called as the granzyme which initiates apoptosis.

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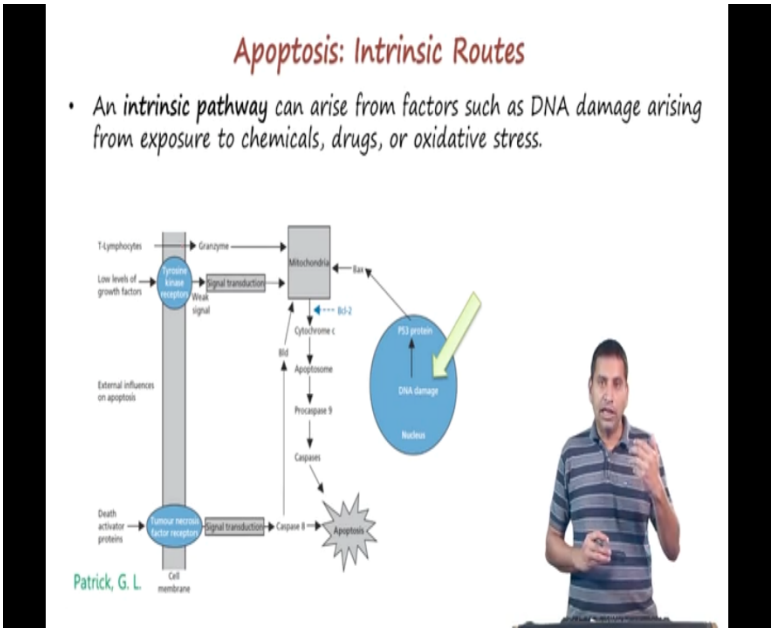

So there also an intrinsic routs that can result in apoptosis so one is the intrinsic Pathway due to DNA damage as we already discussed the genome integrity and the is really important and once

the DNA is damaged because of chemicals or drugs or oxidative stress then what happens is that you need to trigger apoptosis.

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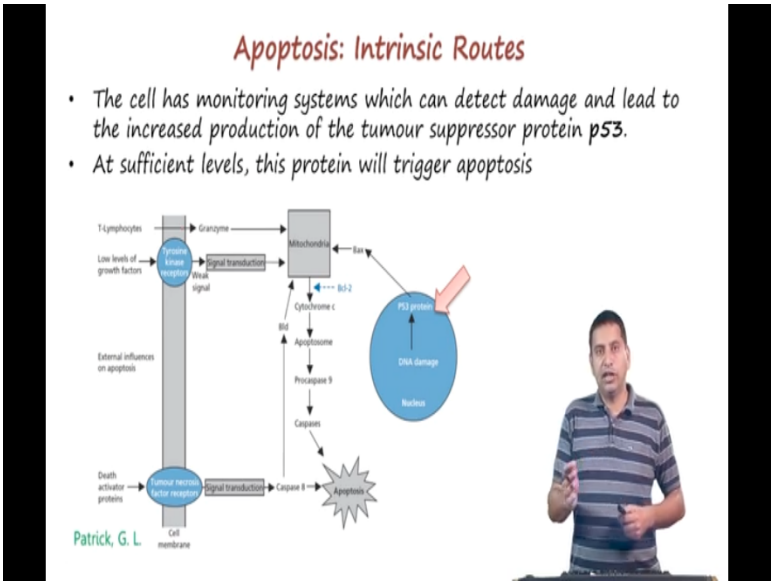

So the cell monitor the systems the integrity of the genome and one's its detect the damage it leads to increased production of the tumor suppressor protein P53 at sufficient levels the 53 will actually trigger apoptosis.

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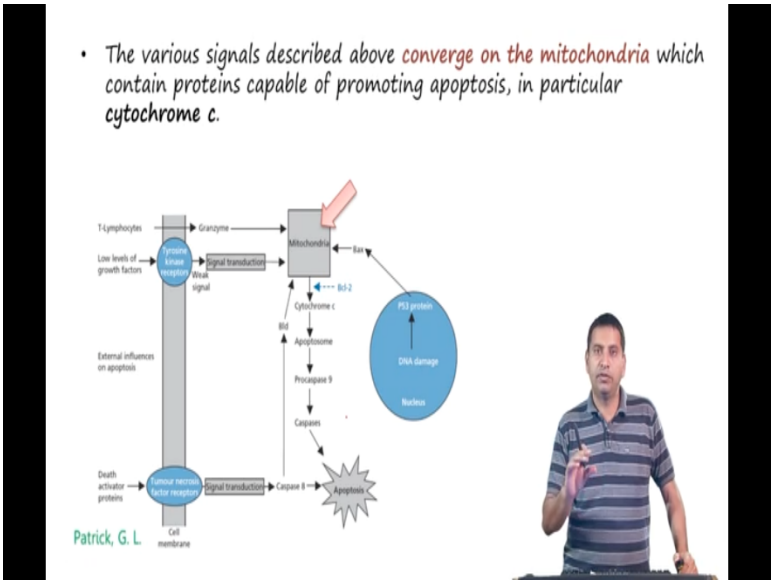

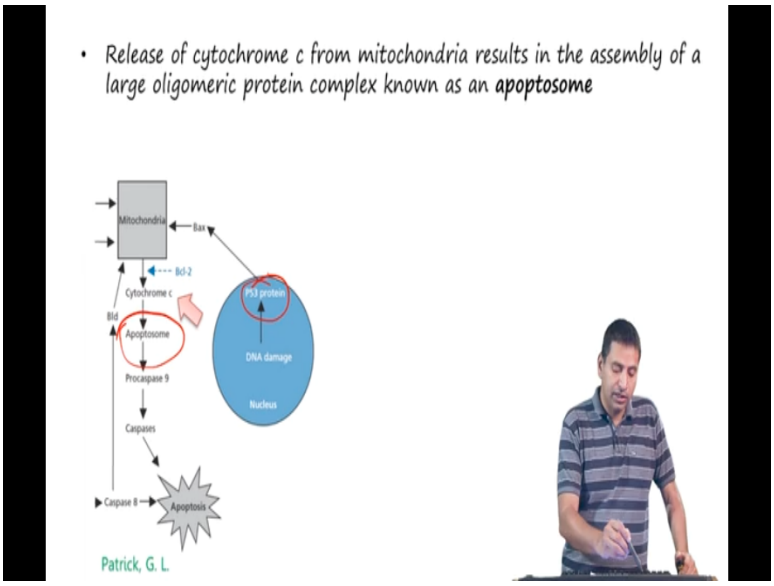

So the process in which this happens is that P53 of the various signals that are induce P53 actually converge in the mitochondria And the mitochondria contains what is known as a protein known as cytochrome C And the cytochrome C actually secreted by the mitochondria and the release of this from mitochondria results in a series of events which leads to the formation of what is known as an apoptosome ok so the process is this once P53 goes up it is all seen and interaction with mitochondria mitochondria then the releases this cytochrome C which then triggers the formation of a protein complex known as apoptosome.

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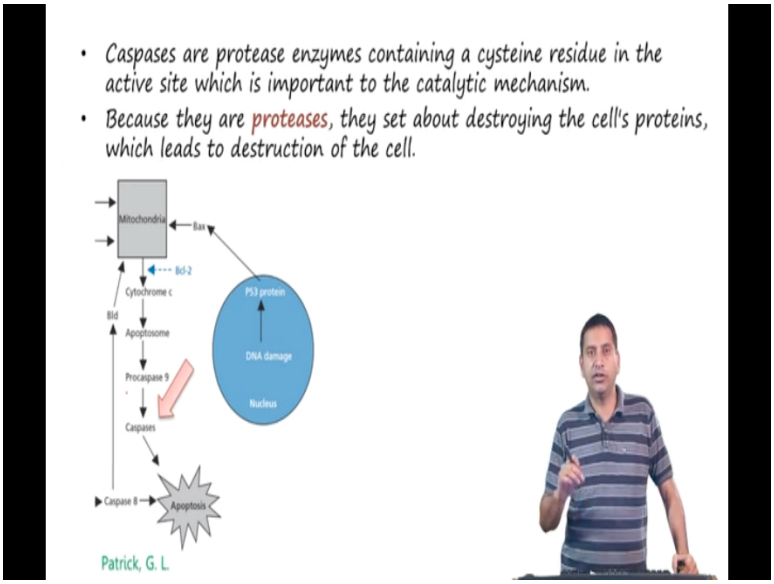

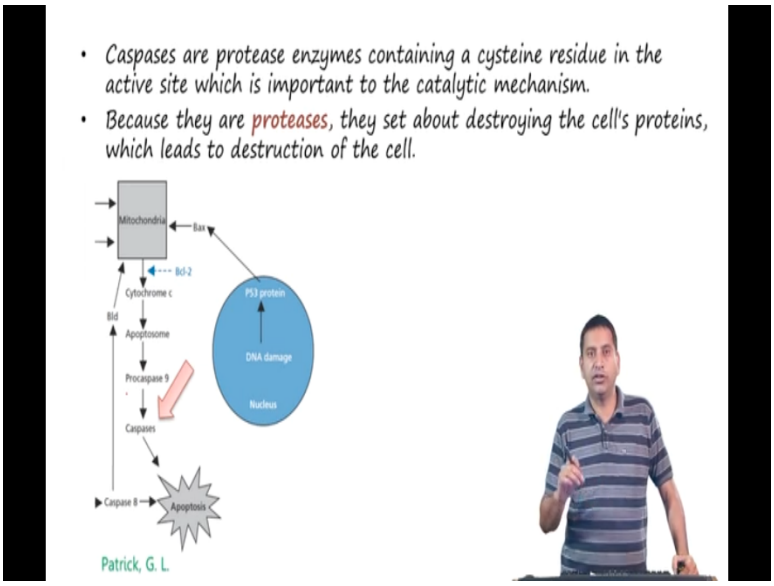

The apoptosome then recruits and activates an enzyme known as procaspase ok so procaspase mine is in a really important enzyme in the whole cascade of apoptosis this in turn activates modernist caspases ok so caspases belong to Proteases glass off enzyme and these are cysteine proteases and the contain cysteine residue in the active site and they're important to the catalytic mechanism we've already looked at cysteine base proteases previously So because these proteases what they do they destroyed the cells proteins which leads to the destruction of the cell.

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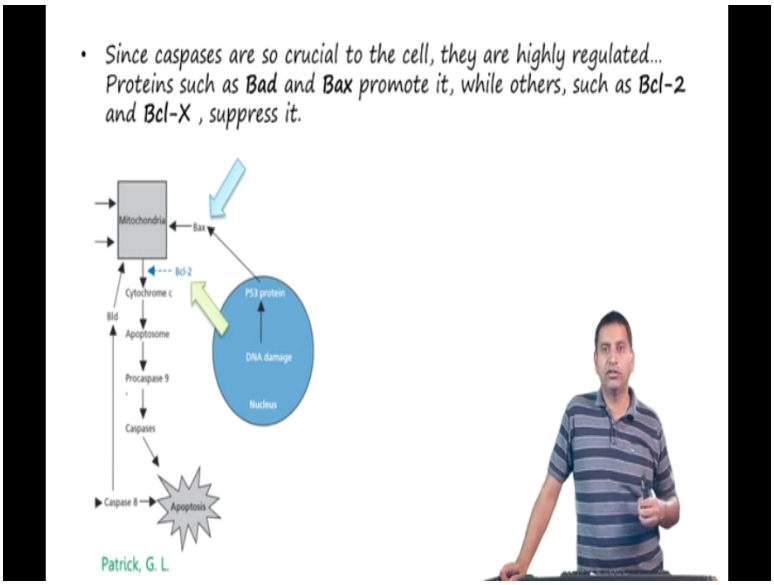

Since caspases also crucial to the cell they are highly regulated So there are proteins which promoted while they're proteins which also suppresses the example of suppresses is BCL 2 And BCL X.

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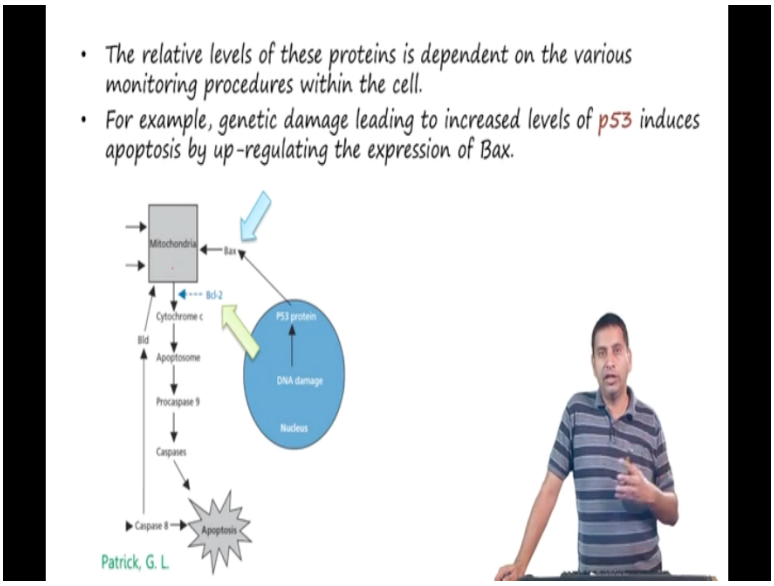

So the relative levels of these proteins is dependent on the various monitoring procedures within the cell so once there is a high level of damage that is induced then the levels of inhibitors of apoptosis may go down and the promoters of apoptosis may go up ok.

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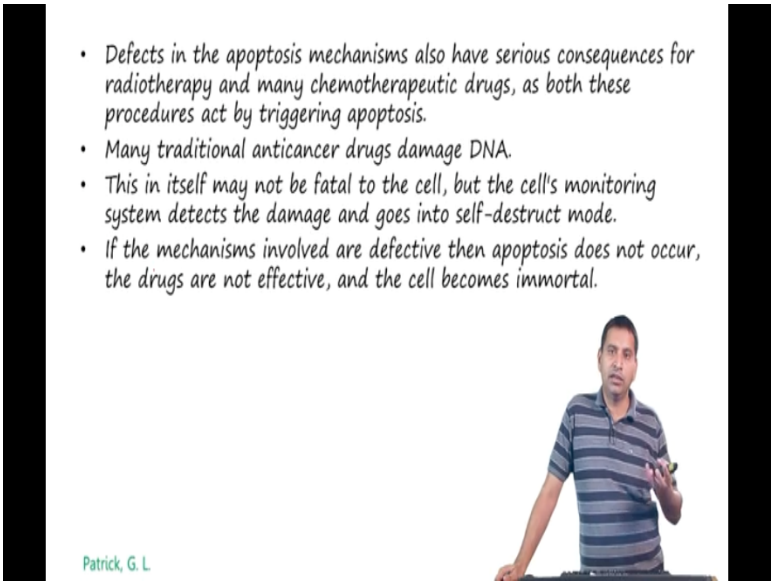

So no it's quite obvious for us to understand that these defects in the apoptosis mechanisms will have serious consequences So for example in the case of radiotherapy and many chemotherapy regimens both these processes are occur by triggering apoptosis However if the apoptosis process is not well regulated these molecules are not going to be work on this strategies are not going to work So this in itself will not be fatal to the cell So if the mechanisms involved in inducing apoptosis or defective then the drugs don't become effective can the cell continues to be immortal ok.

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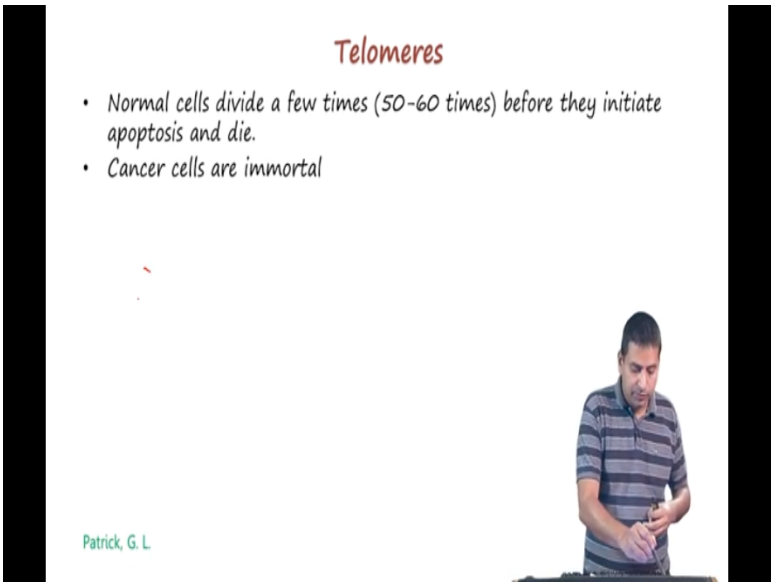

Now with that let's look at another important concept known as telomeres so when a cell is divides and it forms a two daughter cells it can subsequently divides and so on right what happens is that does division process can occur a few times maybe around 50 times or so before the initiate apoptosis and die but as I discussed right as a discussed cancer cancers cells evade this and they don’t die right.

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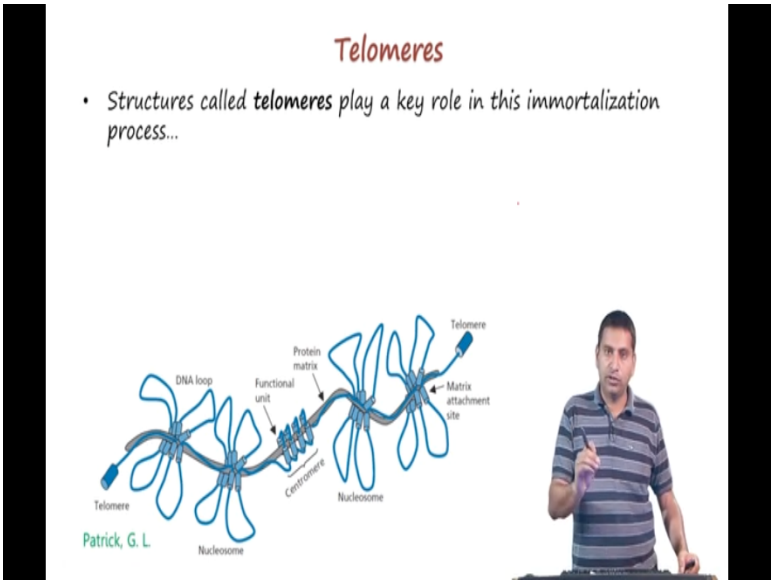

So therefore this division process or the process by which certain the number of divisions are occur and which there they want to stop is mediated by enzymes by structures known as telomeres these are very crucial for the immortalization process so here is the telomere which is attached to the DNA it's a part of the genome ok.

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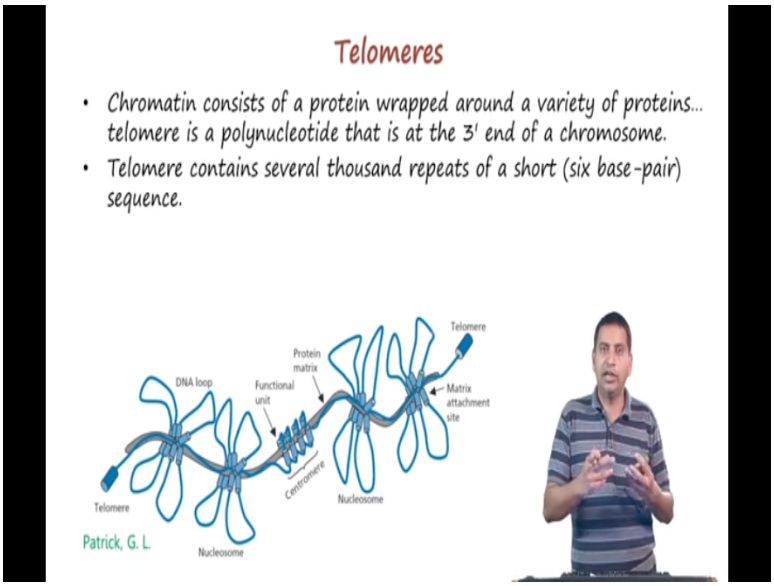

So chromatin we've already discussed previously consists of a protein which wrapped around the variety of the protein and telomere is polynucleotide that is at the 3 end of a chromosome so these contain several thousand repeats of a short six base pair sequence ok.

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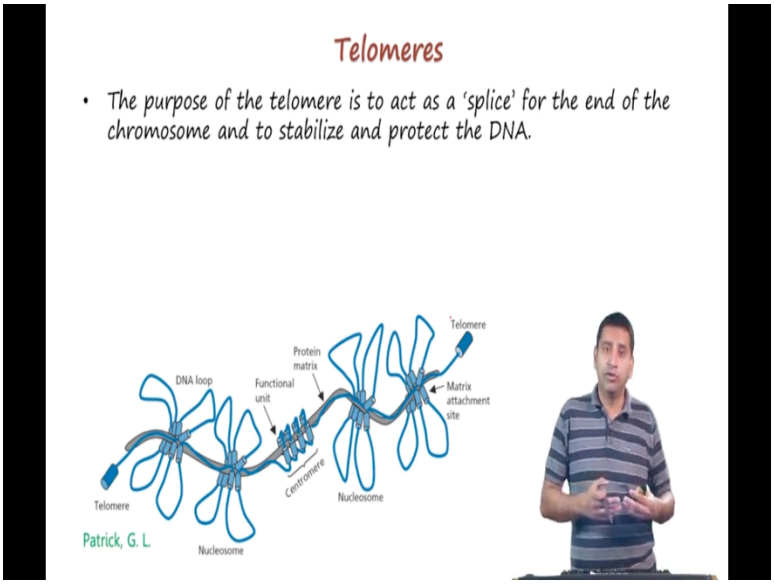

So the propose of the telomere is to act as a splice for the end of the chromosome and stabilize and protect the DNA So after replication process about 50 to 100 base pairs actually lost from the telomere in this process so because DNA polymerase is unable to completely replicate at the 3 prime ends of chromosomal DNA so each time the cell divides you lose about 50 to 100 base pairs.

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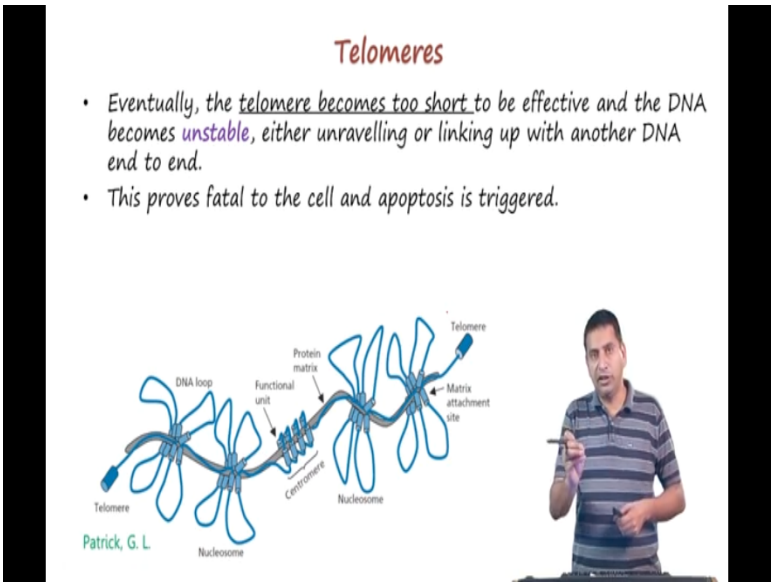

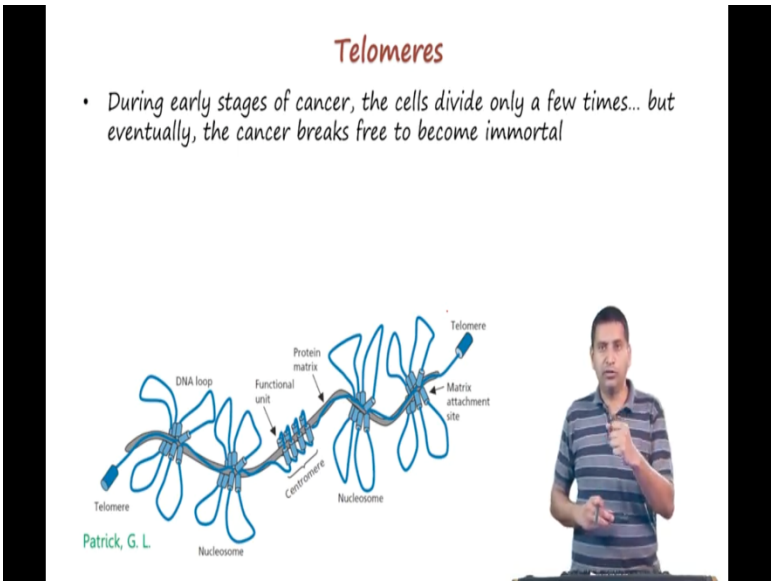

Eventually the telomere becomes too short to be effective and the DNA becomes unstable either unraveling or linking up with another DNA end to end So both of these processes are going to trigger apoptosis and the cell will die So during early stages of cancer the presence of telomere is going to imply the cell will divide only a few times ok but somehow the cancer breaks free from this process and becomes immortal.

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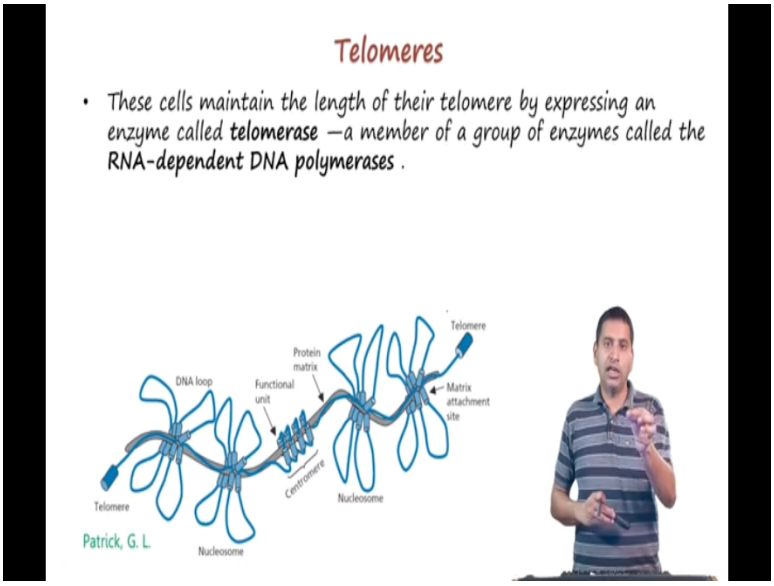

So the cells maintain the length of the telomere by expressing an enzymes known as telomeres So this is a member of the group of enzymes known as RNA dependent DNA polymerases.

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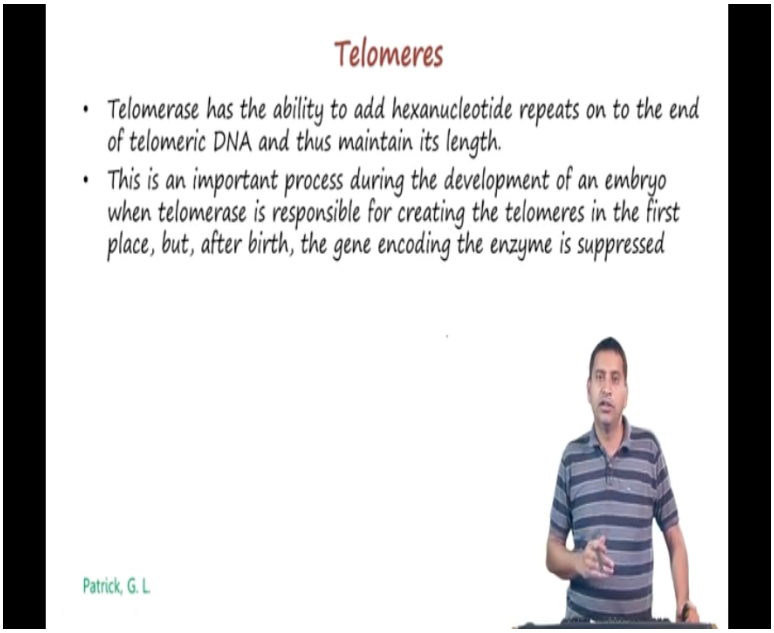

So telomeres has the ability to add hexanucleotide repeats on the end of the telomeres DNA and thus maintaining its length so this is an important process during development of an embryo we're telomere is responsible for creating telomeres in the first place but after birth the gene encoding the enzyme is suppressed so during the Development stage in the embryo still over race is actually Active However after birth the enzymes was suppressed.

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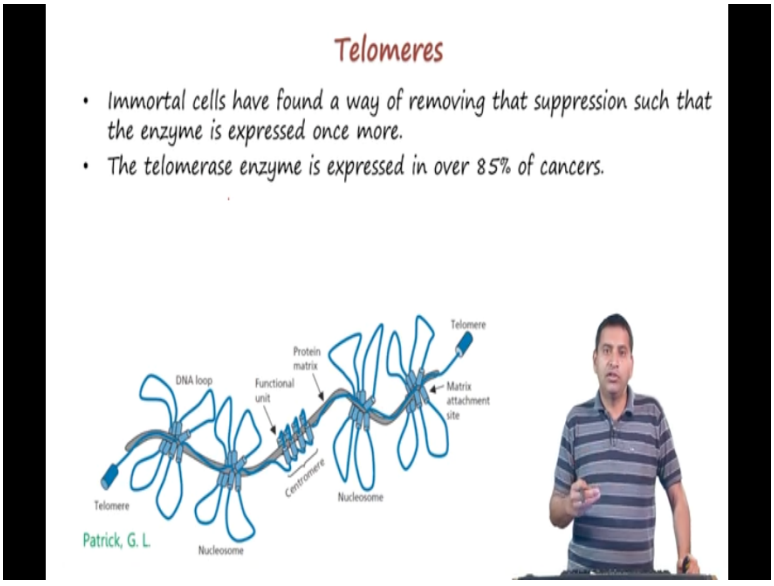

So a immortal cells have found a way of removing that separation such the enzymes is expressed again So now telomerase enzyme is expressed in over 85 percent of the cancers So number of efforts have been made to design drugs which is inhibit telomerase but so far there's been no success in developing it towards the clinic.

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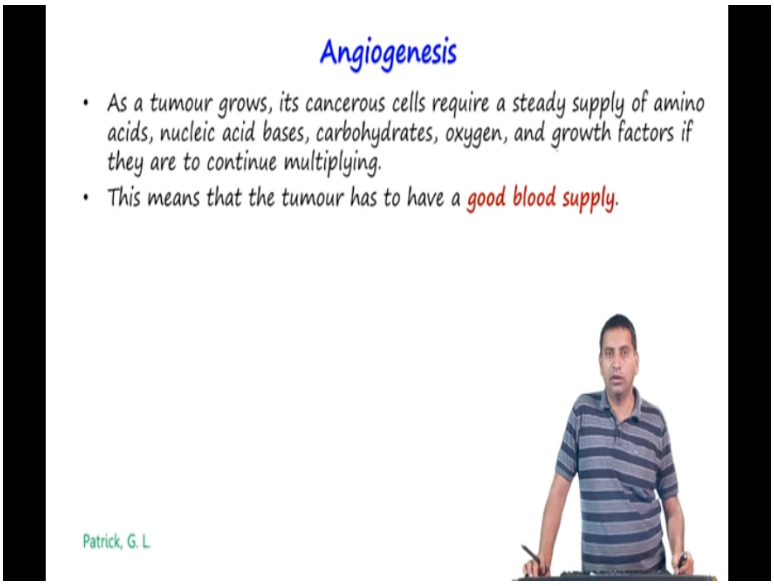

Next we're look at another important concept which is angiogenesis so as a mentioned earlier the problem or the situation with cancers is that they keep need to have a steady supply off of nutrients including amino acids nucleic acid basis carbohydrates for you know constant growth and division and of course the need oxygen and growth factors So for all of this to happen the tumor would need to have a good blood supply.

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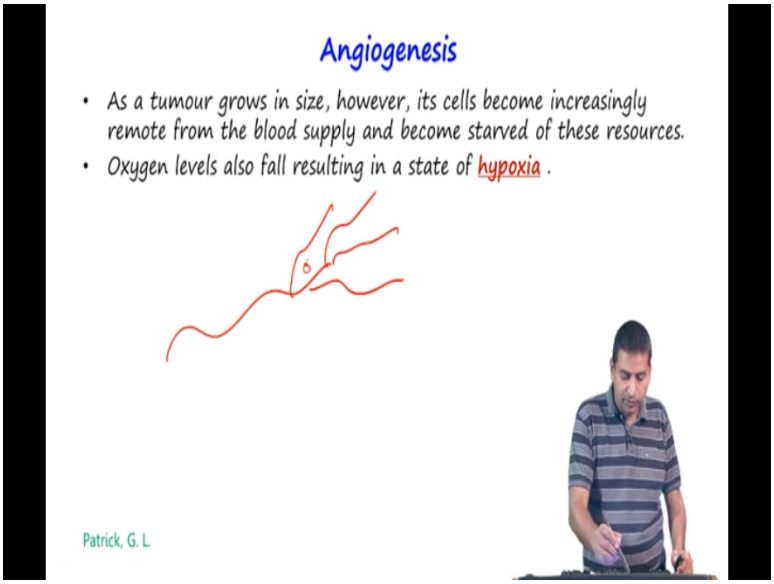

So as the tumor grows in size it cell becomes increasingly remote from the blood supply so let's say you have a of a blood Capillary network like this And the tumor is located here as it grows bigger and bigger what happens is that the distance from those blood vessel goes higher and higher So this results in the center of the tumor in the cell having low oxygen tension so this a situation is called as hypoxia.

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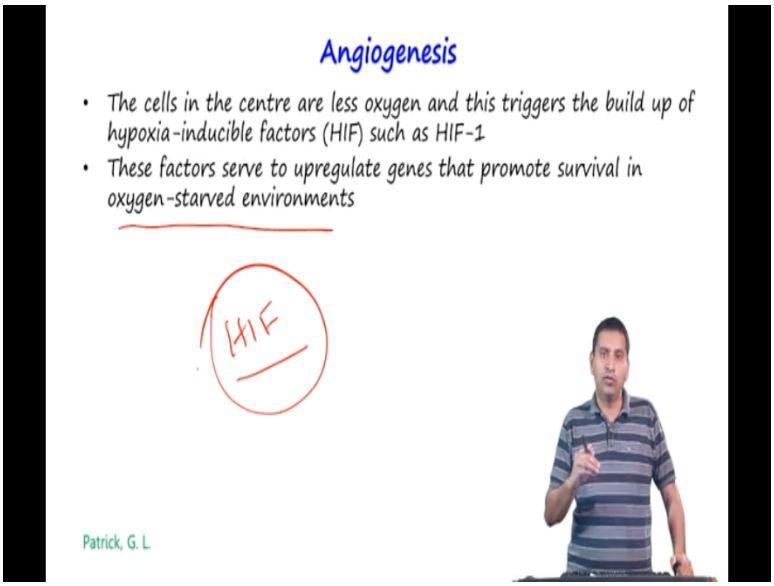

So the cells in the center have less oxygen and this triggers the buildup off an important protein known as hypoxia inducible factor or HIF an example of this HIF 1 So these factors actually

operate the late a number of genes that promote survival in oxygen starved environments normally one would expect that if a cell is present in oxygen starved environment for too long it would die but this set of proteins known as HIF hypoxia inducible factor play a crucial role in the survival of cancers in these Oxygen starved regions.

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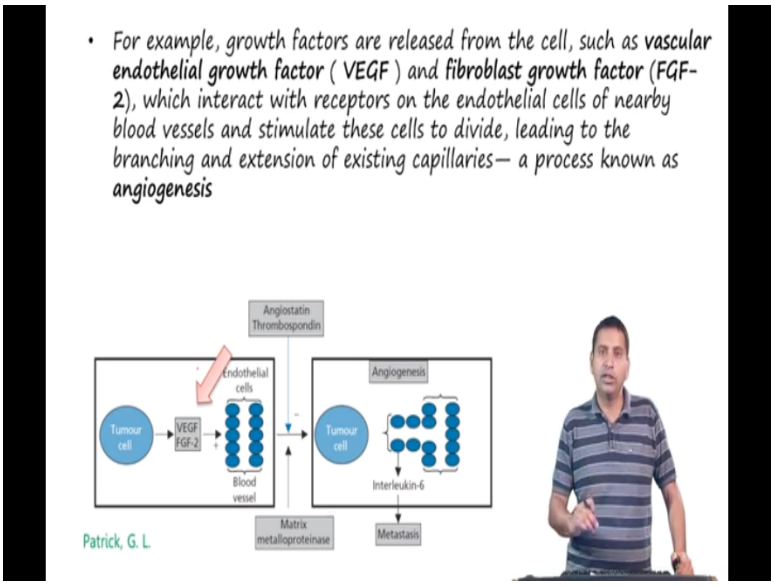

So for example the growth factors are released from the cell such as VEGF which is vascular endothelial growth factor and fibroblast growth factor which is FGF 2 These interact with receptors on endothelial cells of the nearby blood vessels and stimulate the cells to divide Leading to branching an extension of the existing capillaries so what we were looking at earlier was the tumor is quite far away from the blood vessels so it secretes these factors which can go and stimulate The process known as angiogenesis where branching and extension of capillaries can occur.

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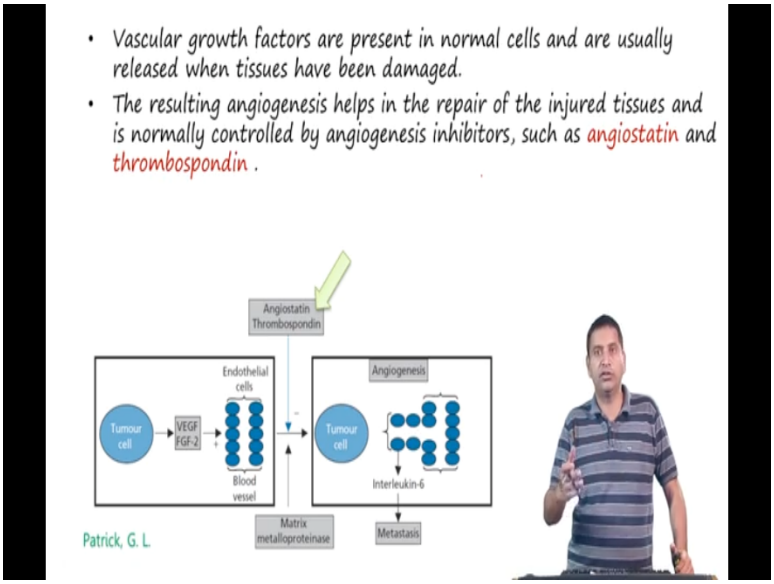

So these vascular growth factors are present in the normal cells and usually released when tissues have been damaged So the resulting angiogenesis helps in repair of the injured tissues and is normally controlled by angiogenesis inhibitors such as angiostatin and thrombospondin so during injury these become important in order for the body to repair itself and after that this suppresser such as angiostatin and thrombospondin suppress the angiogenesis and everything becomes normal.

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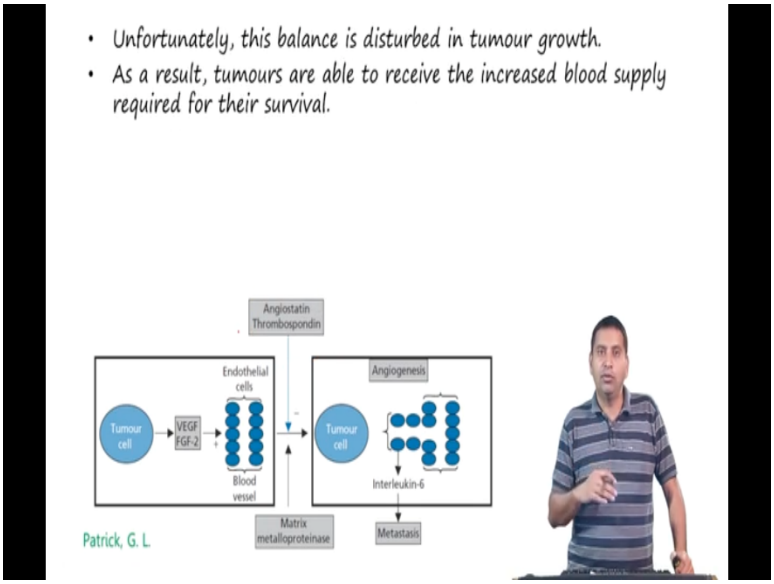

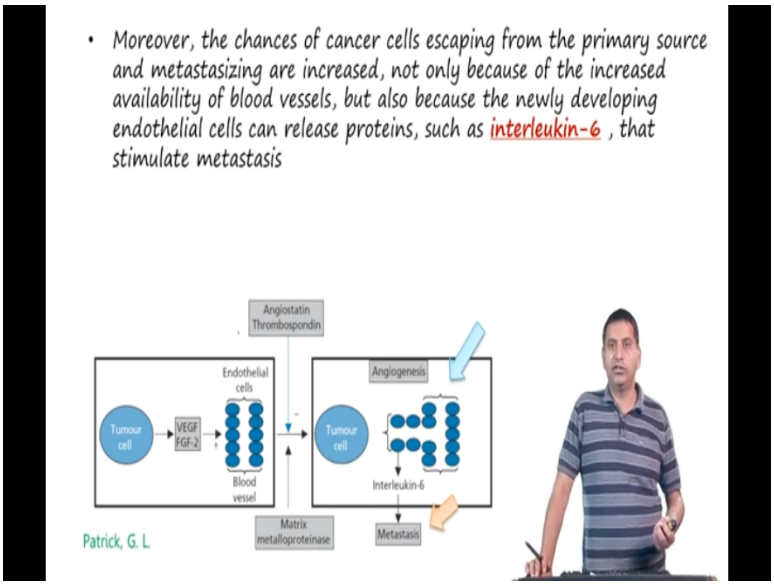

However this balance is quite alright in the case of tumors as a result the tumors was able to receive the increased blood supply required for the survival so the chances of cancer cells escaping from the primary source of metastasizing are also increased not only because of the increased availability of blood vessels but also because of newly developing endothelial cells can release proteins such as interleukin six that stimulate metastasis.

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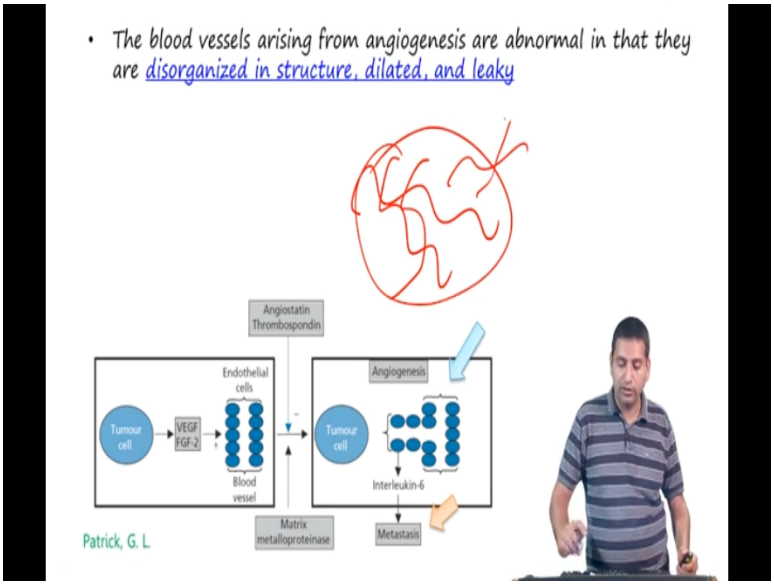

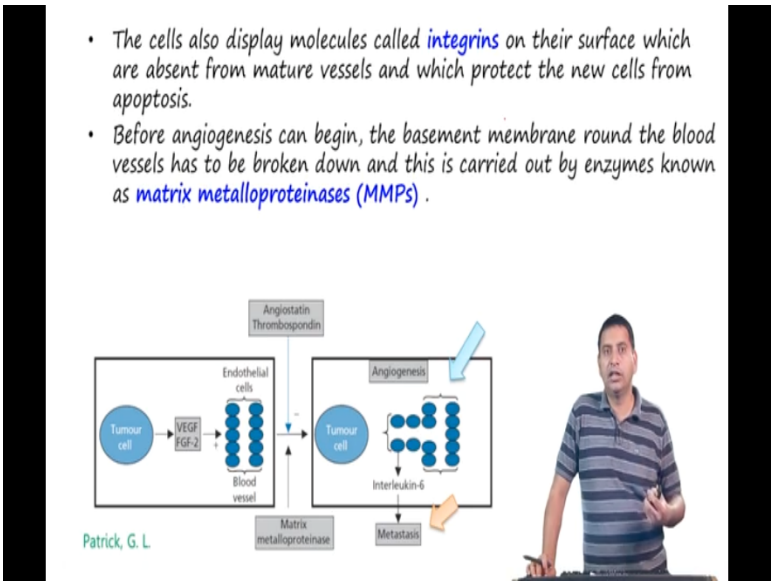

So the blood vessel arising from angiogenesis are abnormal ok and they're quite of sort of disorganized in nature and they're quite leaky ok So these cells also display Molecule known as integrin's ok this integrin's appear on the surface off of the cells and that absent from mature vessels which protect the new cells from apoptosis So before angiogenesis can begin the basement membrane round the vessels has to be broken and this is done by enzymes known as matrix metalloproteinase or MMPs.

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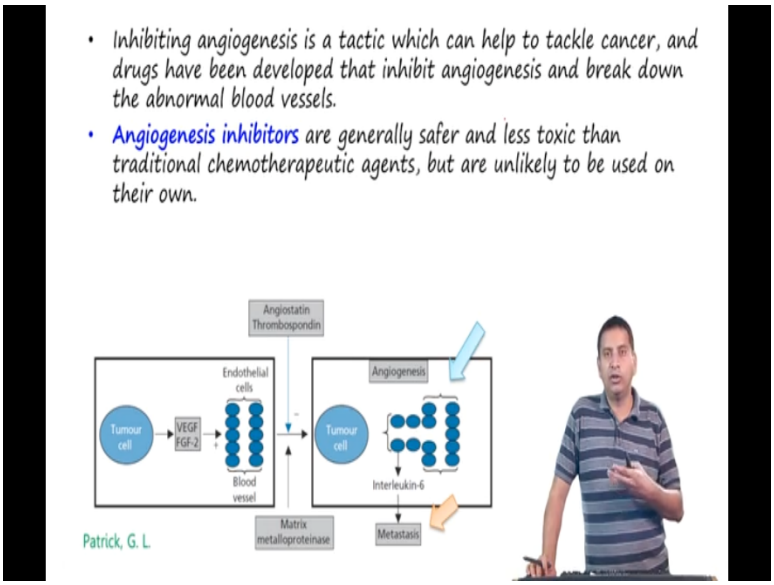

So interpreting angiogenesis is a tactic which can be used to tackle cancers and there have been drugs that have been developed that inhibit angiogenesis that break down these abnormal blood

vessels So angiogenesis inhibitors in generally are much safer and less toxic than traditional cytotoxic agents which are used in the clinic ok but these cannot work on their own because what they would lead to suppress certain kinds off of some certain parts of the tumor will not go but you can give it all along with a traditional cytotoxic agents to completely killed the tumor ok.

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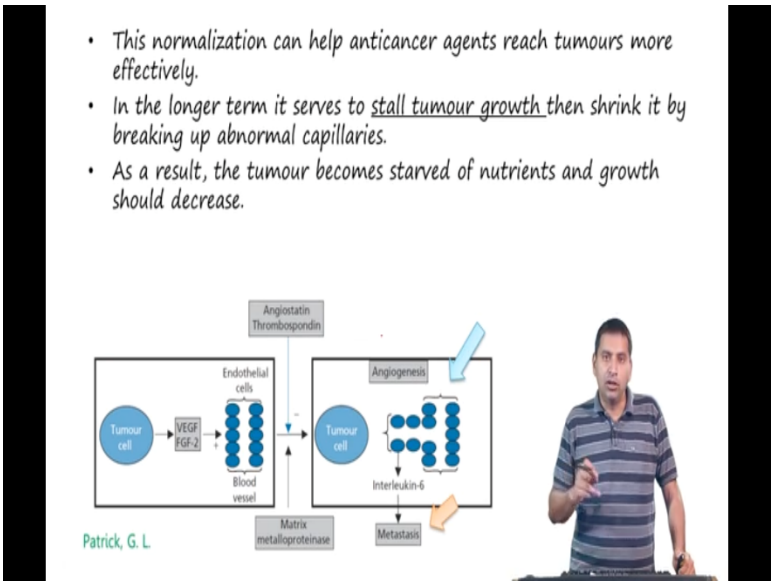

So this normalization can help anticancer agents reach tumor more effectively In the longer term it serves to stall tumor growth then shrink it by breaking down abnormal capillaries so as a result the tumor becomes starved of nutrients and growth should decrease so these are some of the advantages off inhibits angiogenesis.

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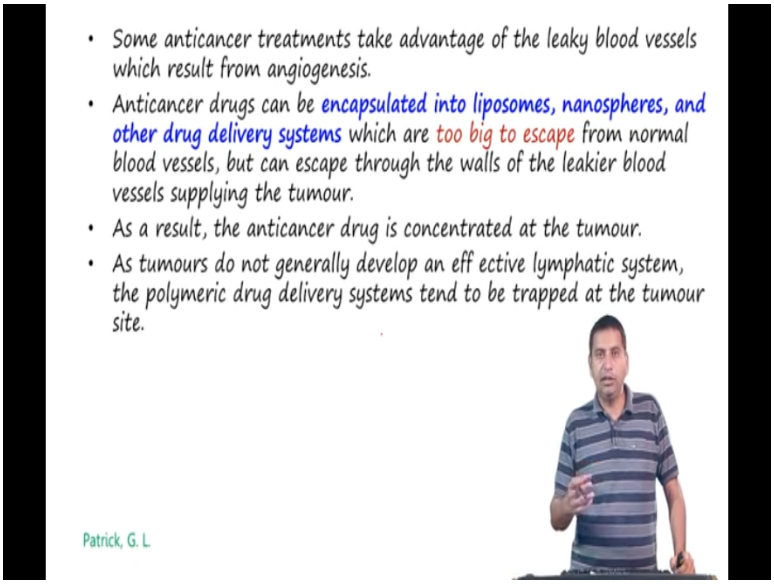

So some anticancer treatments take advantage of the leaky blood vessels which resulted from angiogenesis so sins of the tumors quite disorganized there are a number of leaky blood vessels in this So what we can do is we can encapsulate these cancer drugs into what are known as liposome Nano materials or drug delivery systems Which are too big to escape from normal blood vessels ok but they can actually escape from these leaky vasculature that is presented in tumors So the anticancer drug is actually considered at the tumor As a tumor do not generally develops effective lymphatic system where an you know this is kicked out this polymer drug delivery systems tend to be trapped at the tumor site.

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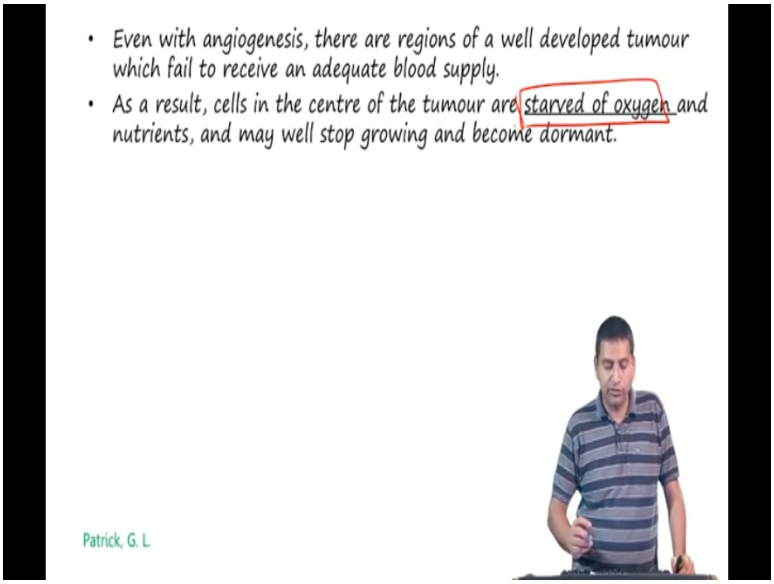

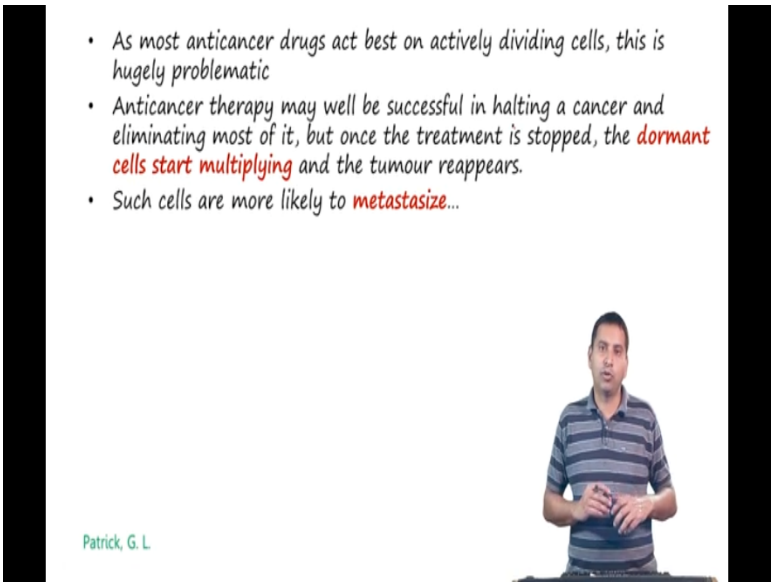

So even with angiogenesis there are regions off well develop tumor which failed to receive an adequate blood supply And as we discussed earlier these are known hypoxic regions ok so as most anticancer agents act best on actively dividing cells this becomes a huge problem So anticancer therapy will be successful in Halting a cancer and eliminating most of it but once the treatment is stopped the cells which are in the center dormant they can start multiplying and the tumor reappears The problem with these kind of cells is there are more likely to metastasis.

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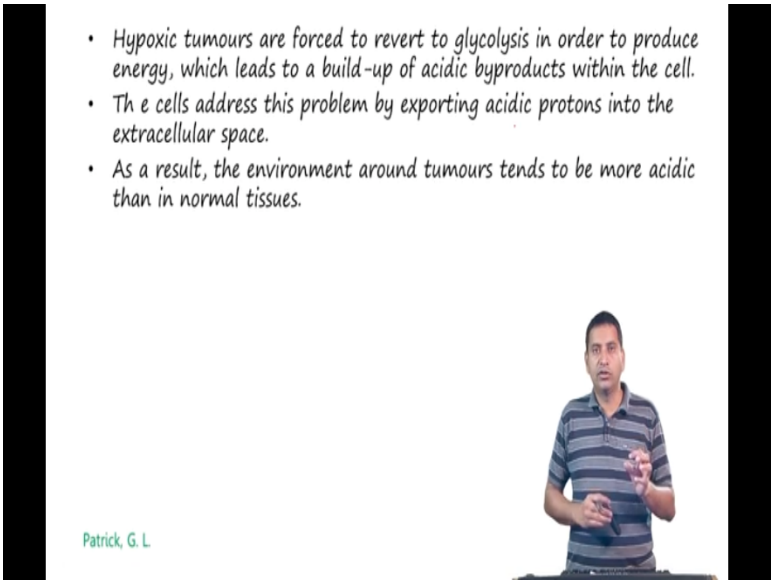

So hypoxic tumors are In order to survive we'll have to revert to anaerobic respirations which is glycolysis and this results in large buildup of acidic byproducts The cell addresses this problem by exporting acidic protons into the extracellular space so ones there is a lot of acid that is present so it exports though H plus ok so because of this the tumor environment tends to be more acidic than normal tissues.

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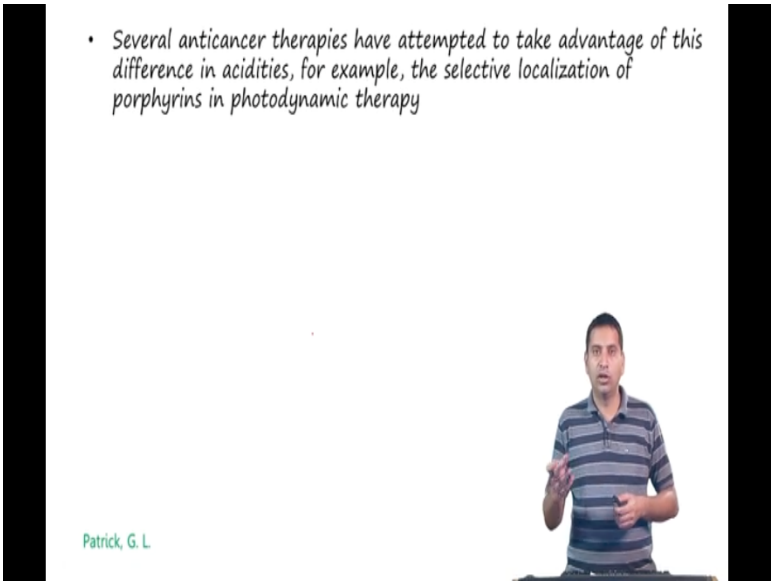

So number of anticancer therapies have attempted to take advantage of this difference of PH so for example one could think about selective localization of porphyrins which we have discussed previously in photodynamic therapy.

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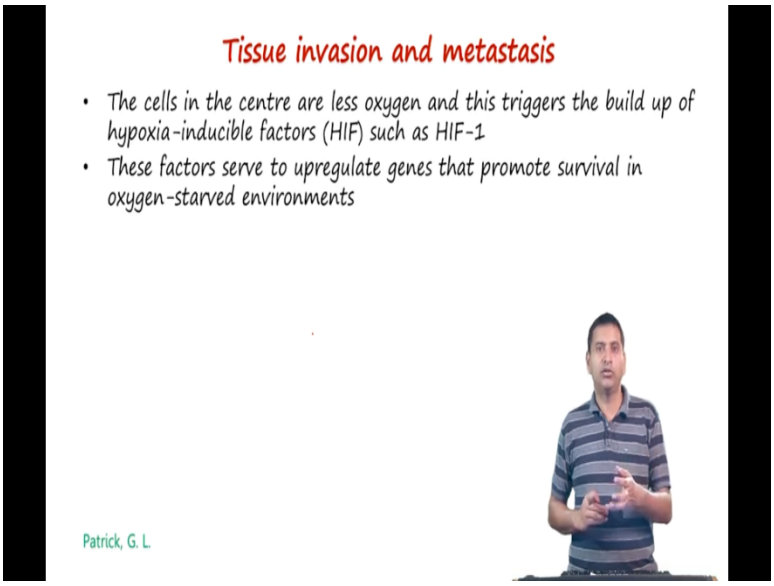

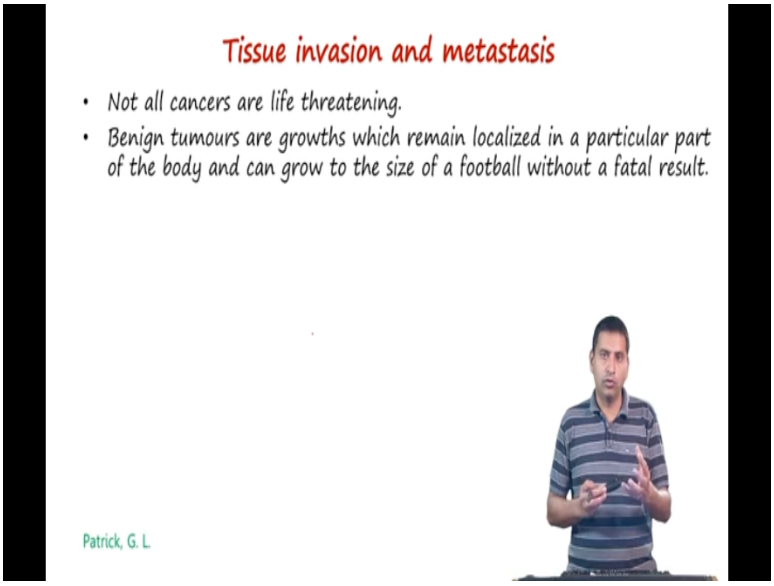

The next concept that we've look at tissues invasion and metastasis so like we discussed earlier there's a large buildup of hypoxia inducible factor in oxygen starved environments so of course not all cancers are life threatening so there are a number of benign tumors which got highly localized and they can grow to the size of a football without any fertility.

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But malignant cancers on the other hand are life threatening Because the cells have the ability to break away from the primary tumors invade a blood vessel or lymphatic vessels travel through the body and set up tumors elsewhere in the body.

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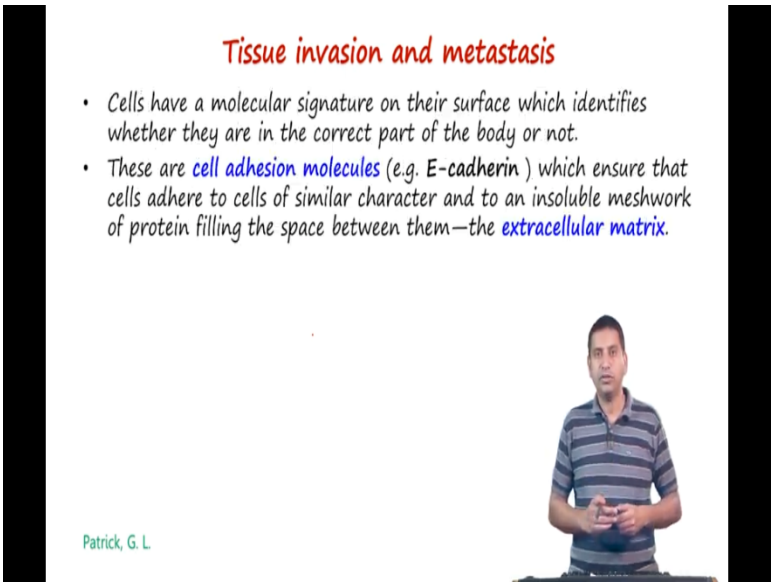

So in this process there's a number of changes on number of cellular processes that need to occur So cells have a molecules signature on a surface which identifies whether they are correct part of the body or not so like we discussed earlier muscles cells if it is escapes and gets to another part of the body then the immune system is able to recognize it so these are there are molecules

known as cell adhesion molecules or E cadherin which ensure this to occur so these help in of cells adhering to the cells similar characters ok and the foreman insoluble meshwork of protein filling the space between them known as the extracellular matrix.

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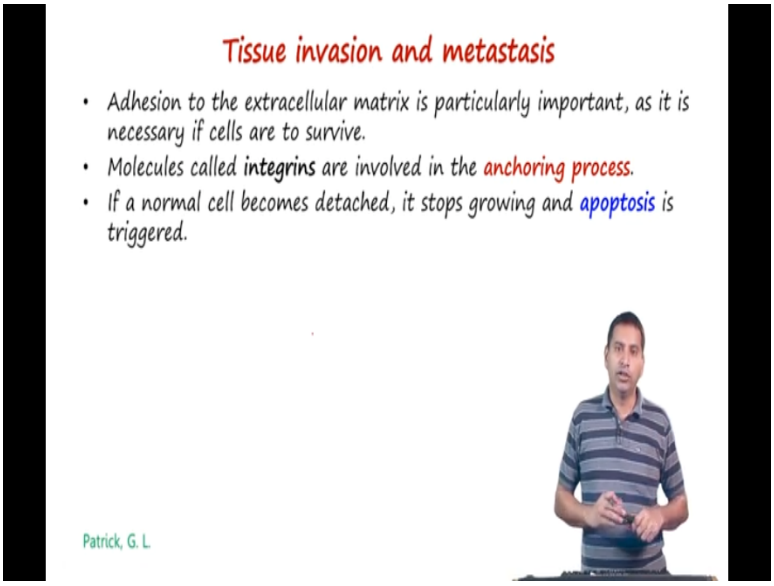

So this is true for epithelial cells that is the ones lining the gut lung etc so adhesion of the extracellular matrix is particularly important because it is a necessity if the has to cell survive so here there are molecules known as integrin's are involved in anchoring process so you have here is the cells which are anchored to a surface and then there is intricate mesh off E cadherin is form and then there is a molecules known as integrin's which are involved in the anchoring process

See for normal cell becomes detached but this let's say this is the It becomes detached so here is your other cell so this is the detached cell right Now because if the normal cell becomes detached it stops growing And after some times this of apoptosis a triggered.

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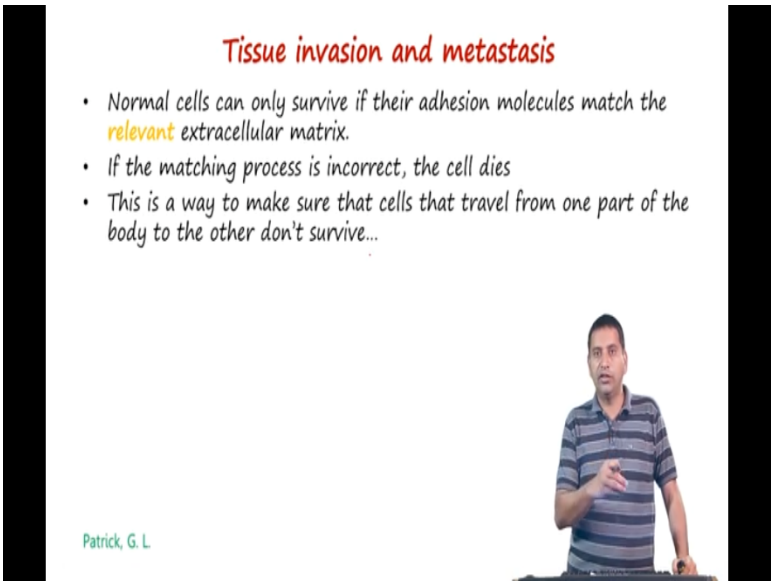

So this is because the normal cell can survive only if their adhesion molecules match the extra cellular relevant molecules so here your cell surface I mean your tissue surface area cells and so unless there is a matching of these two it doesn't survive so therefore if the matching process becomes incorrect it triggered apoptosis and the cell dies So this is one of the ways in which our body and shows that there is a no transfer of inappropriate cells across the body.

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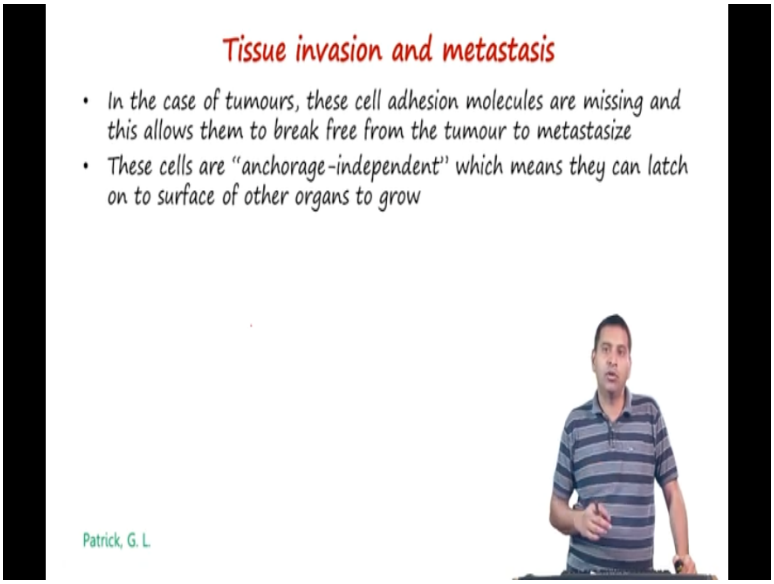

So the case of tumors these cell adhesion molecules are missing and so this allows for them to break free from the tumor and metastasis So these cells are called us anchorage independent cells so here is one type of anchor And here is another type of anchor So the tumor can attach itself here it can metastasis and attach itself here So therefore these tumors become anchorage independent and that this allows for this the tumor to grow and this is the process of metastasis where in the tumor starts to spread.

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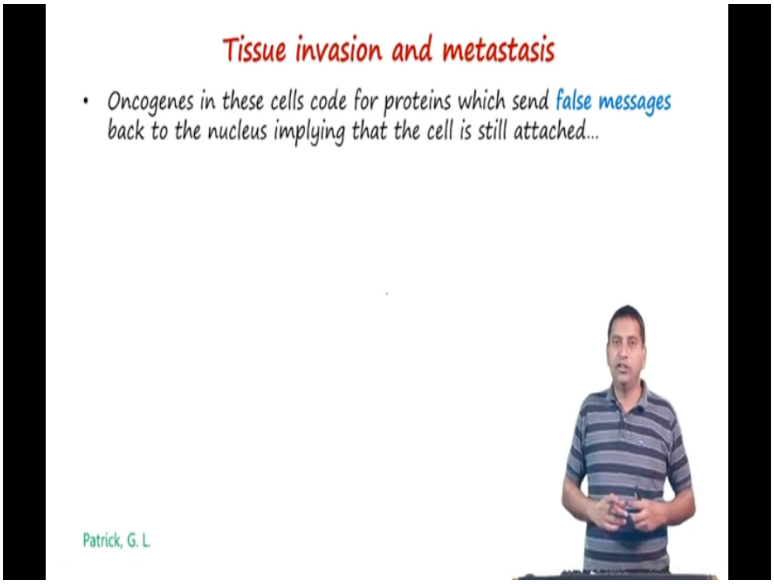

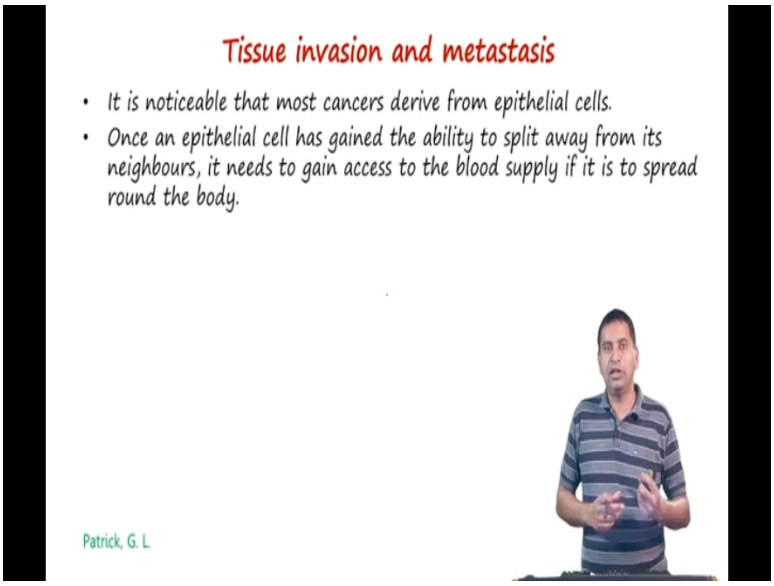

So oncogenes which are present in the cells or which code for proteins which send what are known as false messages back to the nucleus implying that the cell is detached ok So it is noticeable that most cancers derive from epithelial cells so once the epithelial cells gain the ability to split away from its neighbors it needs to gain access to the blood supply if it is to spread round the body.

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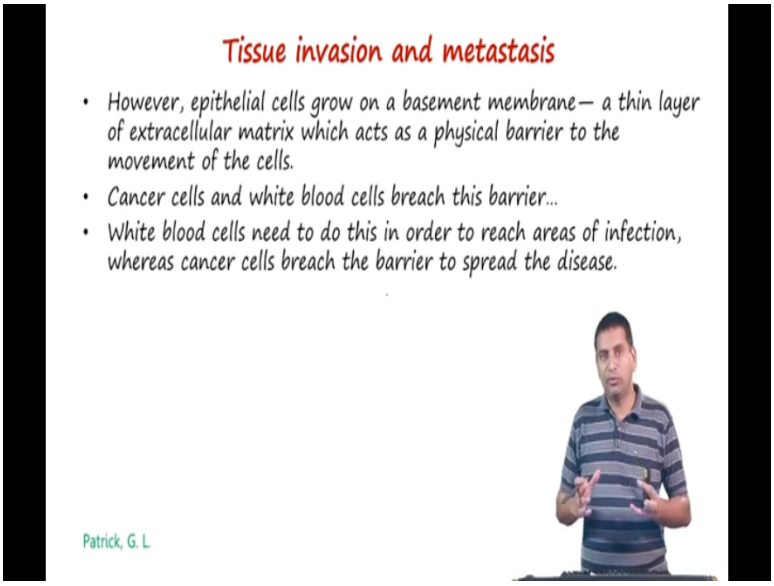

However epithelial cells grow on a basement membrane that is a thin layer of a extracellular matrix which acts as a physical barrier to the movement of the cells so there are only two types of cells which can breach the physical barrier one is cancer cells and the other one is white blood

cells So white blood cells are needed I mean white blood cells need to breach the barrier because they can be reached the area of the infections and address it whereas when cancer cells breach his barrier they spread the disease.

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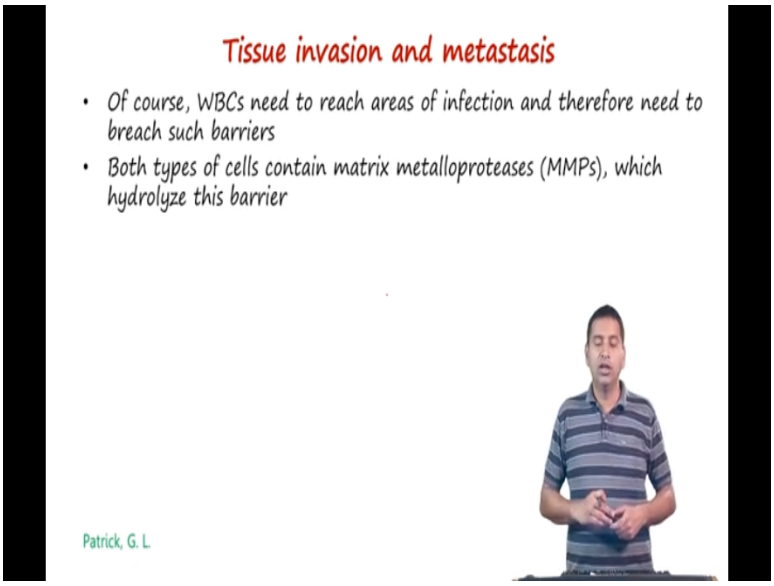

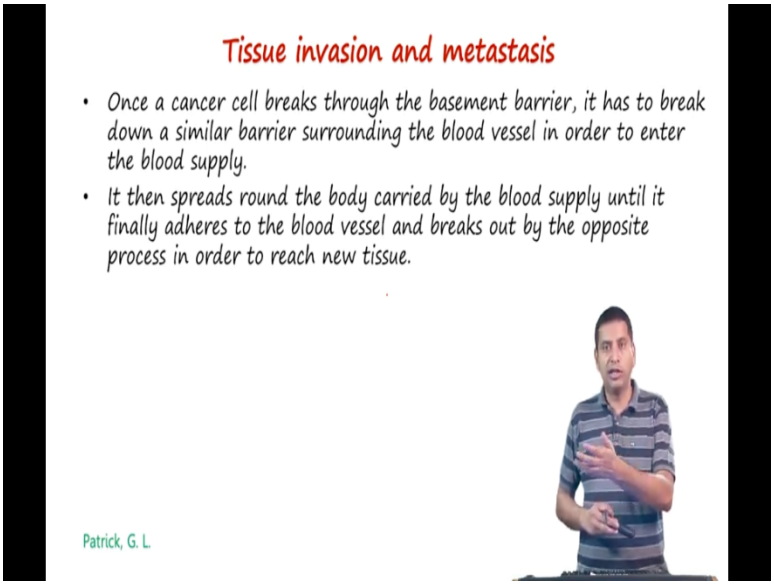

So both of these required the use of matrix metalloproteases which we have discussed previously so these matrix metalloproteases which will help with hydrolyze of this barrier So once the cancer cell breaks through the basement barrier it has to break down a similar barrier surrounding the blood vessel in order to enter to the blood supply so for a cancer which it has to

cross the epithelial layer and then there is a blood vessel that it has to cross the bridge and then it has to metastasis.

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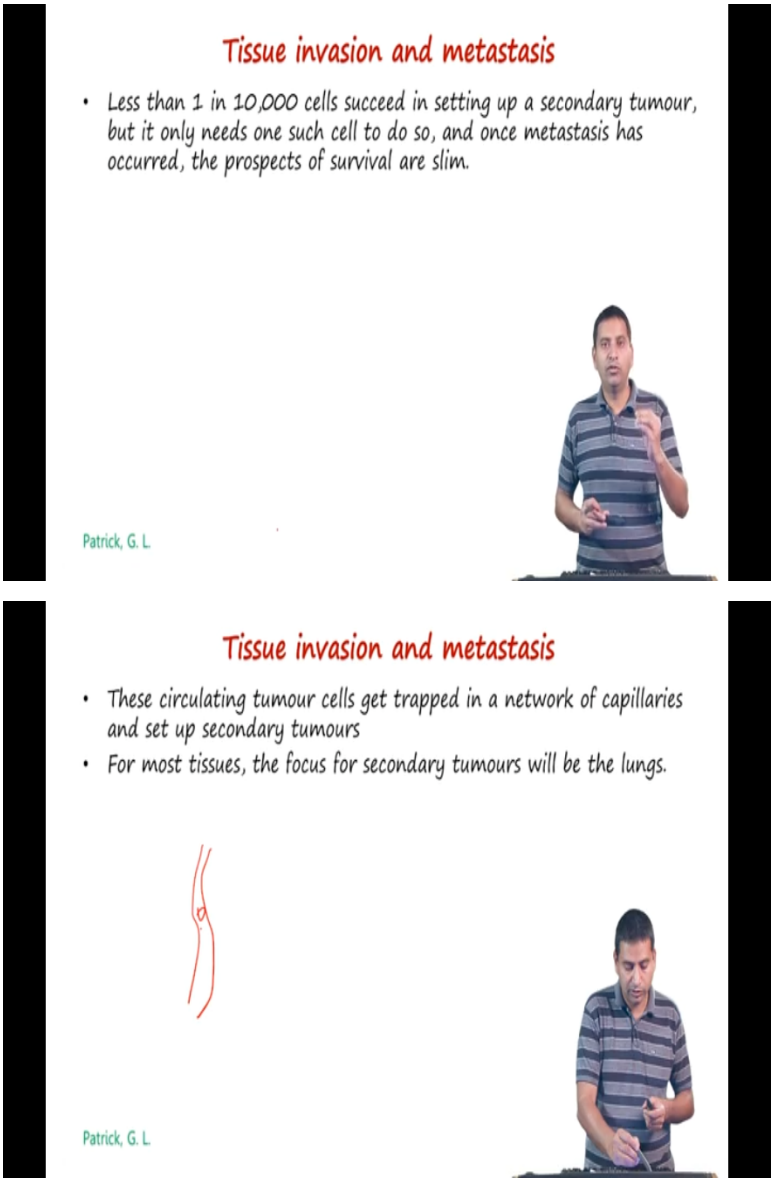

So statistically less than one in 10000 cell succeed in setting up a secondary tumor But the problem is all we need is one cell to do this and so then metastasis as a occur so this circulating tumor get trapped in a network of capillaries and then set up secondary tumor so here is your blood supply which your tumor is Going and then what happens is that there is a network of capillaries and here once it gets to a network of capillaries it lodges it's self-there and then started

growing and starts making a secondary tumor and for many of these the lungs turn out to be the focus for secondly tumor.

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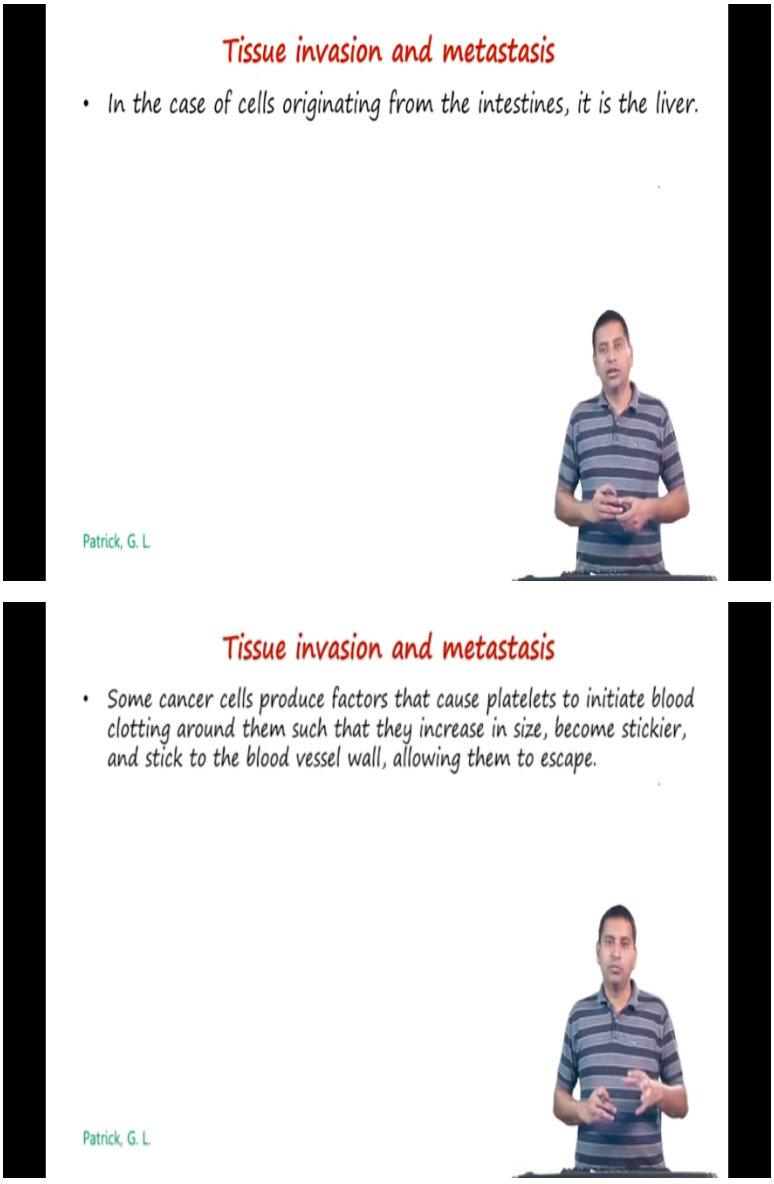

So in the case of cells originating from the intestine it is the liver Some cancers produce factor that cause platelets to initiate blood clotting around them such that they increase in size become sticker and stick to the blood vessels wall which allows them to escape.