Biological Inorganic Chemistry
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Lecture 18
Transport of metal ions in fungi and mammals

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Hello, everybody. So, again, welcome back and we will continue where we have finished last time. So, only thing is that your module number and lecture numbers are different. So, it will be 18. So, but we will talk about, again, the assimilation pathways. Now, the substrates are different. We will now go for the fungi or the fungus and the mammals.

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And the transport mechanism for these metal ions we will try to cover following these ideas or the concepts that we will talk about, everything we are talking definitely about the transport, storage and metabolism, if it is in fungi. Then if we go for, if we apply this particular information or knowledge what we are gathering by studying, we have already seen in case of plant, we have already seen in case of bacteria, now we try to have this information to put on the information what we are gathering from fungi then we will try to compare and ultimately our extreme goal is that for your mammals or the human being or our system.

How our system is also following, it can have the same thing or it can have the different thing, but remember that we can have the fungal infection, we can have the bacterial infection and we are dependent on plant. So, all these things in a collective way the knowledge of metal ion assimilation, transport, storage and metabolism finally, because we talk metabolism in terms of your carbohydrate metabolism, we talk metabolism in terms of lipid metabolism, we talk metabolism in terms of fat metabolism, but here we are focusing our attention only on the metal ions.

Whatever we are seeing even in a test tube full of some solution, always we try to see, our eyes are only focusing on attention on that particular attention, we try to have that where is your metal ion, what metal ion is there. So, for mammals, we can also see the transport and storage and the intracellular iron metabolism. So, these three, four metal ions we are only considering so their

coordination chemistry is also helpful all the time in understanding all these things, because finally, what we try to understand is the corresponding metal ions and their metabolism.

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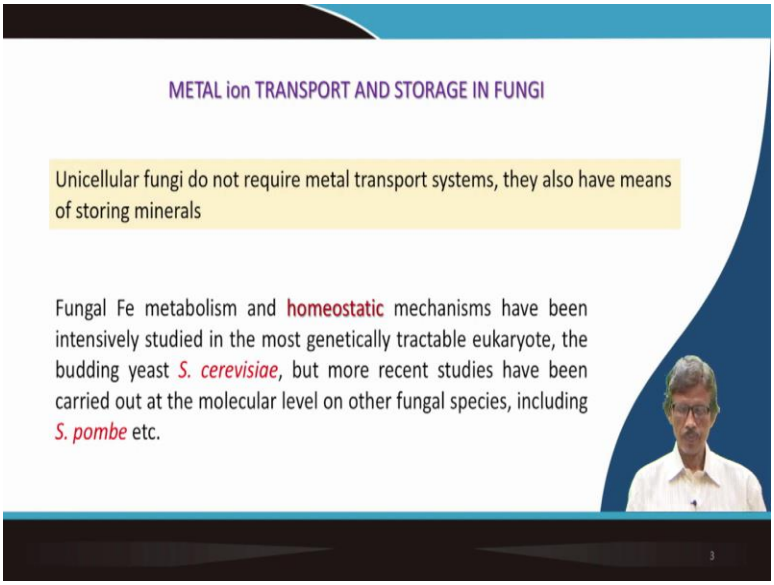

So, if in fungi, metal ions are there and that metal ions are taken up. What we have seen in our previous few classes that metal ion assimilation process is the very beginning is your assimilation, how you get the metal ions in the environment from the environment, then how you grab it, how you bind it, and how you move it for your transport.

So, if you have the unicellular fungi which do not require any specific metal ion transport system, because is, mostly its random, so no specific, because as we move for the higher order biological or living systems, we go for more sophisticated instrumental part that instrument in terms of your metal ion transport mechanism, the system which are sophisticated in nature, for us also. The human being is much more complicated, not only sophisticated, but is also complicated.

But they can have some good means of storing minerals. They do not have very useful transport mechanism, but they know how to store the minerals and how to store the metal ions, because the metal ions we all know they are also minerals. So in mineralized form how the metal ions will be available to this fungus or fungi? So, we are, we do not know much about all these things in the different other classes. We have not seen these things that okay the different types of these fungal things, the fungus things, we also have the mechanism for the metal ion dependence.

So, if we talk now that iron metabolism in one type of fungus, we will be talking about something in our future classes about the homeostasis. Finally, what we will be looking for the homeostasis mechanism, which have now been intensively studied, where we can use the genetics because they are genetically tractable eukaryotic now, because we know eukaryote, we studied prokaryote, eukaryote all these things in a different way under a microscope to everywhere. But the genetic thing how they are forming which particular proteins are involved, what genes are involved that is the latest discovery or the latest understanding and the latest knowledge what we can gather.

So, if you have a yeast sample, all we know yeast, is a very simple one, a simple substrate, model subject we call. Yeast we use or require for bread making. Yeast is to use for winemaking also, even for the production of ethanol. So, most recent studies have carried out on this S. cerevisiae and the molecular level for the other fungal information including S. pombe. So, if we consider one or two such model substrate, we can have all this information nicely, we can gather, we can study also. So, this sort of detailed study is very important.

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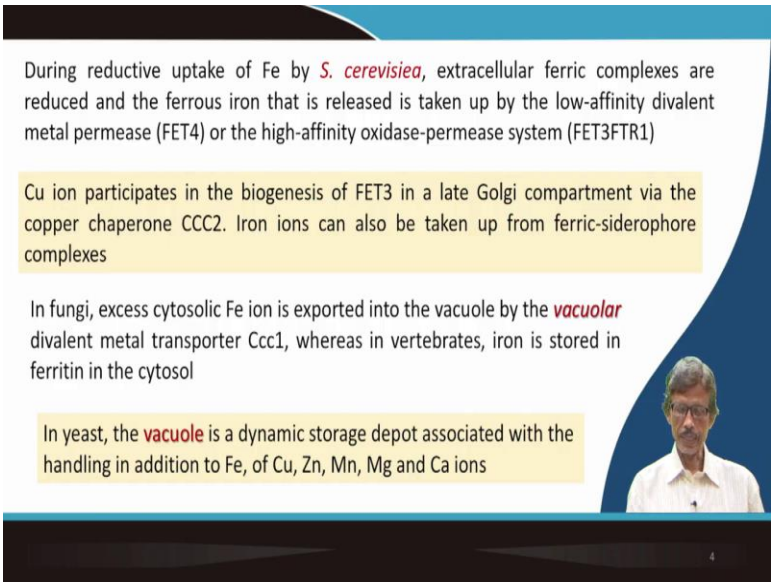

And during reductive uptake of iron that means you always try or force the abstraction of iron in an environment which is reducing in nature. That means whatever iron is we will be getting, initially we take up as ferrous ion then it will be converted to the ferric. So, the extracellular

ferric complex, even in the extracellular ferric complex which is available, which should be reduced then first and that is released and taken up by low affinity divalent metal permease.

So, it is related to Fe, so it is called as FET4. So, iron T4 or FET4 or it can go for high-affinity oxidase-permease system. So, this is another group of molecules. So, low-affinity bivalent one and the high-affinity oxidase form is there, which controls all these detailed things, do not worry about all this detail mechanism, but how people have identified these things, because whatever we are talking in a scientific fashion, we should know that how it has come out, how the information has been gathered.

Similarly, in case of copper also, they are participating in biogenesis of FET3 now. And in a late Golgi compartment via the copper chaperone. So, chaperone is there. So, the copper chaperone CCC2 is involved. And these iron ions, so these are the assimilation process or the metabolism processes of iron and copper. They are not separated. They are closed by and they are interdependent. So, iron ions can also be taken up from the ferric siderophore complexes. So, always we know that the source is there. Iron can be supplied by all these siderophores which are already bound to ferric ions.

So, in these fungi the excess cytosolic iron ion is exported into the vacuole, just last, in our last class we have seen that how the vacuoles are used by the vacuolar divalent metal transporter. So, if everything is on vacuole and the origin is also vacuole so we consider these are the transporter of what type, transporter of vacuolar type, so transporter of vacuolar type which are handling bivalent ions. But in case of vertebrates, iron is stored in ferritin. So, the mechanism is little bit complex or different in the cytosol.

So, in our case it will be only the ferritin. So, in yeast this vacuole is a dynamic storage depot. We call, we know as the storage depot, so is the storehouse. The store we always have in our home

also; we have the kitchen store. In the laboratory we have also the store where we have stored the different metal ion salts and the bottle of all the different other metal, even the metals also sometimes the iron powder, iron wires and all these things sometimes they are also required.

So, the storage depot is associated for the handling. In addition of this copper, in addition of this iron, other metal ions like copper to calcium, so copper, zinc, manganese, magnesium and

calcium. So, many such mental ions are there and all these metal ions have some important role to play.

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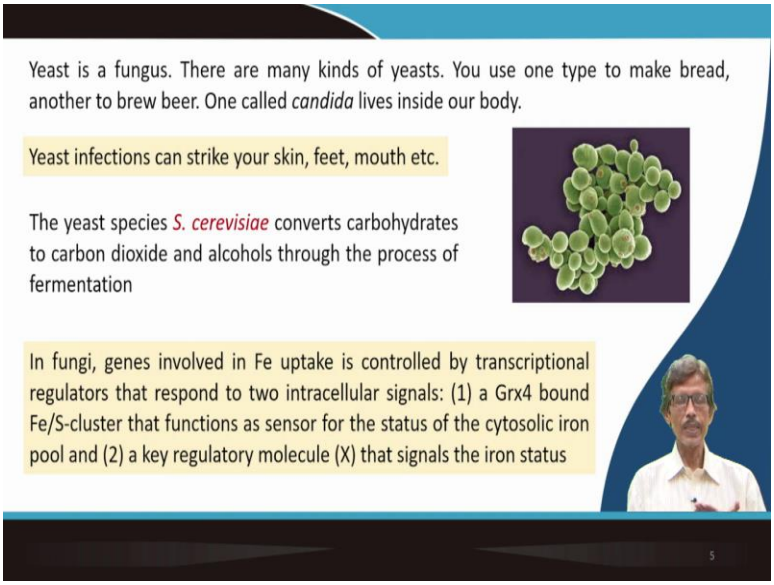

So, what do we know now that what is yeast we all know. So, we can go back a little bit to our school level that yeast is the fungus. And there are many kinds of yeasts are available. Just now I told you that from bread to beer making thing. You can make beer with the yeast also, the fermentation process. Bread is also giving you the fermentation.

So, if we have these one such is there in our body also the skin, the skin fungal infection, the black fungus nowadays we are hearing. So, if it is dependent on that, so the disease causing this, all these fungus one is the candida which is living in our body also. That is why some Candid B and all these ointments are very useful available in the market.

That is why if you have this yeast infection also can strike your skin, feet and mouth. But we do not look at it in that fashion that whether they are dependent on iron or the availability of the metal ions. If the metal ions are not available, the growth of the survival of yeast will no longer be there. So, the species from S. cerevisiae converts carbohydrate to carbon dioxide and alcohols through the process of fermentation. So, this particular species is available. S. cerevisiae is, therefore, required. So, this is yeast is, actual name of this particular yeast what we require for the fermentation process. So, we know all the microscopic picture of this yeast how it looks like and what are there.

But, if we bring gene that your life will be a little bit complicated, what are the genes involved for their metal ion uptake. So, you will have definitely some transcriptional regulators and they follow some signals. These signals are of two types; one is there you have the iron sulfur bound cluster. So, Grx4 bound, the Grx4 is one particular species which is binding your iron-sulfur cluster and it is functioning as a sensor that means whether you have iron concentration is less or iron concentration is more; and another one is a key regulatory molecule that signals again your status of iron, how much iron is there present in the cell.

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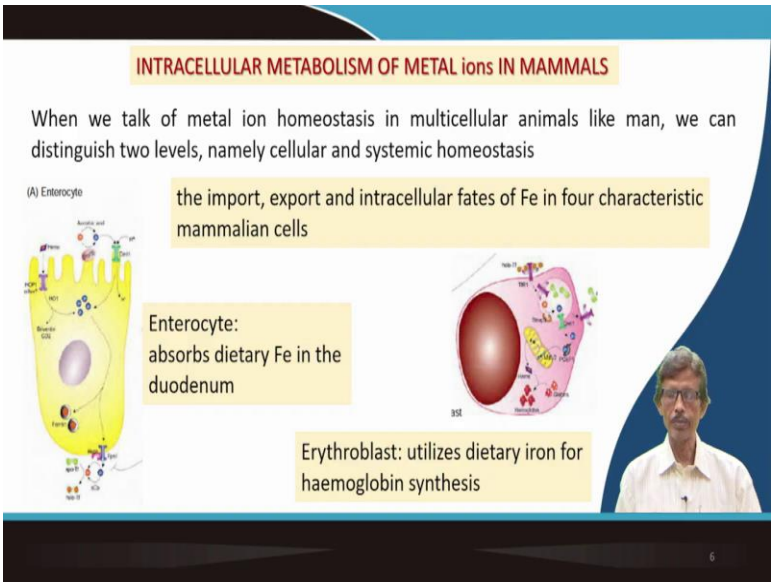

So, if we now find that intracellular metabolism of metal ions in mammals, you see all are mmm, so metabolism, metal ions and mammals you think of in that way. You will remember also that what we are talking. So, then again because we definitely talk about in our future two classes the homeostasis. So, if we have not a unicellular system, because why we study the unicellular system, the unicellular systems are is important to study nicely. But ultimately our goal is to go for our system, to see our system, our diseased condition, our fungal infection and all these things.

So, if we move to the multicellular animals like man, we can distinguish the two levels namely cellular and systematic. These are two different types of homeostasis and we will definitely be talking in our future classes, next two classes definitely talk about these two different types of homeostasis. Then this homeostasis and corresponding metabolism or the transport and storage

mechanism is dependent on the import and export and what are the fates of these iron the extracellular fate and intracellular fates, what is there within the cell and how these particular iron, how much iron you can have, where we want to store. We have learned that we need iron. We need for our survival for hemoglobin, myoglobin molecule, but this particular iron where we can store it within the mammalian cells.

So, there are four such characteristics cells are there; one such type is the enterocyte. So, this enterocyte is available to us, is there in our body also and it what it does. The function of this enterocyte is such that, when you take up any food material and that food material can have iron and when it is passing through our GI tract, the gastrointestinal tract it is also passing through duodenum. And duodenum can have some mechanism, some absorbing part, the surface of that particular, inner surface of the duodenum which is available there and that can recognize or identify the availability of the iron from the digested food molecules in our body.

So, they required for that particular iron absorption in duodenum. So, this is your the cartoon drawing or the cartoon picture for enterocyte. So, this enterocyte is there. So, all these details, we will not talk about all these details, but at least you should see the cell like arrangements, what is the corresponding figure, what sort of thing is there, but we require this entire cell, the enterocyte we require to take care of iron from our food material, and it is present in our duodenum in our body.

Then another group of this particular mammalian cell is also available which is known as erythroblast. So, this erythroblast is utilized for taking up iron during your hemoglobin synthesis. So, it is a very useful function it will do. That is why the erythrocytes it can form, so that is why it is known as erythroblast.

And the iron what is absorbed in your duodenum can be utilized for your hemoglobin synthesis and you should also know where it should go there from our body, where we are absorbing then where it is going for your synthesis, because your bone marrow, we all know, the bone marrow is the site where you can have the hemoglobin synthesis. So, that dietary iron will then be transferred either it can be stored or it can be directly moving to that particular bone marrow side to use for your HB synthesis or hemoglobin synthesis.

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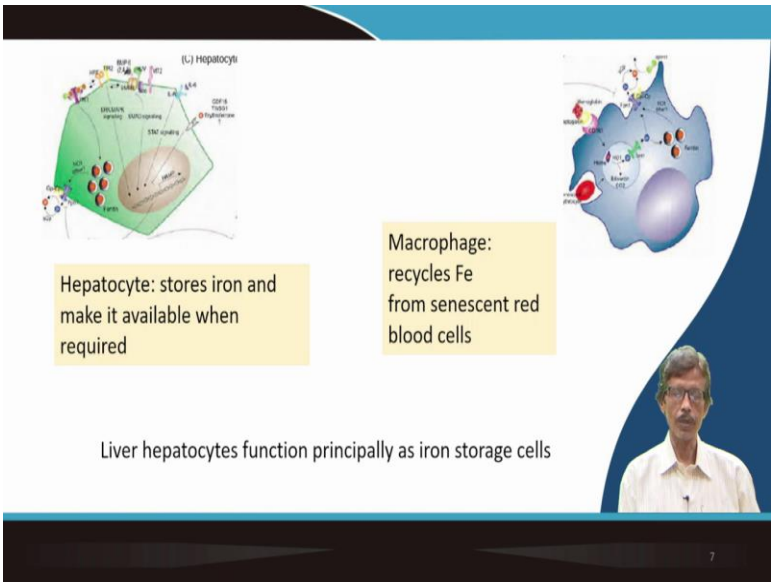

Then the third category is your hepatocyte. This third category of these cells is the hepatocyte. They store iron and make it available as and when required. When you are not taking food, you are in starving condition, but you still required the production of iron. Your body will not stop in producing your blood molecules, synthesizing your blood molecules. So, these are also look like these. The cartoon drawing of these hepatocytes are like this, and these are available for your iron management.

Then finally, the fourth category of these cells are the macrophages. These recycles the iron from senescent red blood cells. So, these red blood cells if you have and we know that the breakage of these red blood cells also gives you the corresponding one as the supply. So, this is your cartoon figure for you macrophage. So, where they are? So, you have the liver hepatocytes and they function principally as iron storage cells, so where we can store these irons is your liver cells which are the liver hepatocytes. So, that is why we always call liver is your mother organ, because you have the liver hepatocytes and these liver hepatocytes are useful for handling and storing your iron.

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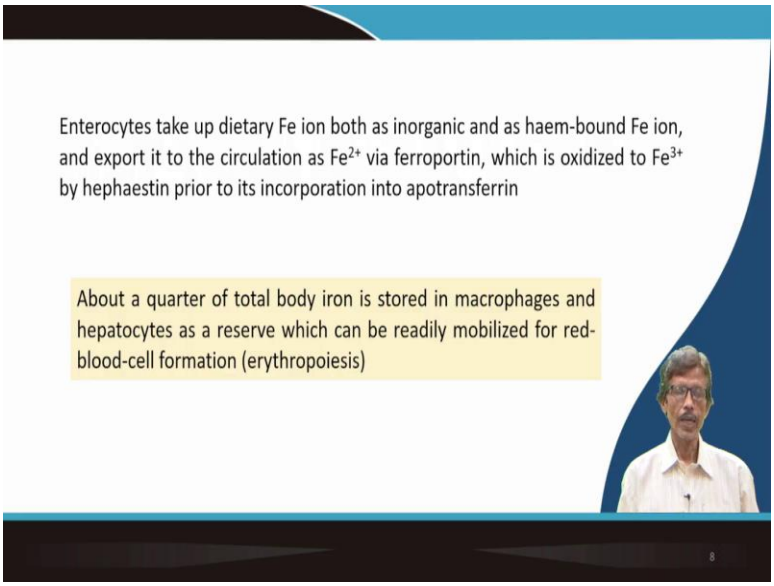

So, these enterocytes which taking up your dietary iron both inorganic and haem. What are the differences? Always every time we are talking about that; inorganic is the hexa eco iron 3 plus, iron dissolved in your water molecule or in your water system. But haem is your, nothing but your bound porphyrin ring. So, if your bound porphyrin ring is there so that bound iron porphyrin is important to make that particular character of iron to a haem character and it is there to export it to the circulation of iron via ferroportin, which is then oxidized to Fe3 plus by hephaestin prior to its incorporation into apotransferrin.

So, apotransferrin molecules we know. These are the transfer molecules. Again, we will study in detail this apotransferrin which are very much needed to us. But for these all these living organisms starting from your plant to human being, they how they are correlated with regard to these available molecules that we are comparing right now, though the hephaestin prior to its incorporation to your apotransferrin is important. Then the biggest molecules which we are having there for the iron is their corresponding cells there the fourth category the macrophages.

So, about one quarter of that is stored in the macrophages and the hepatocytes of the liver and reserves which can be readily mobilized for blood cell formation or erythropoiesis. That means erythrocyte formation.

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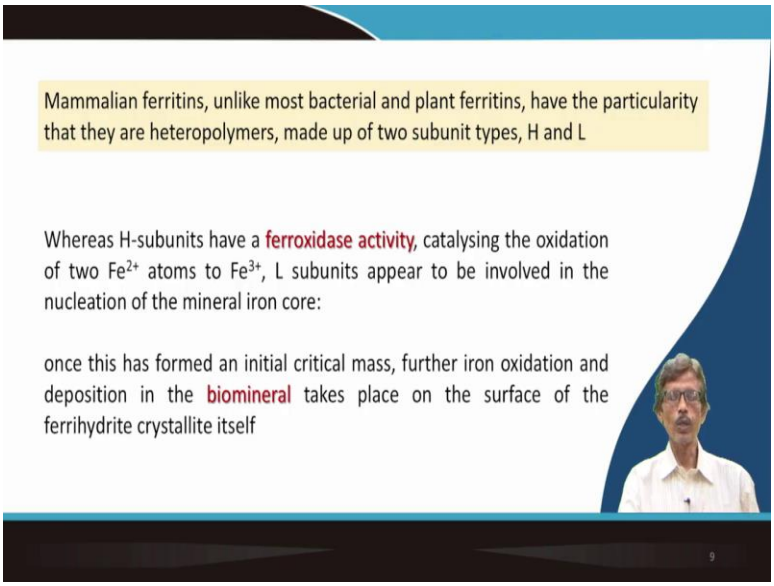

Then, if we see that these mammalian ferritins, unlike most of our bacterial and plant ferritins, we have seen that we can have the bacterial ferritin, we can have the plant ferritin also, they have the particularly they have the heteropolymers made up of two subunits types H and L. So, now, we are talking about, a little bit about these ferritins. Already we have seen the sphere type of arrangement having 24 subunits. Now, where you have H and where you have the L?

So, in H subunits, it will have the ferroxidase activity, catalyzing the oxidation of two iron atoms to Fe3 plus and the L subunits appear to be involved in the nucleation of the mineral iron core. So, nucleation means when you go for the crystallization process from the solid state say one particular molecule can separate out from the solution medium to the solid state. So, that one molecule can give you more number of molecules. It will attract more number of molecules in the solid state. So, that is being separated from the solution.

The crystallization thing that we know from the sugar crystals, how we get from the solution, the saturated solution, the super crystals or any other crystals of say any metal ions salts like your copper acetate or copper sulfate. So, from the saturated solution, the solid is separating one by one and this particular one when they are separating out, so nucleation is starting over there and that nucleation is starting point of this particular big ferritin formation.

And you know the biomineralization process we are talking about having an iron core, because you have, at the center, you have the iron core, very hydrate type of iron core, but it is covered

by the protein sheet or the protein envelope. So, once this is formed an initial critical mass for the further iron oxidation and deposition. So, you have more and more iron is coming, is a continuous process and it you consider it as a catalytic process also.

It is not that one time you have the material what we are looking for your crystallization in a test tube or some beaker or some petri dish or watch glass. You allow it to evaporate. When the solvent is going away, the water medium is going away, we will be leaving behind with something, either you have the amorphous material or the crystalline material. But here you will have the continuous flow of these materials, the continuous supply of iron ions.

So, that continuous supply is responsible for your biomineral formation on the surface of the initial crystal and which is nothing but a very hydride type, because the solid state structure determination tests such that its composition is similar to that of your iron mineral which is very hydride, which is well known iron mineral.

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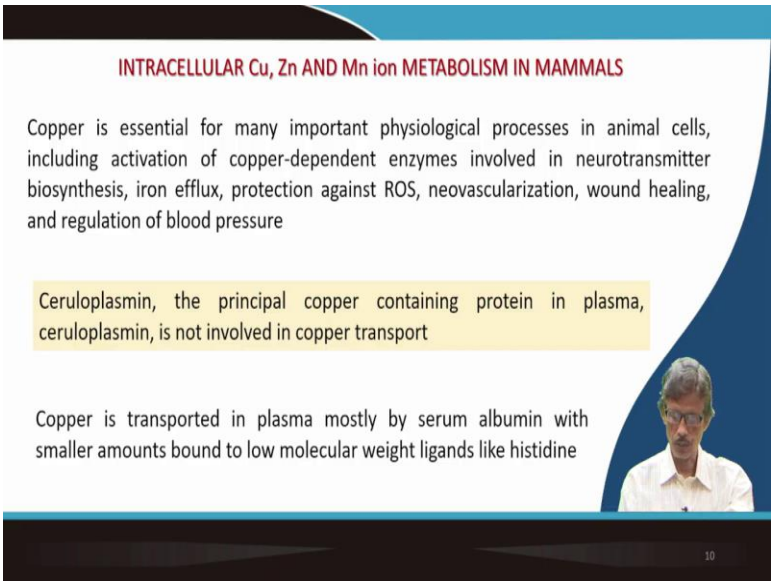

Then out of this iron, we can go to copper, zinc and manganese. And we all know the copper is also essential and which is also important for different physiological processes in animal cells, including activation of copper dependent enzymes. So, why do we require copper, because the copper should be incorporated not only in different copper metalloenzymes, but it is also incorporated in the different enzymes and these enzymes are useful for synthesizing very important molecules.

Here we have listed some of them and is involved in neurotransmitter biosynthesis, iron efflux, that means, as I told you earlier that is dependent, the copper mechanism or copper homeostasis or copper metabolism is also giving something some impulse such that you also consider about the corresponding iron efflux.

So, this iron efflux is also dependent, therefore, on the presence of the copper, than the redox behavior of the different reactive oxygen species, the superoxide or the peroxides. So, when we form these for oxidation of the dioxygen molecule, the reactive oxygen species and ROSs are formed and how we can protect these through some reduction.

If we are able to go for reduction of these the superoxide or peroxide we can take help of some copper in the reduced form. So, copper ion in the reduced form what is that? Copper ion in the reduced form is your cuprous state. So, the enzyme, if the enzyme can subtle between the cupric state and the cuprous state what you find that in the reduced form that the copper is in the plus 1 state can be a very good reducing agent. So, it can take care of the problem which is arising out of your ROS, the presence of huge amount of ROS in the, in your body.

I mean, oxidizing form your aging process, you are slowly oxidizing with that environment, then neovascularization, so that we will also talk about some time when we find time, wound healing and also very important thing is that regulation of blood pressure. So, these are all new findings. So developments what we are getting about we can try to connect the metal ion homeostasis or metal ion assimilation or metal ion metabolism to that of your simple blood pressure thing.

Ceruloplasmin all we know from our very early days that which is known as a very good copper bearing protein, which is present in the plasma, but it is not involved in the copper transport. We know that it is involved in copper transport, but is not there in (()) (25:30) that of your copper transport, because it has been established now that people who are deficient in ceruloplasmin they do not have any problem related to making the copper enzymes or other useful copper molecules in their body.

So, ceruloplasmin if it is involved in copper transport, the people who are deficient in ceruloplasmin can have some other effect. So, these copper centers or copper ions is transported again from the fluid which is your plasma serum albumin is taking care of all these things. And

some smaller amount of these copper ions are also bound to some low molecular weight molecules like histidine residues or histidine side chain of the amino acid residues.

So, amino acid because the copper will always have, we all know, in two of its oxidation states cuprous as well as the cupric. Copper can have a very good affinity for nitrogens also and another very good nitrogen bearing ligand biogenic ligand is your histidine residues, the imidazole side chain. So, imidazole nitrogen can come and immediately bind to your copper centers.

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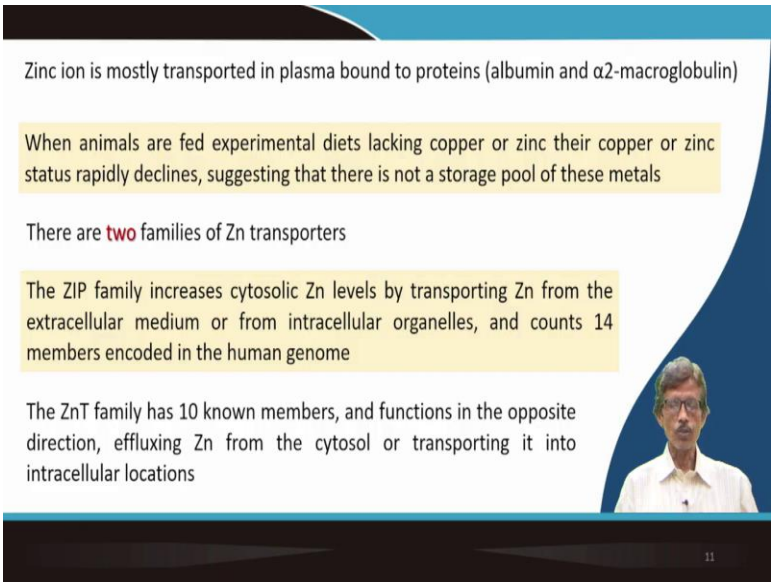

Then if we think about the zinc, so zinc ion is mostly transported in plasma bound to proteins, so, again, albumin and alpha 2 macroglobulin. So, alpha 2 macroglobulin is important for taking care of zinc like that of your ceruloplasmin for copper. So, when animals or human being also fed with experimental diet, lacking copper or gene and then we can monitor their status. So, the status is rapidly declining that the amount of copper and iron in their body is also declining.

So, it is also suggesting that for that particular reason, there is not a shortage of pool in their metals. So, their pool is not getting shortage. So, you can have the lower amount of copper and zinc in your diet which is having less amount of copper and zinc, but the corresponding copper and zinc is decreasing, but in the storage pool in these are not also decreasing. So, there should be some other transporters or other mechanisms.

So, let us know here about two such zinc transporters which are important for the transport of zinc ions; one is the Z-I-P family, the ZIP family increases the cytosolic zinc ion levels by transporting zinc ions from the extracellular medium or from intracellular organelles, and counts about 14 members. You see the number, this is very big. 14 numbers are encoded in the human genome. So, that is why you will be able to produce ZIP and whether we have some malfunctioning of this particular thing that we can also find out. So, ZnT family has 10 known members and functions in the opposite direction and effluxing zinc ion like iron from the cytosol or transporting it into the intracellular locations.

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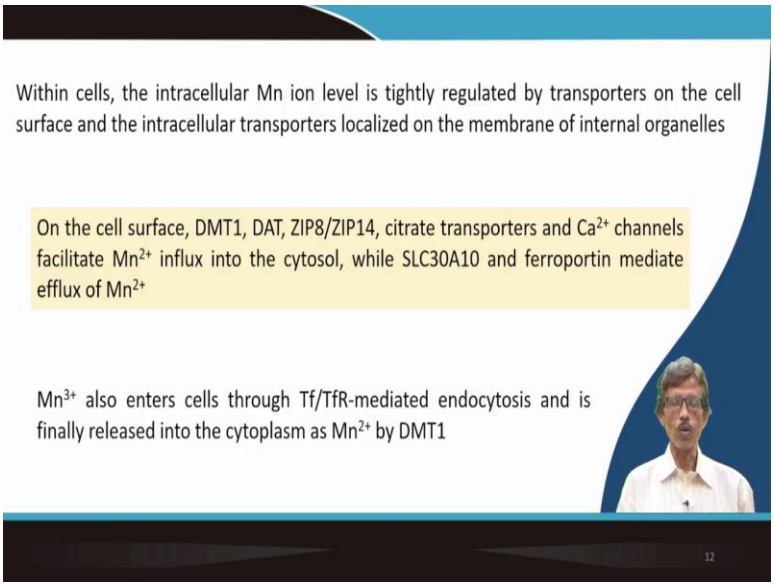

And within the cells, the intracellular manganese also can have some good levels and the transporters are involved on the cell surface and the intracellular transporters localized in the membrane of internal organelles. So, organelles are connected, transporters are connected, these all are involved for your metal ion.

But on the cell surface, some citrate transporters and other also DMT, divalent metal ion transporters already I discussed earlier. Similarly, some other groups I have also labeled like that. But the calcium channels are also important, because the properties of calcium and manganese are similar in terms of its charge and some other properties in terms of metal ion property with regard to coordination chemistry.

So, you can have some interference at the calcium channel also. So, these channels we will talk afterwards also the calcium channel and their role. They facilitate the manganese 2 plus influx and they also dependent on the ferroportin mediate efflux of manganese 2 plus.

Then finally also that another oxidized form, oxidized form you need other material for it they are endocytosis and the manganese 2 again DMT1 the divalent, since it is the divalent one, it can take care of that particular metal ion also like other iron 2 and other bivalent metal ions.

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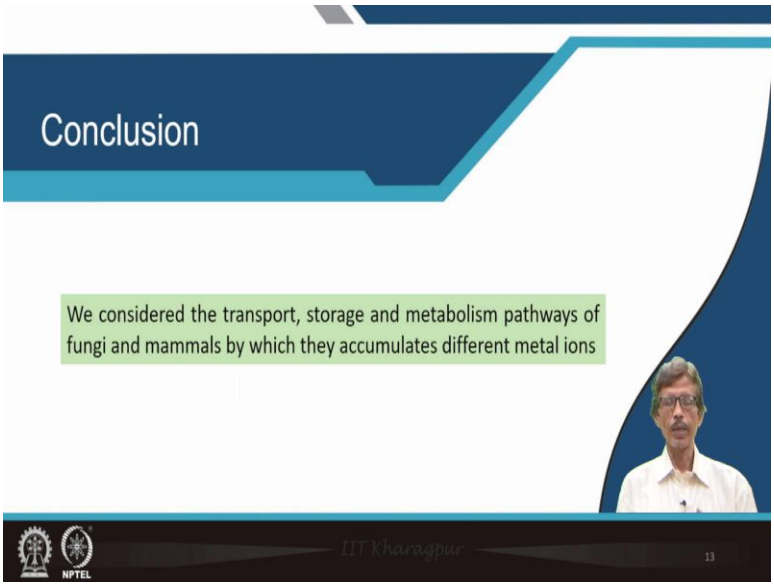

So, in conclusion what we can say now is that we have considered so far the transport, the storage and different metabolism pathways apart from only the homeostasis part. So, next two classes will be devoted to those homeostasis discussions in all these categories from plant to mammals, but here separately we have discussed these two things that transport storage and metabolism part. Here today we have finished it that the fungal thing and the mammalian thing where these are important for the very basic thing what we are talking is the accumulation of these metal ions.

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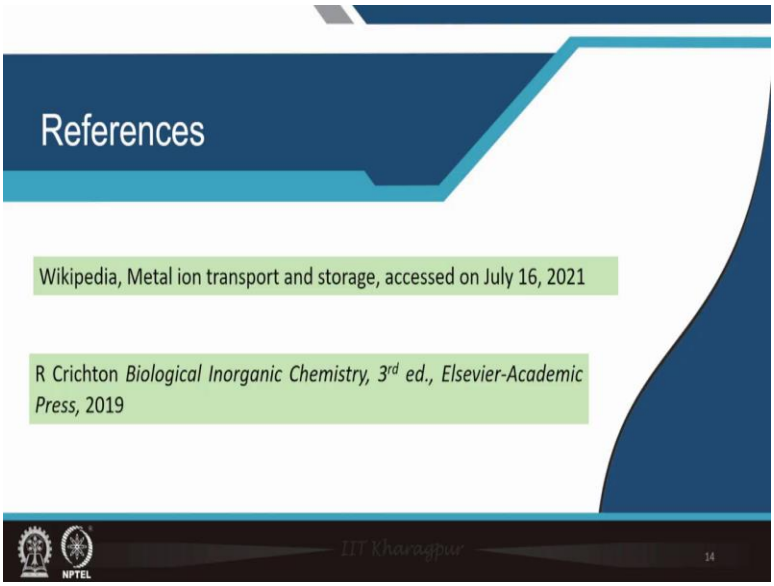

So, again we can think of the metal ion transport and storage in Wikipedia page and the book, the only book I am giving you all the time the same book. There is no burden for your literature. Only you follow these lectures and if possible you go and see a little bit of this book. You will have good idea about what we are telling or we are discussing. Thank you all.