Introduction to Biomaterials

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Module No. # 01

Lecture No. # 06

Cell Communication-II

Now, processing a signal, now, these processing a signal... I think, I will explain to you more with a... yeah. What you see here?

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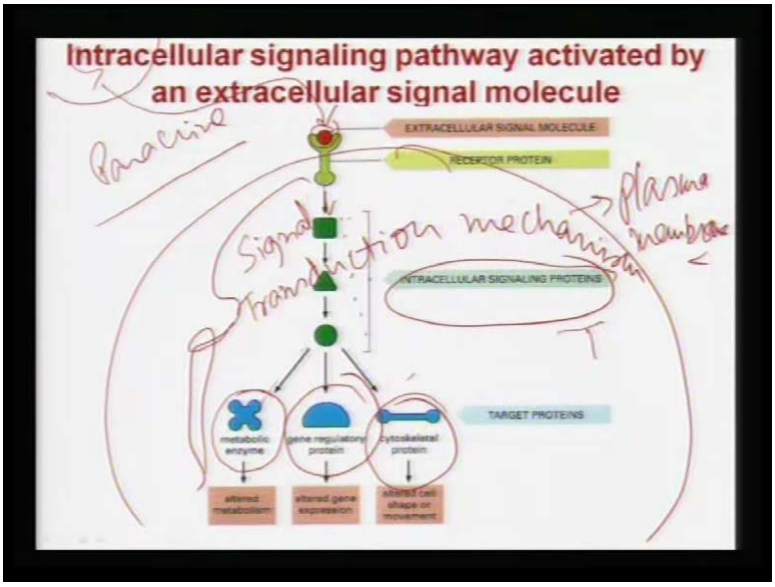

So, this is a part of a one cell, one eukaryotic cell. And, this is your target cell. Your source cell may be somewhere here. And, that is the soluble signal and these signal molecules, which is red, here. So, these signal molecules, it is coming to the target cell. Source to target cell, it is coming by molecular diffusion means, what kind of signaling it is? It is called paracrine signals. Clear. Autocrine means same cell. Paracrine means, true extracellular matrix and Endocrine means through blood stream. Right; Auto, Para, Endo.

Now, this is a paracrine signal it comes. Now, it is actually being attached to the receptor protein. So, these receptor proteins means, the (( )) receptor…, the proteins which had exposed to the extracellular space, while being attached to your plasma membrane, that is, your cell plasma membrane. So, this is your receptor protein. Now, once this is activated, now, the (( )) what will happen? This will activate, so, entire this one is known as the Signal Transduction mechanism. So, Signal Transduction mechanism means once the receptor proteins are activated in the target cell, what will happen? They will activate a few other Intracellular signaling proteins. And, this few other Intracellular signaling proteins, if you see here, this proteins they are identified or they are designated in different symbols, like one is square, one is triangle, one is circular. That means different shape. Different shape means; they are essentially different type of proteins.

Now, this different Intracellular signaling proteins, they are being activated. Now, the net result is that, that they can ultimately act on the target protein. And this target proteins can essentially, modify the metabolic activity of the proteins. Metabolic activity means simply, lot of protein molecules will be synthesized of the ribosome. Gene regulated protein means, that it will activate the DNA and RNA in the cell. And, that will lead to the more cell division process. Cytoskeleton protein means, your cytoskeleton is the acting filament is there, so, it will help in the in the depolymerization and repolymerization acting filament. So, that cell can migrate or cells can crawl over the substrain. So, what I am trying to say here that, one extracellular signal molecule, ones it activates that Intracellular signaling proteins, it can have a large number of activities. It can enhance the protein synthesis process, it can enhance the gene regulated protein and it can enhance the cytoskeleton protein.

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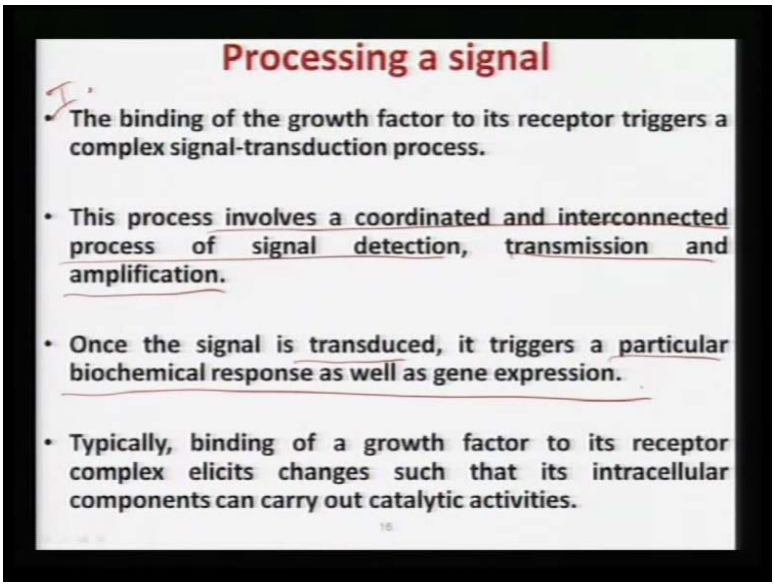

So now, if I go back to the slides, this is what is being mentioned, have Processing a signal, then all this points would be very clear to you. The point number 1 is that, if the binding of the growth factor to its receptor triggers a complex signal-transduction process, now, this has been mentioned in a very simple manner. But, I will show it later that, how complex this signal Transduction mechanism can happen. Second one is, the process involves a Co-ordinated and interconnected process of signal detection, transmission and amplification.

Now, what is called detection? That means, the cells at detecting a particular signal, it is just like your mobile. Your mobile, if you are in the far of place, it cannot detect a signal. So, therefore, you cannot communicate to another person. So, simply, you can understand that a cell is trying to send signals to another cell, the see the target cell is not able to dictate that signals. Transmission means that, how the signal is going internalized in the cell that is transmission. Amplification means what amplification means? Suppose, your target cell signal molecule concentration is very low then, you are activating some Intracellular signaling complex which will amplify; that means, which will, actually increase the concentration of these signal molecules which are coming inside. So, these amplification proteins, this amplification is also important.

Now, once the signal is transduced, it triggers a particular biochemical response as well as gene expression. So, that means this signal transduction, actually triggers a particular

biochemical response as well as gene expression. And typically, binding of a growth factor to its receptor elicits changes, such that, its Intracellular components can carry out catalytic activities.

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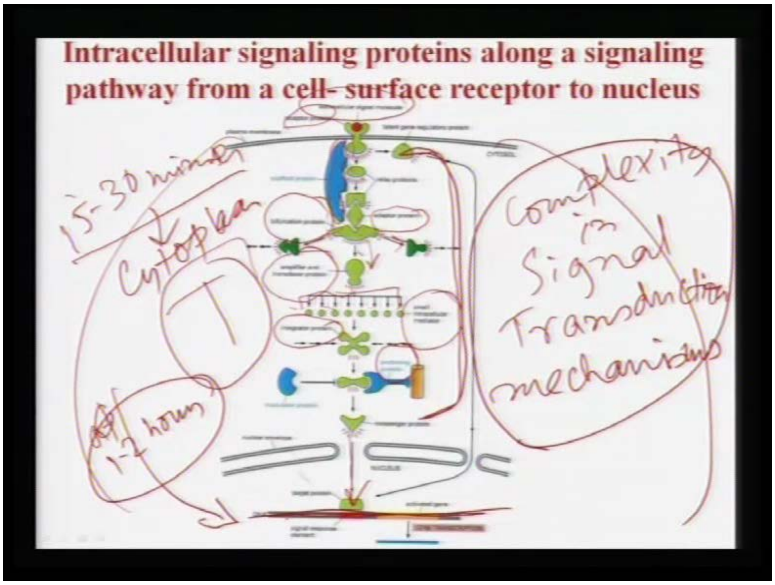

Now, those scenes, I will explain to you in a small type. Now, this particular slide actually shows you, how complex can be. What I am writing here, complexity in Signal Transduction mechanism.

So, this is that, complexity in the signal Transduction mechanism means like you have these extracellular signal molecules, which is red balls here, it will come and interact with a receptor protein from your target cell. This is your target cell. So, this is your target cell. Now, once this signal comes then, that will in turn, actually activate a large number of protein molecules in the path. And, these protein molecules, they are like part of a one large scaffold protein. So like, they are called relay protein. Relay protein means you have, you remember the relay race, on the ground right; that means and you transfer your button to your friend. Who will run again, transfer the button to another person, who will run, further.

So, like relay race, here also, inside the cells, different protein molecules can act as relay proteins. Like, they will simply transfer the common signals or communication to another protein and then, there is an adapted protein. Adapted protein means this protein,

which will adapt. Then, here comes your bifurcation protein. The way, this proteins are named actually, you can understand what the function is, that these proteins play a role. Bifurcation protein means, whatever signal molecules that are generated here, it simply bifurcates to 2 or 3 bifurcation protein. Then; it comes to the amplifier and Transduction protein. As I said earlier, amplification means it increases the concentration of the signaling molecules. So, as you see, those amplification proteins, from that there are 5, 6, 7, small Intracellular mediators that are build. That is generated. All this Intracellular mediators, they can again come with the help of an integrated protein.

Integrated protein means the protein, which will integrate all the signals from 6, 7 integral extracellular mediator. They will come and they will GenCorp the protein. And, there is a modulated protein that finally, the messenger protein, will quote inside and that will change the gene expression level. So, these type of things, it can take place in few minutes, like 15-30 minutes. If this, has to change in the cytoplasm, but if it goes inside, then it takes 1-2 hours. You understood, what I am saying? What, I am saying, is that this entire cascade in Biological language, it is called Signaling cascade. This entire cascade, take place, if it is to change in the (( )) metabolic activity of the cells or cytoplasmic activity of the cytoplasm, then it takes 15-30 minutes. But, if it has to change the gene expression, then it takes 1-2 hours. And, this entire slide essentially, it (( )) shows you that, how complex these cells signaling process can be, in general. So, this is that another factor of the Intracellular signaling complexes.

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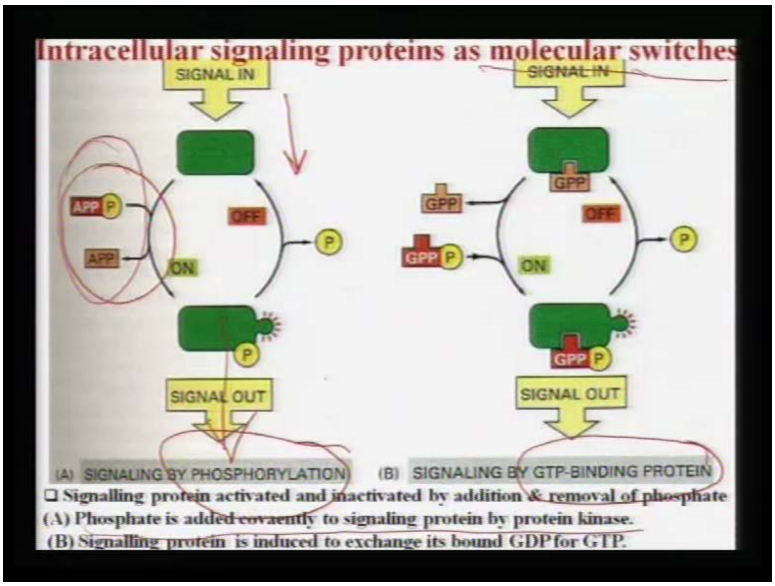

Now, before, I…. These Intracellular signaling processes essentially, act like a molecular switches. So, let me, first tell you that, what are molecular switches? Why it is called molecular switches? Because this is essentially, mediated (( )) protein molecules or growth factors, which are Biological molecules. So, that is why, it is called as molecular. Switches means what, it is like electrical switches. You switch ON; that means lights will be ON. In switch OFF; that means lights will be OFF.

So, similarly, you switch ON the fan and switch OFF the fan. So, what it shows here, once the signal in; that means the signal comes in then, there is a particular process, that activates, like, Phosphate is added covalently to a signaling protein to a protein kinatase and signaling proteins induce to exchange its boundary to GDP to GTP. So, signaling by the GTP binding protein and signaling by Phosphorylation. So, this is just examples.

So, what you have to understand here, that unless it receives the signal, this APP (P) to APP, that reaction cannot take place. So, this is ON and ones this is OFF; that means it goes back to its original position. Now, once it, when it is OFF, then the signal will get out of the cell. So, that time, this reaction cannot take place.

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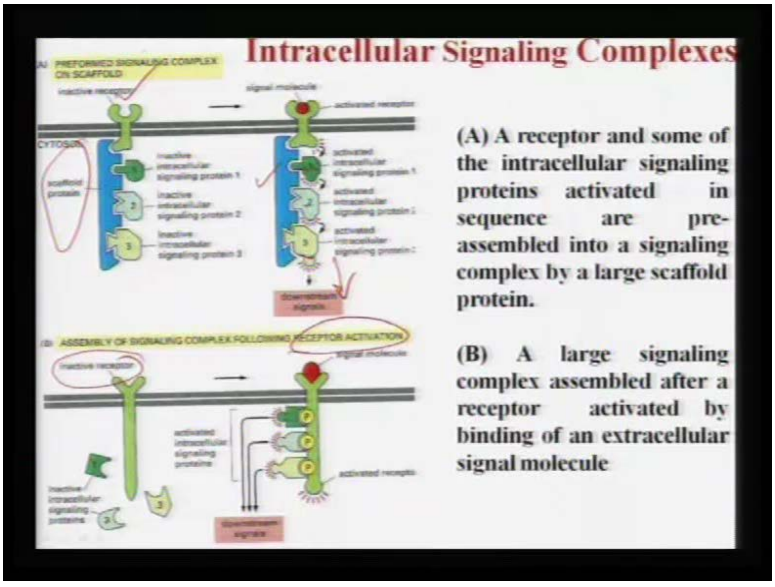

So, similar molecular switches activity that has been mentioned here, you see. So, this is your large scaffold protein. Large scaffold protein you can consider the scaffold protein is that like, a base of like a large structure of the protein molecule, where the smaller

Intercellular Signaling molecules like 1, 2, 3, can be attached to that. This is the smaller signaling molecules. Now, this is your inactive receptor. Once, the signal molecules come, then, this becomes activated. Activated means now, switch is ON.

Now, once the switch is ON, then it will also, activate this scaffold protein and as a result, this 1, 2, 3, this 3 protein molecules, they become activated and subsequently this downstream signals also, will be activated. So, this is called intracellular signaling complexes. Now, B is that assembly of signaling complexes following receptor activation. That is, you have the inactive receptor, your signal molecule comes here, your 1, 2, 3, and these are 3 different signaling proteins. Now, here, you can see that these signaling proteins are activated here because of the molecular switches and again large number of intracellular signaling pathways can be generated.

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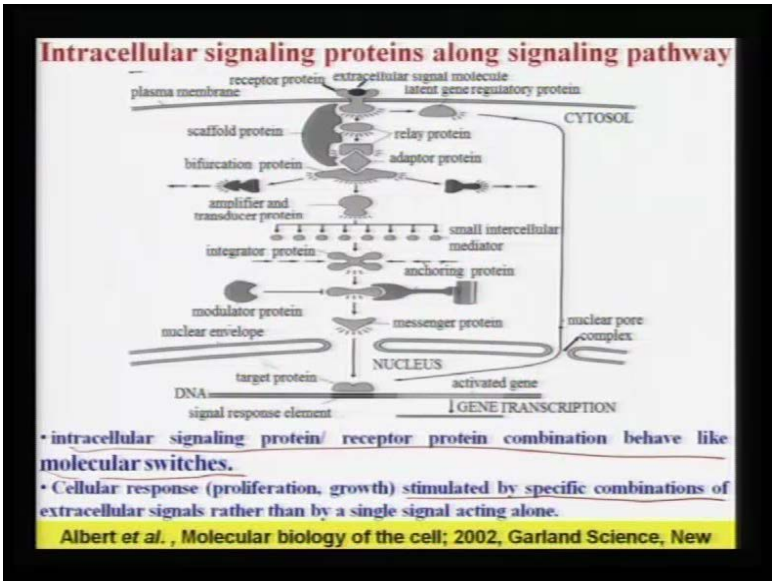

This is what; I have already mentioned to you earlier, that you have the Intracellular signal molecules, protein receptors, and so on. And then, this is like Intracellular signaling protein, receptor protein combination behave, more like a molecular switches and cellular response like, proliferation growth that can be stimulated by a specific combinations of extracellular signals; rather than by single signal acting alone.

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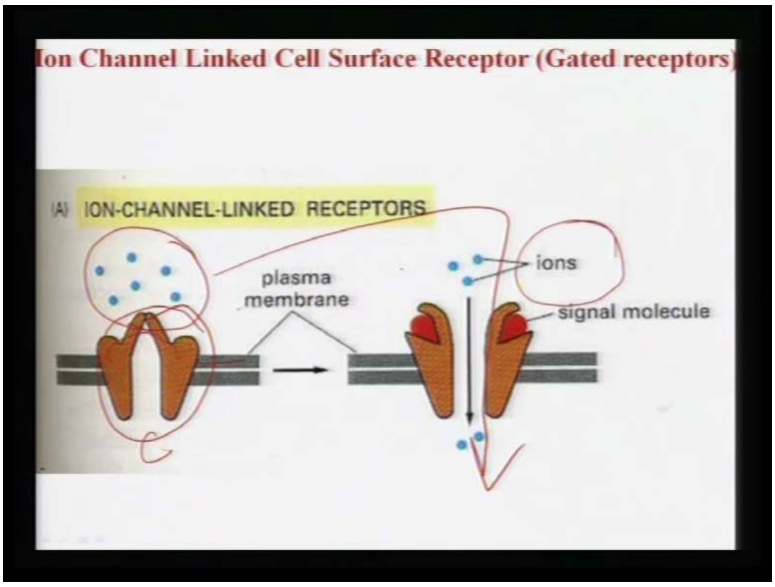

Now, what is the different ion channel, like ion Channel, Link Cells of Receptors? Now, this is a plasma membrane, this is your cell cytoplasm here, so, in the plasma membrane that, all the open is that, gates, this is like gates, like the typical house, your gates are closed; that means, nobody can enter. When the gates are open, people can enter. Similar situation, you can imagine on the cell surface plasma membrane also. When gates are closed then, small signal molecules here, which appear is blue. They cannot simply, enter the cell surface. Once, gates are open, then it can come and then it can go inside. But, for that, what is the primary criterion? That ion should be of smaller in size. So, that it can enter into the, through the gate of the plasma membrane.

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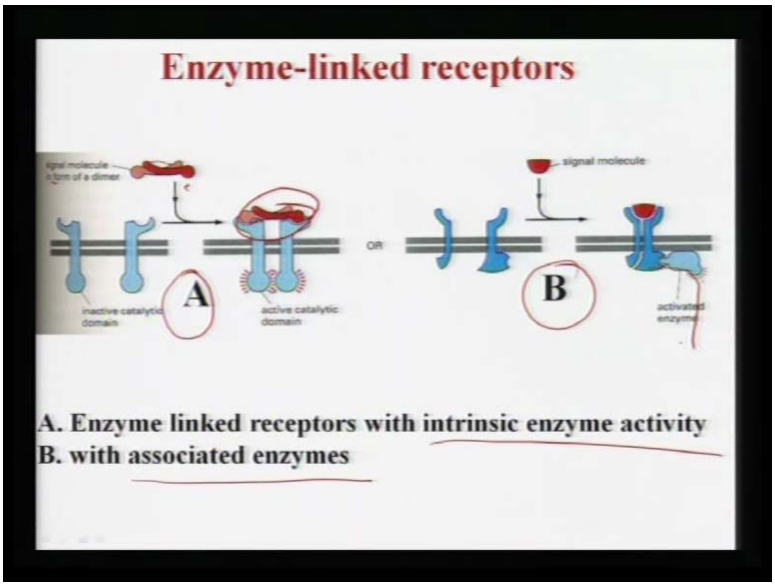

So, this is like, different things that has been mentioned here. Like Enzyme-linked receptor with intrinsic enzyme activity and associated enzyme. What it means here? That this is, signal molecule. It comes, it will be activating that cell surface receptor B is, that it will be activated and then, activated enzyme would take place and will take carry out the further ((...))

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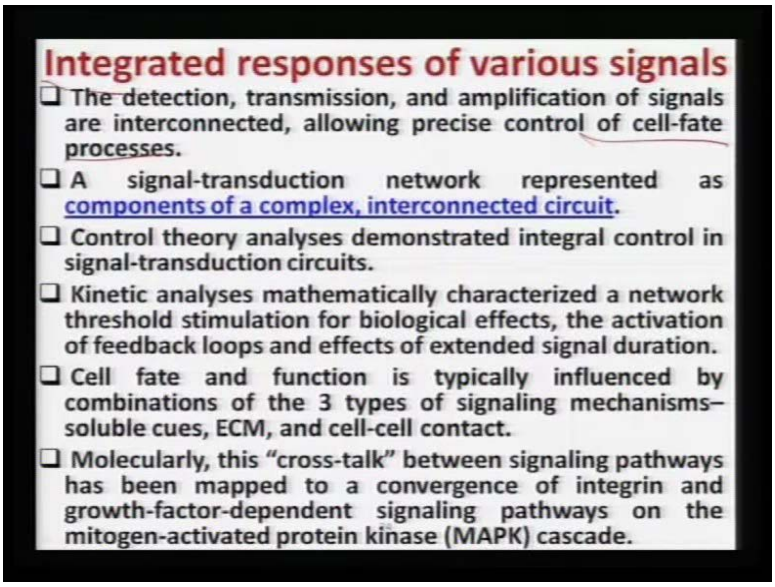

Coming to, the integrated response of various signals, now, detection transmission and amplification of signals are interconnected. And, that allows the precise control of cell-fate processes. What it means by integrated response?

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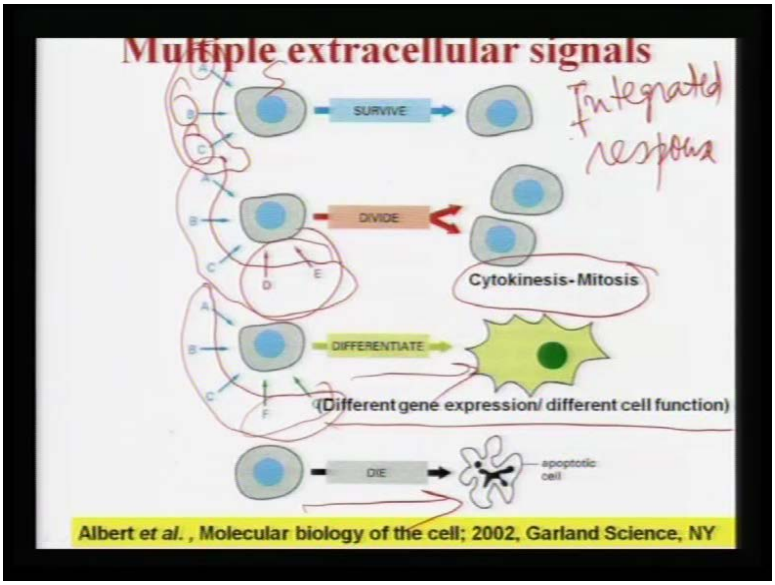

So, Integrated response means; For example, for any type of processes, whether cell wants to survive or cell wants to undergo division or cell wants to differentiate or cell will die. For all these cell-fate processes, this is part of the Tissue homeostasis. Now, one has to understand, that each of these performances or each of these functions requires, not one signals, but multiple signals. That, A, B, C means, what A, B, C means? That your source signals, source cell here, are receiving, at any point of time A, B, C 3 different signals. Now, 3 different signals in combination will be integrated and that will be able to, and that will tell the cell to survive. That means their normal protein synthesis processes are in your mitochondria, all this energy that is produced in a surviving life cell that will be on, that process will be on. So, when you see, that in a culture medium is, cell is live or a cell is surviving. You have to understand that, that particular cell is at any point of time, getting a number of signal molecules from external source. External source means it is a cellular matrix. If, at any point of time, the cell is not getting any signal A, B, C then, what will happen? Cells will die; that means cells cannot survive. And, cell death essentially means, that can be actually useful, for that can take place either by a necrosis or by a (( )) process like.

Second thing is that if a cell is now surviving in a medium or in a particular substrate, now, if a cell wants to divide, then A, B, C signal is not sufficient. You require some other signals, which are.., which has been designated here D, E. Now these, two signals is essentially, will allow the cells to undergo cytokinesis and mitosis process. That is, the cell growth process. Third one is, that now, you have the A, B, C signal and then, you have the F and G, this is like, different other signals. Now, A, B, C and F, G that will help the cells to differentiate. Differentiation means different gene expression or different cell function. Ok.

So, this actually requires, you need to have more signals. So, cell differentiation process essentially, is the result of the integration of A, B, C and F, G signals. Cell division is the result of the integration of the (( )), of the different, with different signals molecules like A, B, C and D, E. Cell survival is the process of the integration of the A, B, C; three different cell signals. You understand.

So, therefore, I repeat any.., this is called integrated response. Integrated response means any activity, any cellular activity, be itself survival, be division, be differentiation, requires the action of the multiple signals. And, if that is, proper integration takes place inside the signal, inside the target cell then, what will happen? Then, this is your target cell here, so, then, certain activity will be promoted. be itself survival; be its differentiation etc.;

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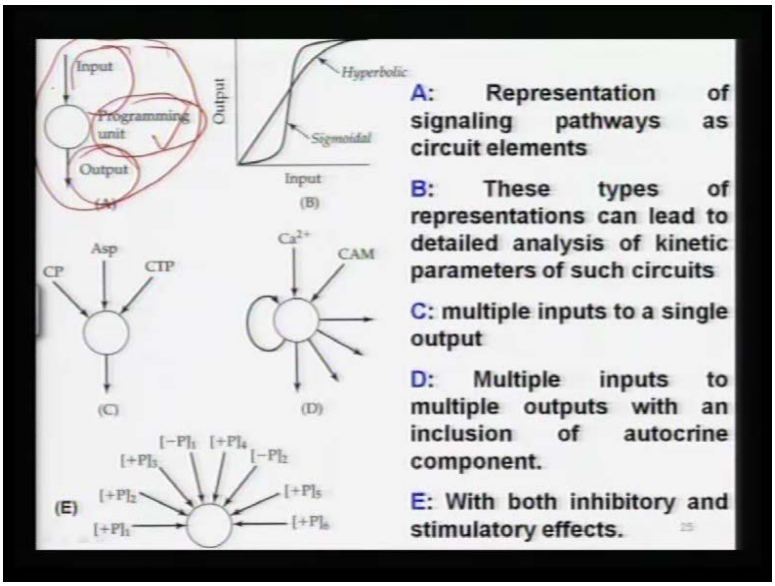

The cell signaling process, some people actually, describe it is like a computer programming process. Now, take that, take the example of any programming, let say, whether it is a FORTRAN, C, C ++, etc.; Then, what you require? You have to keep some input to the programming. Now, there is a programming unit that is the computer language, like software and then it will give some output. So, the output depends on the programming unit as well as the input.

So, similarly, in the cell signaling language, what you have? Your input is A, B, C signal; your programming unit here, is that cell signaling mechanism or pathways, which are activated here. Which are integrating the response of three different cell signal molecule, and your output is what? Your output is, whether it changes the gene expression or it changes the various other activities.

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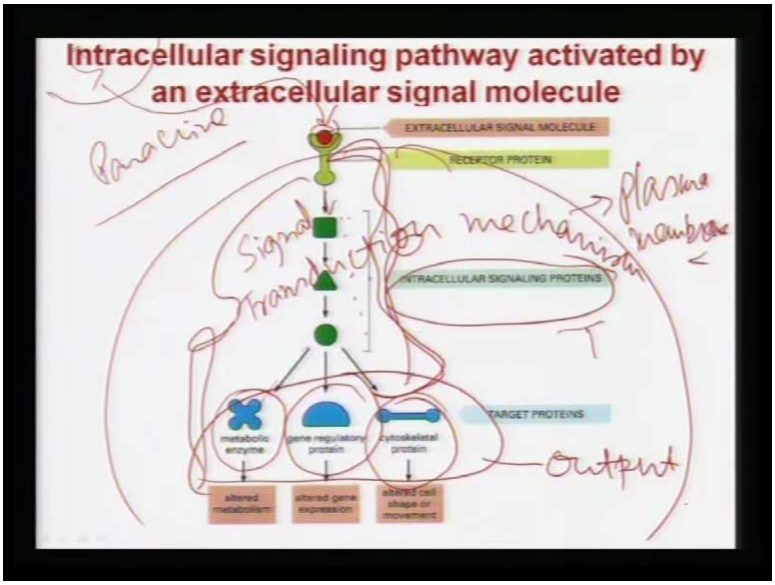

Let us go back here. So, let me, explain to you more clearly that what is meant by input, output and so on. So, here input is your extracellular signal molecule. What is the programming unit here? This is your programming unit, like how these signaling cascades are taking place. What is your output? Output is here, this one is your output. What is the net result of that? Whether it is changing the gene expression, whether it is changing the protein synthesis rate, whether it is changing the cytoskeleton protein, etc.; so, and these three is the output. Your internal this one, is yours.., Transduction

mechanism is your programming language and your input is the extracellular signaling molecules.

So, now, I hope that you understand that you know that, what is the meaning of this input, programming unit, output. So, all these details, things are actually not at this stage is important.

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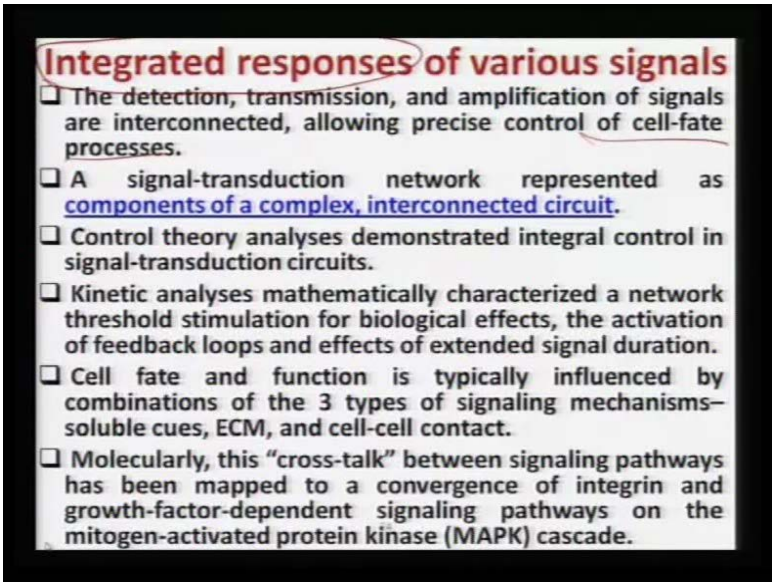

A signal ((...)). The other things, that you have to remember is, that a signal Transduction network is, represented as a components of a complex interconnected circuit. Complex interconnected circuit means, in Electrical engineering language, when you know that there is resistance capacitors assemble and so on. And, if the inter in the circuit is very complicated, like there are multiple of registers, multiple of capacitors, you can understand that similar thing also, takes place in the case, of the signaling also. Like you know, how this signaling takes place? It is more working like a complex interconnected network.

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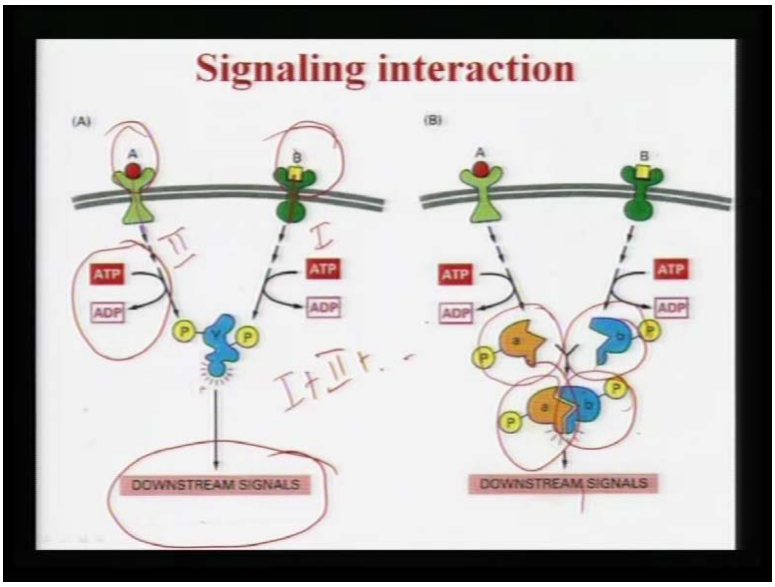

Like, some few slides are left; actually these are like, mostly about the Signaling interaction. So, signaling interaction means like, there are 2 types of signal molecules here A and B. Earlier, I have shown, you that you know a cell has to survive; that means cell has to get A, B, C three different signals. Right. So, what happens? That A signal molecule act different, like ATP to ADP. ATP stands for Adenosine Triphosphate. ADP stands for Adenosine Diphosphate. Now, ATP to ADP, there is a transformation here, transition here.

Now, similarly, B signal molecule, it comes and then, it also gets attached to another cell surface receptor. This receptors, they act more like a, you know that tongs or the scissors like a thing, like that will come and then simply, come and sit here, the signal molecule. And then, it will be activating the downstream signals here. Now, whatever signal, is transmitted through A or through B, they can be integrated and they can act as, more like a downstream signals. Similarly, here, if you see that signaling Transduction signaling interaction, here again ATP to ADP and ATP to ADP transformation. But, here what will happen? Is, that these signal molecule interaction A to B that is taking place, where some intermediate protein molecules here, A and B and they will come together and then, they will call the downstream signals. So, that means the signaling pathway. Pathway means how this individual signal molecule, will cause the signal Transduction process inside the signals. So, this is the pathway number I, this is the pathway number II. So, integration

means it can be either I plus II or it can be more than that. So, that means the net result, will be much stronger then, what you get? Individual signal. Ok.

For example, suppose, there is only one signal is there A and if you have two or three multiples in that, what will happen? A will actually transduce some signaling pathways here; B will transduce some signaling pathways here; C will also transduce some signaling pathways here. It may, so, happen that inside a cell this A, B, C, three pathways, they will come and they will integrate together. And, therefore, your action will be much stronger compare to the action of a..., only one type of signal that is signal A molecule. So, this is what, actually is about a, integration of the signal molecules.

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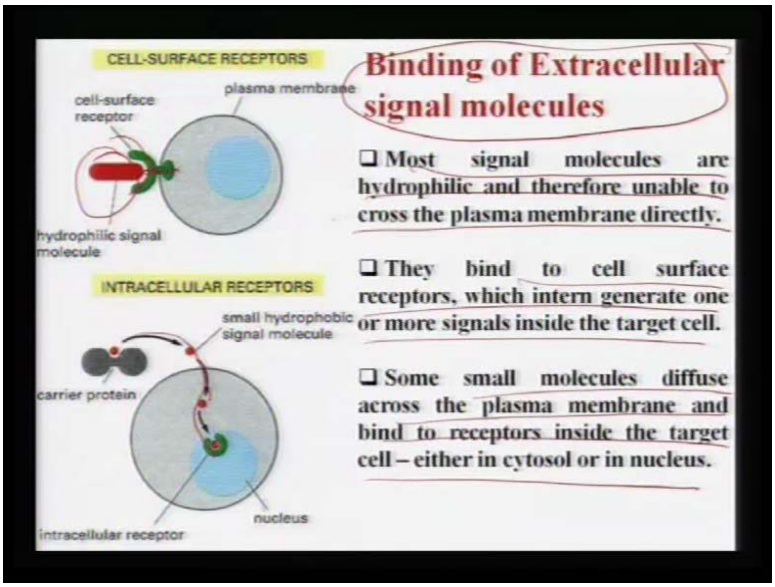

Now, coming to, the pointing of the Extracellular signal molecules, like, which will come by the soluble proteins. So, this is your hydrophobic, hydrophilic signal molecule. Now, hydrophilic signal molecule, that will come, that will get attached to the cell surface receptors. And, this is your plasma membrane and there is Intracellular receptors, like it will carry the protein and then, it is come and then, it goes to the nucleus.

Now, binding of the extracellular signal molecules means what? Most signal molecules, which are hydrophilic and therefore, unable to cross the plasma membrane directly. But, if it is hydrophobic and small molecules then, they can go inside the cells very easily. So, remember one thing, if your signal molecule is hydrophilic, then, they cannot simply get

inside, but they will activate the cell surface receptor. But, if your signal molecule is hydrophobic, then, that will coincide with the cells; they will inactivate the cell cytoplasm. Then, they bind to cell surface receptors, which in turn, actually generate one or more signals inside the target cells.

Now, some small molecules diffuse, across the plasma membrane and bind to receptors inside the target cell, either in cytosol or nucleus. Suppose, that is a carrier protein, there is a small signal molecule here.

Now, this signal molecule, will not attach to the cell surface receptor on the surface just because this signal molecules, can get squeezed into the cytoplasm and this signal molecules actually, will go inside and that you will get attached to a cell surface receptor or that will get attach to a receptors inside the cytoplasm.

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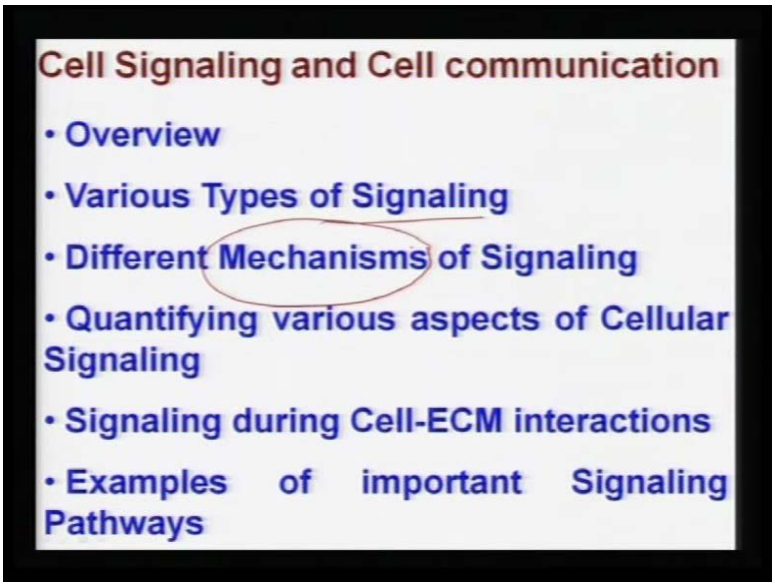

So, in this lecture, we will be discussing the process of cell signaling and how it is relevant for the communication between two cells. So, over all, this particular cell signaling process ((cell communication)) is with... And, as for as, the differential cell... processes are concerned, for example, cell migration, cell differentiation, cell division cell proliferation. So, all these cells at process, one of the essential steps, is the cell signaling. So, if the cell signaling does not take very appropriate manner, many of this cell ((…processes)) cannot take place true or ((…)) conditions. So, in this perspective,

that over all structure of this presentation will include. First, I will go through, some of the over view of the cell signaling processes that will be followed by the various types of signaling. Then, I will come to the different mechanisms of signaling. So, these mechanisms means like, you know, how this signaling processes takes place,, how this signals are generated from the source cell and it is communicated to the target cell, what are the mechanism. Then, fourth aspect is, the quantifying various aspects of cell signaling. That means that the students should have an idea about that, what is the time scalar? What is the typical concentration, over which a signal can be very effective and what is the constant? That concentration should be maintained.

Then, fifth one is, that you know, I will give you some example, for the cell is same interaction and another and different other cell signaling pathways.

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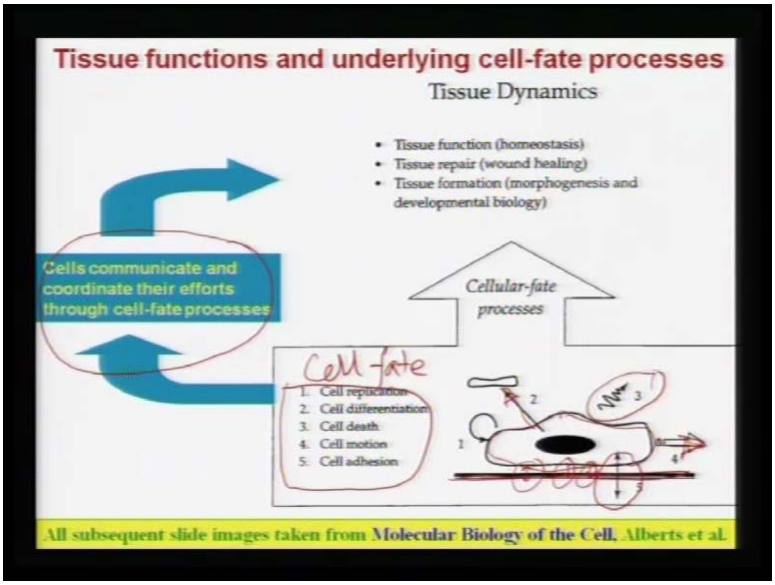

So, this is the over view, of what I was just discussing two minutes ago. That is, the Tissue functions and underlying cell-fate processes. Now, coming to the Tissue Dynamics, like, Tissue function like homeostasis, like, as I will discuss later, that you know, that all these cells survival, cell differentiation and cell ((…)), all these things are essential components for the homeostasis process. The second one is the Tissue repair that is the wound healing process. Third one is Tissue formation like morphogenesis and developmental Biology.

Now, just few minutes back, I mentioned that these are the cell-fate processes, like. This is the cell-fate process, like cell replication; that means cell division. Cell differentiation like different gene expression or different cell functionality. Cell death processes like necrosis or apoptosis. Cell motion like cell motility and cell adhesion. So, all these processes cannot take place, unless, a given cell will receive ((...)) from another cell. So, that is what, is mentioned that cells communicate and Co-ordinate, their efforts to cell-fate processes. So, all these cell communication processes outcome is that cell-fate processor. So, this is a typical eukaryotic cells like nucleated cells and you can see that this process 2 means that if this particular cells, can be going to another state that is the differentiated state. Then, cell application means this cells will increase in number. Cell adhesion means that it is in biomaterial substrate and on, which this, there is protein absorption, as I mentioned before. And, this protein absorption is important for the cell adhesion process.

Cell motility means like a child works on the ((...)). Similarly, how the cells will walk on the substrate or a given biomaterial substrate, so, like that cell motion. And this, how this cells like, maybe I have mentioned earlier that you know cells have also filopodia, lamellipodia like, human beings has legs and hands. So, similarly, the cells these, lamellipodia two extension of filopodia extension the cells can walk on the material substrate. And, number 3 processes, is the cell death, like, you know, cells will no more be surviving because of the ((necrosis….))

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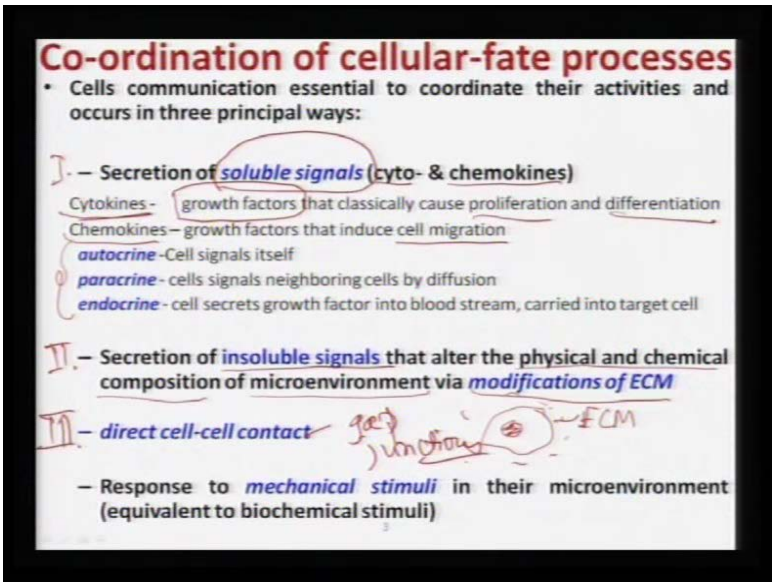

Now, Co-ordination of the cellular-fate processes. So, cell communication essential to Co-ordinate their activities and occurs that, takes place in three principle ways: number 1 is the ((secretion of soluble)) signals. So, here the soluble signals means that a source cell will generate or will essentially secrete some kind of soluble signaling. They will generate some bio-molecules or protein molecules or ((…)) molecules and these, are known as signals. So, it can be cytokines or it can be chemokine. Cytokines are actually growth factors.

Now, growth factors, this time need definition. So, growth factors are essentially, that cause, growth factors essentially, cause proliferation and differentiation, so, these are like cytokines. And, chemokine means growth factors that induce cell migration. So, essentially, cytokines means that is essentially, related to proliferation and differentiation. Chemokine means which is essentially, related to the cell migration. Now, again there are three types of soluble signals, process, signaling processes, and number autocrine. Autocrine means same cell signals to itself, for the divisions, cell division processes, like a mother cell is dividing into two daughter cells. Therefore, its same cell can send the signal to the itself. So, that you know, cells can divide to meet two daughter cells. Paracrine means cells signals to neighboring cells, by diffusion and Endocrine means cell secrete some growth factor into blood stream and carried into target cell. I will show these things, these three things in a few minutes.

Then, this is the soluble signals, the second one is that. So, this is the number 1, number 2 is the soluble signals. The second one is that, so, this is the number 2. Number 2 is the insoluble signals that alter the physical and chemical composition of microenvironment via modifications of ECM. So, insoluble… And then, second thing is that, these cells they cause the changes to the physical and chemical composition of microenvironment; that means if that is a cell here, eukaryotic cells, this is nucleus and this is eukaryotic cells.

Microenvironment means this is called ECM that is extracellular cellular matrix. So, these insoluble signals, cause some modifications to extracellular matrix. So, this is called another type of signals. Third one is the direct cell to cell contact. So, that takes place through gap junctions. Now what is gap junctions? I will come to that in a few minutes. So, this is at, this is direct cell to cell contact. And, fourth one is, the response to mechanical stimuli in their microenvironment, equivalent to biochemical stimuli. So, the

first three are three different principles of the communication. I repeat, that is, through soluble signals; second one is the insoluble signal; third one is the cell-cell contact.

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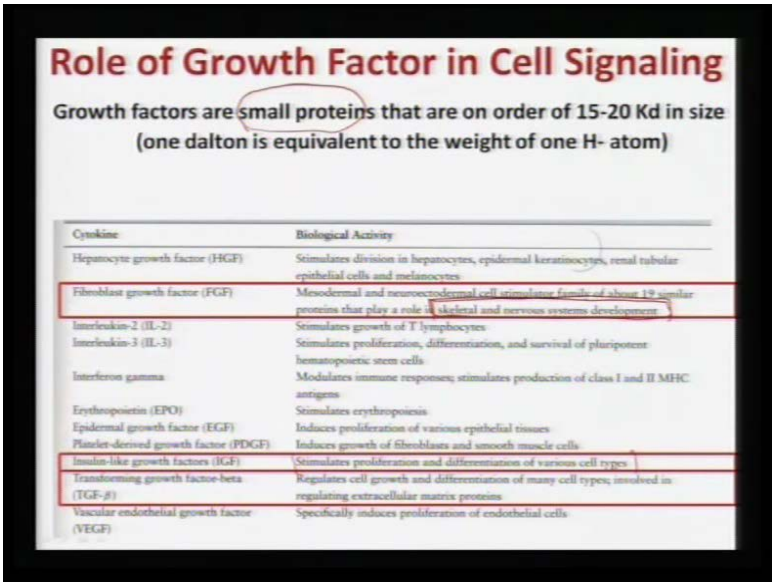

Now, as I said that, what are Growth Factors? So, Growth Factors are essentially, small proteins that are on the order of 15-20 kilo Dalton. So, KD stands for kilo Dalton; that means 15-20,000 Dalton.

Now, what is Dalton? One Dalton is equivalent to the weight of one hydrogen atom. So, therefore, growth factors are nothing but, the small protein molecules which are, which has a molecular weight of 15-20,000 kilo Dalton. So, this is the growth factor. Now, there are different types of growth factors. See, if it is not a course on Biology, as such I would like you to remind.

I would like you to remember the.., at least two or three different growth factor, which are important in the process of a cell-fate processes. Number one is that, fibroblast growth factor that is FGF. Number two is that, insulin like growth factor, that is called IGF and third one is that, transforming growth factor that is known as TGF. Now, what are the functions or biological activity of these three growth factors?

Now, fibroblast growth factor. They are essential biological activities, mesodermal and neuroectodermal ((cell stimulates, family of nineteen similar protein that play a role in)) skeletal and nervous system development. So, this particular growth factor, that is a

fibroblast growth factor, they initially help in the development of skeletal and nervous system development... Nervous systems, Insulin like growth factor IGF that stimulates proliferation and differentiation of different growth factors. So, therefore, as you can see, in the context of the cell-fate processes, IGF is more important because IGF essentially, stimulates, it stimulates or it facilitates, cell proliferation and cell differentiation. Transforming growth factor beta, that regulates cell growth and differentiation of many cell types involved in regulating extracellular matrix protein. So, TGF is cell differentiation of many cell types.

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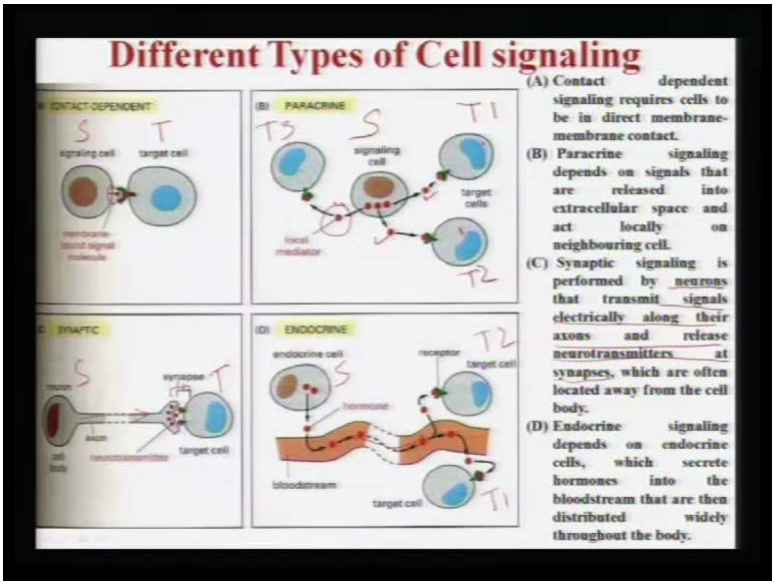

So, as I said in the last lecture by ((….)), last slide that your, three types of growth factors are important. I repeat, FGF is fibroblast growth factor, IGF is that insulin growth factor and TGF is transforming growth factor. And out of that IGF is the main growth factor, which is important for the cell proliferation differentiation. Now, two or three slides back, I mention, that you know, what the different types of cell signaling process are. Contact depended, that is, the through gap junctions and then three other type of growth factors, that I …sorry...

Three other types of signals are that I have mentioned that is, so, if you remember correctly, there are three way signaling takes place. One is the soluble signals, second one is that insoluble signals, third one is direct cell to cell contact (( )) soluble signals, there are three different ways, this signaling can takes place. One is that autocrine; one is

called paracrine. Autocrine means cells produce signals to itself. Paracrine means cells that produce the signal to the target cell. And, Endocrine means cells secrete the signal molecules that will be carried away through the blood stream. And then, it will be transported to another target cell. So, that is a Paracrine.

Now, here you can see, that is the first one is the Contact dependent. So, this is your signaling cells S and this is your target cell T. So, from signaling cell, the signal molecules, you can see membrane bound signal molecule that is the red one. And, this is your target cell; green one is the step target cells cell surface receptor. So, they will come and then, they will attach, they will get attach to the cell surface receptor on the target cell and then, they will cause some changes in the target cell T. So, this is like Contact dependent, like 2 cells are in direct Contact. And, among various cell types, the cell type that comes to our mind that, who, where this Contact dependent signaling takes place is the endothelial cells. Endothelial cells like cells, which are arranged ((…)).

This is your signaling cell S, now, there are 2, 3 different target cells. This is 2, this is one target cell, and this is another target cell. This is T1, this is T2 and this is T3. Now, these are all eukaryotic cells, as you can see, now they ((secrete)) 2 or 3 different type of signaling proteins, for example.

Now, one of the signaling proteins can be transported to this T3, but (( )) local mediator. That means, it cannot directly be transported via protein molecule directly to another target in cell. So, these target 1 will get attached to the local mediator and then. So, this local mediator can be transported through the target T3 cell. Similarly, different term local mediators are present, as you can see, this is another local mediator and this is another local mediator. So, the signaling cell from S to the target cell T1, T2, and T3; if the transport of the signal molecule takes place via the local mediator.

The process of the Paracrine signals. And, Endocrine signals means this is your Endocrine cell S, that is the source cell. Now, this is your target cell. This is T1 target cell, this is T2 target cell all are eukaryotic in nature. Now, Endocrine cell, this will secrete some signal, then it will go to the hormone and then through the blood stream. This is your blood vessels or blood stream it is going on and it is transported to the blood stream and then, it goes to 2 target cell. So, this is like T 2 and T 3. So, essentially, all you can see here, that from T1 and T2 and then it can be transported. So, this is called

Endocrine signals. And then, another one that has been mentioned here is that Synaptic signals. Synaptic signaling is performed by neurons. So, neurons mean, it is actually important in neural Tissue engineering or in general neurons. So, this is the transmit signals electrically, along their axons and release neurotransmitters at Synapses.

So, here you can see, these are like Synapses here. And, this synapses, these are neurotransmitter. So, this signals, as such, it is transported electrically and then, it is going to another target cell. This is your source cell S and this is your target cell T. So, from S to T that through neurotransmitter, this signal is transported.

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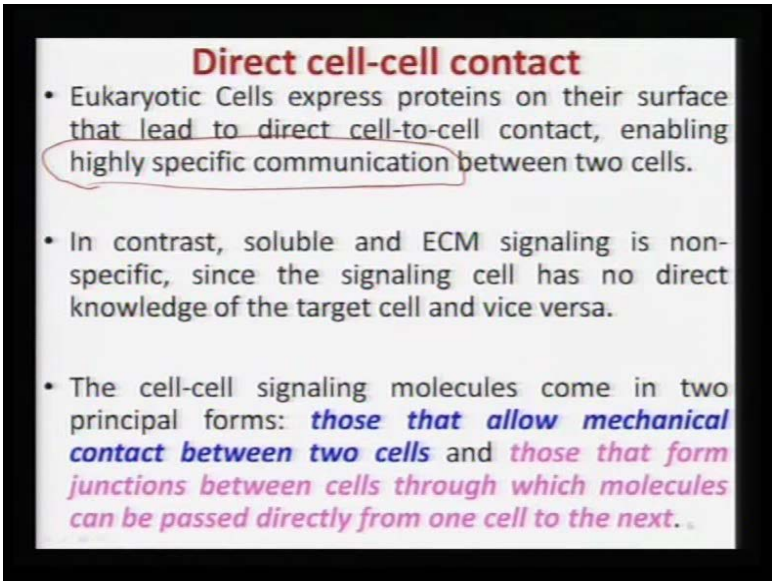

So, direct cell- cell Contact, this is little bit more detailed on the direct cell to cell contact, like eukaryotic cells, they express proteins on the surface, that lead to direct cell to cell contact, enabling highly specific communication.

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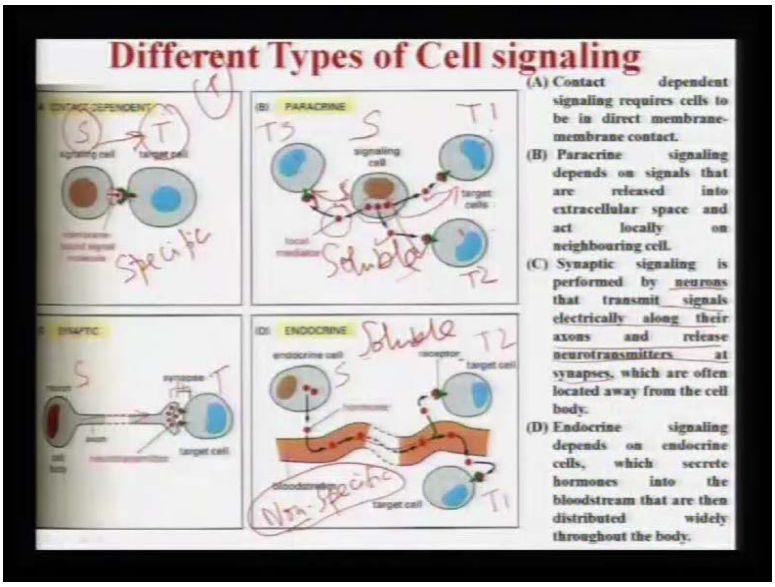

Highly specific communication means if you go back here, that signal molecules that are generated here from this S cell, these same signal molecules can be transported T1, T2 or T 3. So, it can be in nature, non-specific, but when these two cells are in direct contact, you know, that this signal molecule from this S cell, it will directly go to the T cell because it is physically in contact with each other.

So, this is called highly specific communication. Highly specific communication means this signaling communication is exactly, for this T cell target cell, not that another target cell, which are located here. So, in contrast, soluble and ECM signaling is non-specific. Soluble and ECM signaling means, as you can see, this is called soluble signaling or... signaling that is, Paracrine and Endocrine. So, these signals, this source cell does not know, where their signaling proteins will finally arrive at. Whether, it will arrive at T2 or whether it will arrive at T1. So, that means this is like, non-specific. So, I hope you are getting my point. That these are specific means, just because they are contact dependent direct, so, source cell to target cell. This is called specific interaction. Non-specific interaction means like source cell, it is going to 2 target cells and this is called non-specific interaction.

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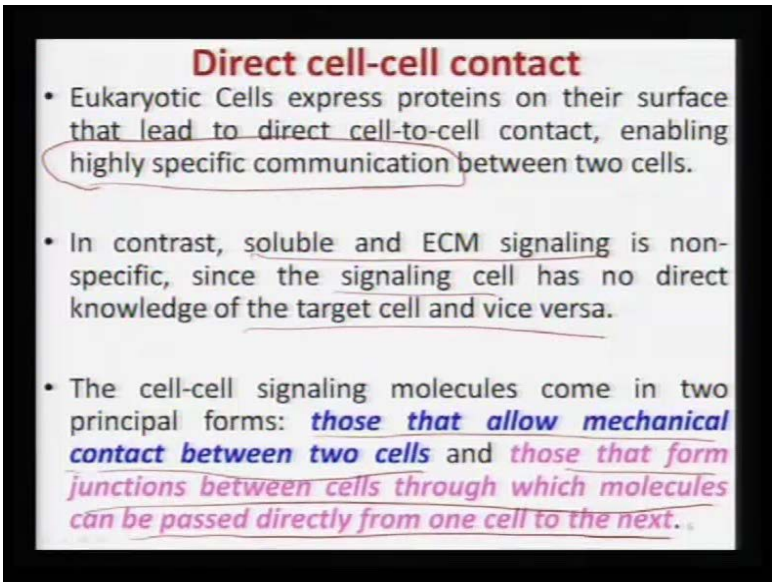

So, it is non-specific, since the signaling cell has no direct knowledge of the target cell and vice versa. Has no direct knowledge means, signaling cell does not know, which target cell, their signal protein will finally arrive at. Then, third point that has been mentioned here, is that cell-cell signaling molecules, come in two principal forms, like those that allow mechanical contact between two cells, through, which molecules can be passed directly from one cell to the next cell.

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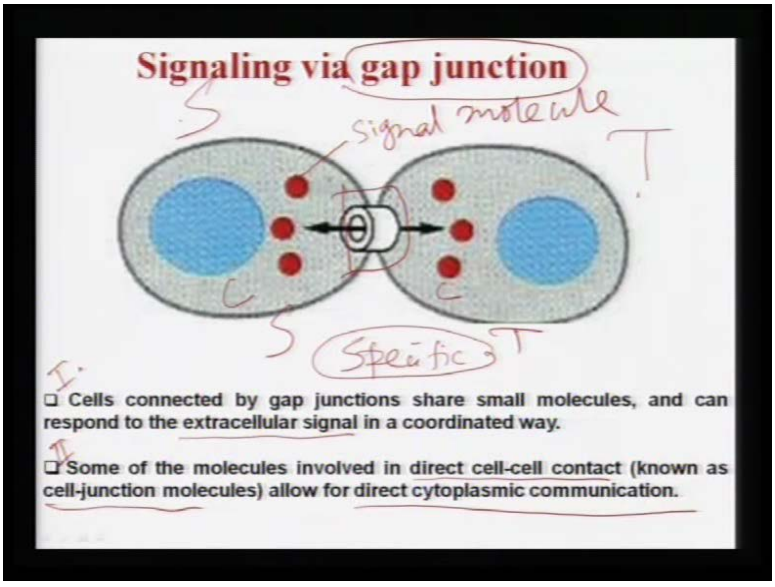

So, this is what I was mentioning there that ((signals...)). this is signaling via gap junctions. So, this is direct contact and this direct contact, here you can see, these are the signal molecules. So, these signal molecules, it can go from source to target; this is highly specific in nature. Highly specific in nature, why because this, if this is source and this is target, source cell exactly knows, this is the target cell where the signaling molecules will directly pass through. And, these junctions here, it is known as the gap junctions. These gap junctions, the communication through gap junctions, only take place in cell type like endothelial cells. Where, multiple cells are lined up one after other. So, there is a direct physical Contact between the two types of cells. So, here it has been mentioned that the two points.

Point number one is, that cells connected by gap junctions share small molecules and can respond to the extracellular signal in a Co-ordinated manner. So, can respond to the extracellular signal, in a very direct cytoplasm communications. So, like molecules were in direct cell to cell Contact. So, this is your cytoplasm C, here. So, that… so, these signal molecules, if it is transported to, between these or in a reversible manner can directly communicate to the cytoplasm.

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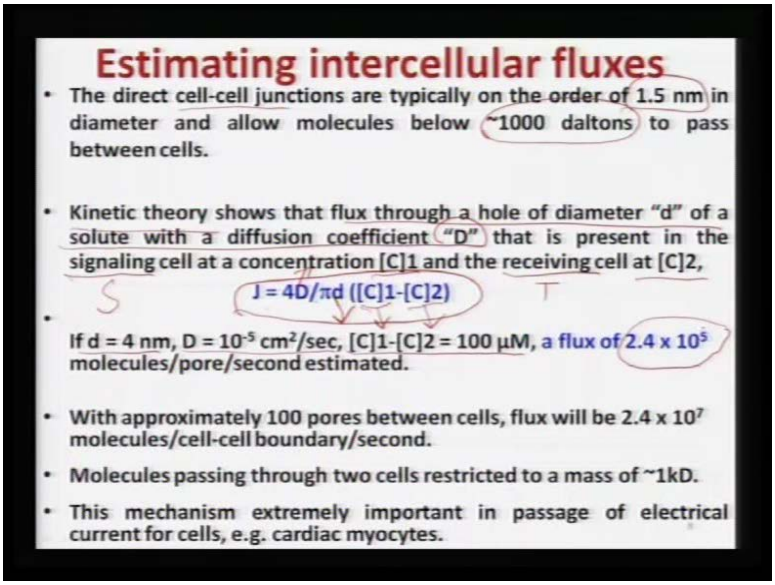

Now, coming to the some quantification, estimating that intracellular fluxes. Now, how to quantify that, what are the typical fluxes that will be generated in these Intracellular, in the signaling process. Now, let me go back. So, intracellular flow fluxes means to be

generated at the source cell surface here. And, how much flux, that will be generated and that will be going to the three different cells, which are mentioned here. So, that means what I am trying to tell you is that, what would be the flux of the target what is what will be the flux of the signal molecules, that will be transported from one signal cell to multiple target cells. yeah. So, now, for the particular case of the cell-cell junctions, typically cell-cell junctions, their dimension is around 1.5nanometer. And, therefore, that allow below “1000 Daltons”. So, most of the growth factors, if you remember, they are very small protein molecule. And, which is the size of 15-20 kilo Dalton means this can be easily transported between these two cells and these 1000 cells. Kinetic theory shows, that the flux through a hole of diameter “d”, of a solute, with a diffusion coefficient “D”, that is present in the signaling cell at a concentration C1 and the receiving cell as a concentration C2. So, this flux is,” j is equal to 4 D”; D is the diffusion coefficient here, d is the cell-cell junction diameter, C1 is the concentration in the source cell, C2 is the concentration in the target cell. Receiving cell means, this is essentially, target cell. And, signaling cell means this is an essentially source cell. You understand what I am saying? So, let me go back to this.

So, what has been mentioned here? Suppose, this is source cell and this is your target cell; here the concentration is C1, here the concentration is C2, D is your diffusion coefficient, that how ((…)), through and this diameter, if it is d here. So, then the flux that, how much flux that will be transported? That has been calculated via simple flux law is” j is equal to 4D, pi over D, C1 minus C 2”. So, always the flux will be from higher concentration to the lower concentration.

So, now, if you see that if you consider the D is 4nanometer, D is 10 to the power minus 5 centimeter square, per second. Like, you know, typical diffusion coefficient. C1 minus C 2 is 100 minus micro molar, then, what would be the typical flux? This, typical flux should be 2.4 multiplied by 10 to the power of 5 molecules per pore, per second.

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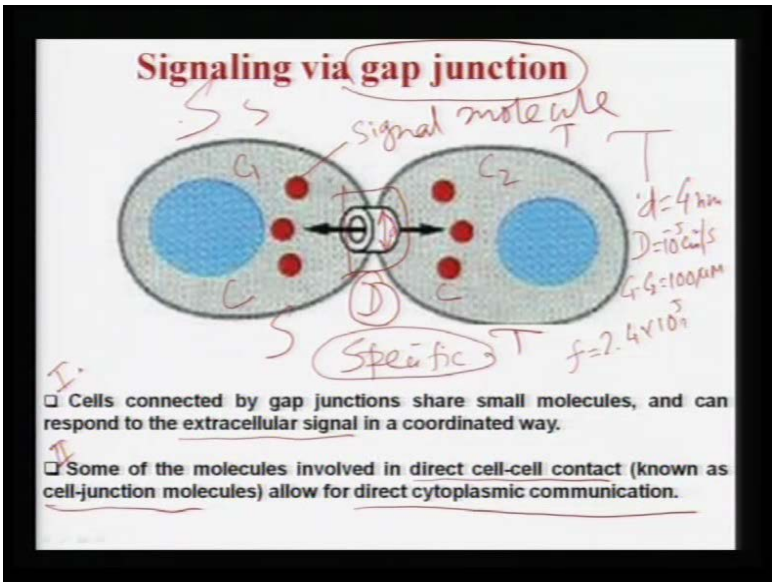

So, let me go back to this slide, and let me explain to them. So, the d has been assumed as, suppose, this is 4 nanometer; so, if you calculate, here d is equal to 4 nanometer that your D; diffusion coefficient is 10 to the power minus 5 centimeters square, per second. And, your C1 minus C2 is, typically like, 100micro molar. Then, this flux which is f, it is like 2 multiplied by 2.4, 10 to the power 5.