Bioinorganic Chemistry
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Lecture - 3
Iron storage and Transport - II

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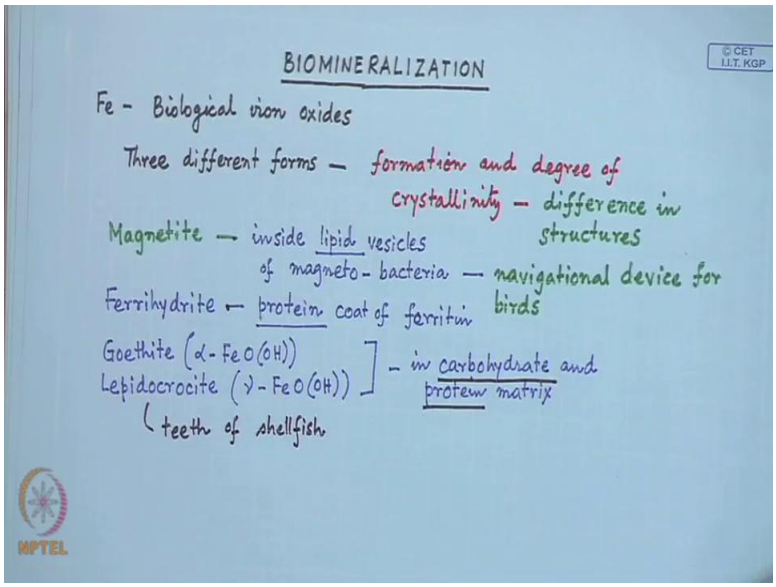

Hello. So, in this class we will be talking about biomineralization. So, the formation of ferritin from the iron source, from our food material or any other thing, is also can be talked as biomineralization. So, within our body or some of the bacteria, so iron is stored in a definite form for the different functions, and those iron molecules are utilized afterwards for the synthesis of some important bio molecules. So, in case of iron, when we see that iron is present in the ferretin molecule, and the biomineralization process can be termed as the formation of biological iron oxides. So, we all know that how nature is, giving us some mechanism, such that iron ores and iron minerals are formed in nature and on the earth crust.

So in the same passion, the mechanism of formation of biological iron oxides are pretty difficult. And there are basically some forms, and at least the most studied one we read here; there are three different forms, because these forms are very important to know, because they are related to some of other interesting areas, to know that the biomaterials. So, how we get the nature is devising all these things, and if we can understand little bit of the formation of these materials, and their typical functions, because some of them are

magnetic materials, some of them are not; like magnetite and all these thing. So depending up on their simple crystallinity, how they are crystallizing in to the systems, what we have. We have a typical matrix, the protein envelope what is a typical natural one. So, biological part is there your reaction vessel, or the micro reactor is nothing but your protein envelope, and within the protein envelope, iron centers are entering, and that are typically crystallizing within the particular core.

So, the different forms, they are basically controlling the formation, of all this bio minerals. How they are formed, and their degree of crystallinity, because their crystal structures are different. So, the crystal structure for this particular form, when they are forming one after another; that means, they have different structures, the different structures. So, one such example for this material is magnetite. So, they are magnetic in nature, but they are formed in a typical environment, which is little bit different, which is nothing but inside the lipid. The biological part which at taking the help of for the crystallization of these iron centers, are lipid vesicles, of some magneto tactic or magneto bacteria, because these particular things are also present in different birds, which can fly from one place to another, for navigational purpose, which is therefore a navigational device for birds.

So, they can fill for, within their body the magnetic part is there, and they can fill the corresponding direction, when they travel from one side to another. Then another important material is, ferrihydrite, which is forming from the protein coat of ferritin, just we have seen. So, one is the lipid vesicles, another is the protein and next is goethite, which is alpha form of F e O O H hmoxohydroxo iron alpha form, and lepidocrocite, which is nothing but its gamma form, and these two are forming in another medium. So, matrix is different, the medium is different. So, they are formed in carbohydrate, and protein matrix, this is the mixture of these two.

So, this lepidocrocite is present in the teeth of some shell fishes. So, all this formation of these; that means, whether they are lipid, or protein, or carbohydrate and protein mixture. Not only the availability of the iron site, but some other thing; that means the other, an ionic form which is utilized for precipitating the iron in this particular form. If they are purely oxo and hydroxo, if no phosphate or others an ionic form is not there, but the concentration, or the gradient of these an ion, can control the corresponding structure, and morphology of the species.

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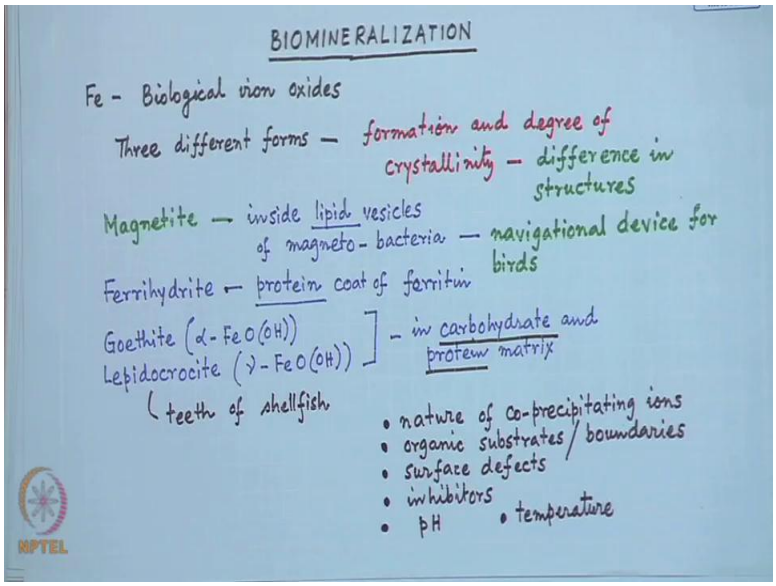

So, the nature of the co precipitating, ions are important, then we have seen that these lipid protein and carbohydrate matrix are the corresponding organic substrates. Those organic substrates are also important, and those substrates are giving us typical boundaries basically, as we have seen the phosphate boundaries in case of ferritin formation. So, these are the insight coating and the boundaries. Then if we can have, some surface defects.

So, if there is some defect, so defect will be there within the growth of this particular cluster molecules, then the different inhibitors, which inhibits the growth; that means, which is taking away the iron centers, which is not reaching there for the cluster formation or the agro migration process. So, they are basically taking away or solubilising those irons. So, they are functioning as typical inhibitors, and lastly the two most important controlling factors; one is the p H, and the temperature. So, all these factors, basically control the typical growth of this particular species, whether they will form the magnetite or ferrihydrite in a typical form. So, these are all corresponding iron biminerals, but little bit we should know.

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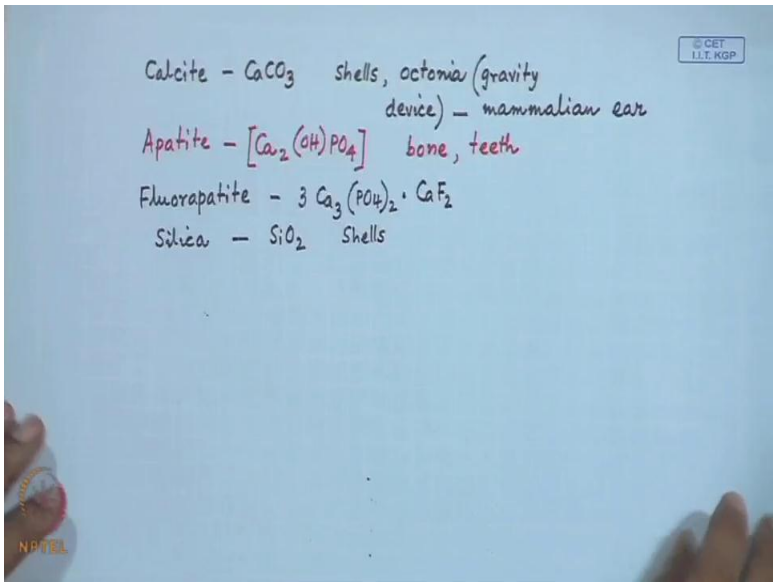

We all know from our childhood that what are there, but again we can recapitulate all these things that how these materials are important; one is calcite, which we all know that this is nothing but our calcium carbonate, which is available in different shells, in some octopus like species or octonia, and some, this octonia is basically a gravity device, which basically controls our balance, in mammalian ear it is present. So, here basically the bimineralization process, which is not completely known like ferritin formation, because incase of ferritin formation, most of the things are now known to us; that means, how the protein is forming, how iron is entering, how the corresponding accumulation of iron is taking place, but not in the case of calcium, not in the case of silicon, but we should compare the formation of this calcite, or like apatite which is giving us through this bimineralization process Ca 2 OH PO 4 present in our bone and teeth.

Then the cloro hertzen of this apatite, which is fluorapatite, calcium fluoride, and the growth of silica also in some cases, in different shells, is also important and we do not know much about all these things, because how silica is accumulating in to the system, and how the corresponding fine structure of this silica's material, is also forming there. So, this particular part we have seen, that how iron is getting stored; that means, we can store iron, or not only iron, but some important metal ions, for their corresponding biomineralization process. So, the next part will just go for the corresponding transport mechanism.

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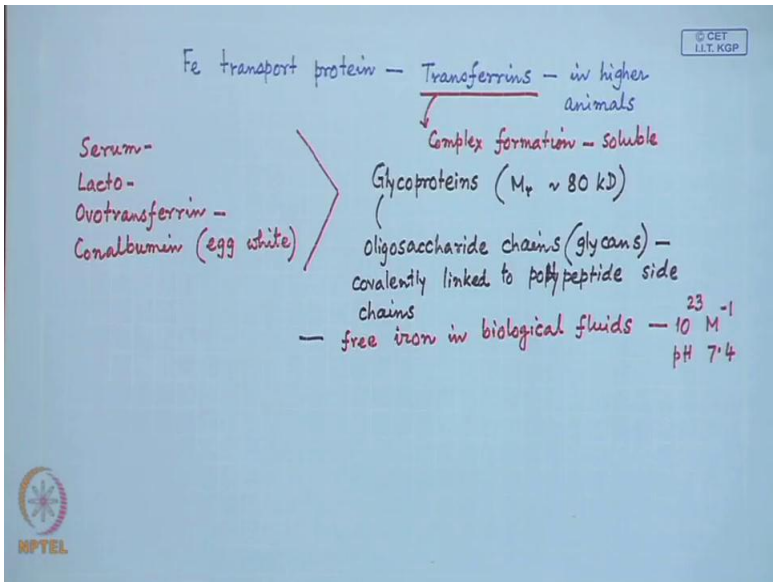

So, the protein molecules again an important for the transport of iron. So, we have now the iron transport protein, we have stored, and we have to transfer those iron centers from those ferrtin molecule, to the right side, where you can go for the synthesis of your hemoglobin or iron sulphur proteins or cytochrome molecules, and these are known as transferrin's, and these are for human body, or for higher animals only, in higher animals, because bacteria and all others small organisms they follow different mechanisms for iron transport. So this particular molecule the protein molecule, is strictly utilized for the transfer of iron, and these transfrerin molecules are utilized for what, for the complexation reaction; the most important reaction we know. So, for complexation or for complex formation, which keeps the iron in soluble form, which is very important.

So, once we have the iron in the soluble form, and then that particular iron we have stored in the oxo hydroxo form, and which is the insoluble form. Then again if we take back those iron, we have to solubalize again, and some good groups, and some good ligands would be available, which can bound to these iron, and can transfer those iron from the ferritin site, to the site of the synthesis of the important molecules. So, there are several such transferin molecules are available, when they are present in our blood, they are known as serum transferring. When they are present in milk, they are known as lacto transferin; serum transferring, lacto transferin, then ovotransferrin, and conalbumin, which is present in egg white, present in egg white. So, all these molecules, these

transferrin molecules, are basically monomeric in nature, and they are glycoproteins, of molecular weight about 80 kilo Dalton.

So, molecular weight can be determined also, and these are therefore, proteins that contain what, that glycomin, they have oligosaccharide chains, which are also known as glycans, glicoligons means few. So, two to ten saccharide chains are there, and which are ultimately lent covalently to the polypeptide side chain, covalently linked to polypeptide, side chains, and these particular mechanism is useful, to control the free iron, which should be useful in biological fluids, because these irons we have to deliver to the cells. So, some important groups should be available, which can bind to this particular iron, and this tranferrin molecules are very high effinity for iron binding.

So, the formation constant for this complexation is pretty high, which is sometime 10 to the power 23 mole inverse at p H 7.4, which is also very important, when they are very strongly complexed, it is not possible to take out that iron by some other groups. Some of other donor groups are also available in the biological system, but if your formation constant is not very high, it will only related to that particular side, otherwise it will just go to the other molecules.

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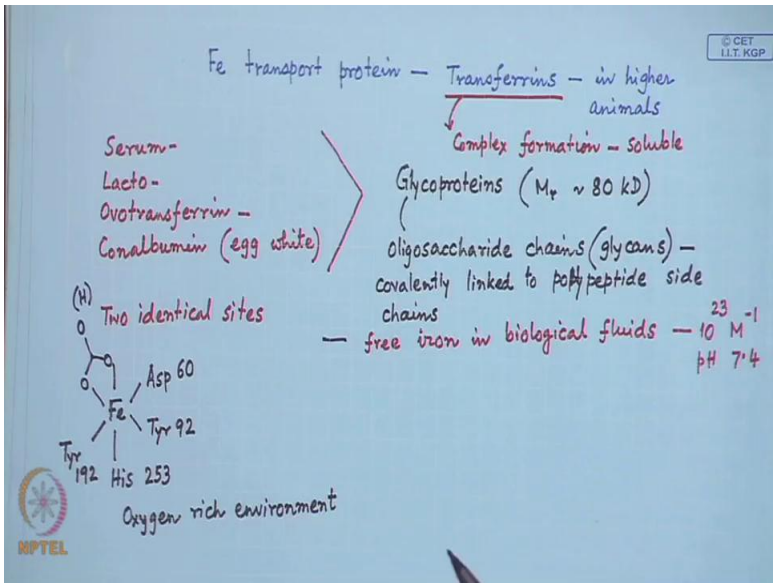

So, when it is delivering those irons to the cells, it has two identical sites for iron binding. Two iron identical sites, and these two pockets have been identified, and that is why, it can be considered as the diferric unit. So, transferrin molecules are therefore, the

diferric unit. So, two particular domain is available, where it can bind iron sites. So, again the most preferred coordination geometry will be followed here, in the octahydral geometry of iron, and for knowing these complex molecules. As a co hydrogen chemist what we always prefer to know, because we are always trying to locate the corresponding metal site, and it is immediate coordination environment. So, iron site is there, then the ligands.

Now our ligands will be the corresponding 10 10 groups what is available from the polypeptide chain which is as parted 60. 60 is your sequence number from the polypeptide chain then tyrocin 92, then hysterin 253, then again tyrocin 192. So, we have four positions fulfilled by the polypeptide chain. So, we have the sequence. So, the polypeptide numbering is from 60 92, then 192 then 253.

So, is recalling is there and two other positions are occupied by a very interesting group which is nothing but your carbonated iron. So, which is which can be considered as your co precipitating agent, what we are just discussing. So in presence of carbonate, and if you do not have the ligand system what you get; you get the ferrous carbonate. So, when it is ferro cyanide, it is only the ferrous carbonate and ferrous carbonate can be precipitating out from the system, but in this particular case, the insertion of the iron within the transferring systems, is due to the presence of that carbonate or bi carbonate iron. So, it is not only the carbonate or sometime it can be a bi carbonate anion, both of them both of the carbonated anion as well as bi carbonated anion, can function as a very good o obidented ligand. So, these are from the carbonate or bi carbonated species, so most of these.

So, this is phenol tyrocin is phenol as part it is carboxine, only one is nitrogen. So, again the iron center and mostly we see, you can see that this particular thing is again in oxygen environments. So, only one is nitrogen, so it is in oxygen rich environment, and the function of these particular carbonate is also important, because without this particular carbonate, your iron cannot be strongly bound to that transferrin molecule. So, this has a typical synergistic effect. So, whenever the carbonate or bi carbonate anions are available; that means, the basic iron carbonate or bi carbonate species, as they whole is trapped inside the transferring molecule. So, if you can have some mechanism, where you can dissociate the carbonateor bi carbonate anion from the systems; that means, sometimes it is only controlled by p H. So, p H is the most important factor over here.

So, if you can control the p H, it can be protonated in one step to bi carbonate, and then to carbonic acid.

So, when you take out the carbonate, your iron will also go away, because without this particular carbonate anion; that means, when all the four coordination sides are there, but that particular arrangement is not very much stable, you must have this corresponding carbonate; why this particular carbonate is not only bound to the iron, and this particular fashion which is not a very well known fashion of binding to a first transition metal ion; like acetate we know that acetate in bidented fashion, it is not going to bind very nicely, because it is forming a four membered ring. So, four membered ring most of the cases it can function only as a biging motive. So, when they are bound to the iron center and if we can determine, because if this structure is known very, we will find that one of the f e o bond is short and another is long; that means, it has some weak interaction with the second oxygen. So, basically it is functioning as a monovented ligand, since the other position is not available for binding, by some other donor atom, it is only occupying that particular position loosely.

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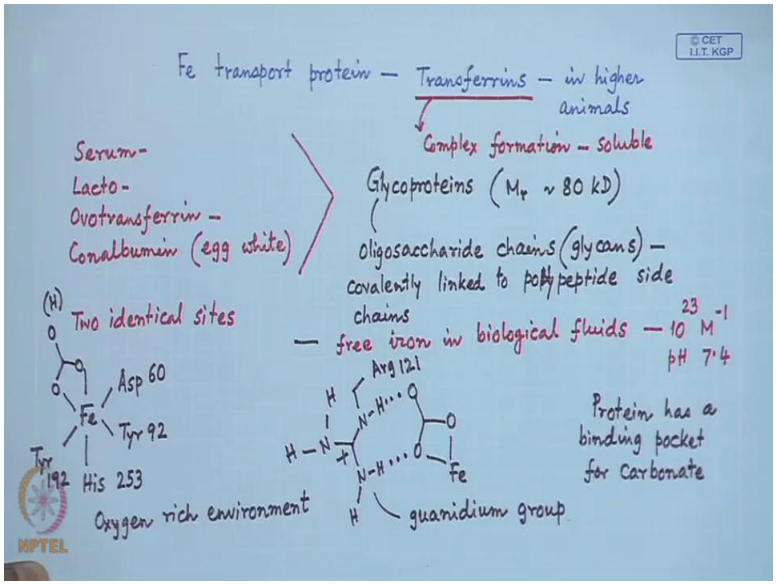

So, these carbonate an ion has some other pocket, which is by the protein itself. So, the entire protein molecule, has a binding pocket for carbonate; how, by some non covalent interaction, because you have some free groups; three oxygen groups are there. So, this oxygen, which is forming iron, and these will form some hydrogen bonding interaction,

which some other amine acid side chain, which is argnus, which is A R G 121, so we have argnus 121. So, this side basically, this side of the envelope of the transferring molecule. We have another arginine residues, and that arginine residues number you can also find out is 121. So; that means, 60 92 then it goes to 121 then it is coming to tyrocine and then to hysterin.

So, the hysterin has the n numbers as 253. So, this interactions with this hydrogen bonding, with the arginine residue of the polypeptide chain, further stabilize the carbonate anions. So, these non-covalent interaction only the hydrogen bonding interaction, from the protein side chain can stabiles this particular small molecule, within the cavity of this particular transferrin molecules, and this particular part is your guanidinium group. So, guanidinium group of arginine, is utilized for stabilizing your carbonate anion. So, we have a mostly oxygen rich environment, and where you can have the corresponding carbonate anion, and that carbonate anion is stabilized by hydrogen bonding interactions.

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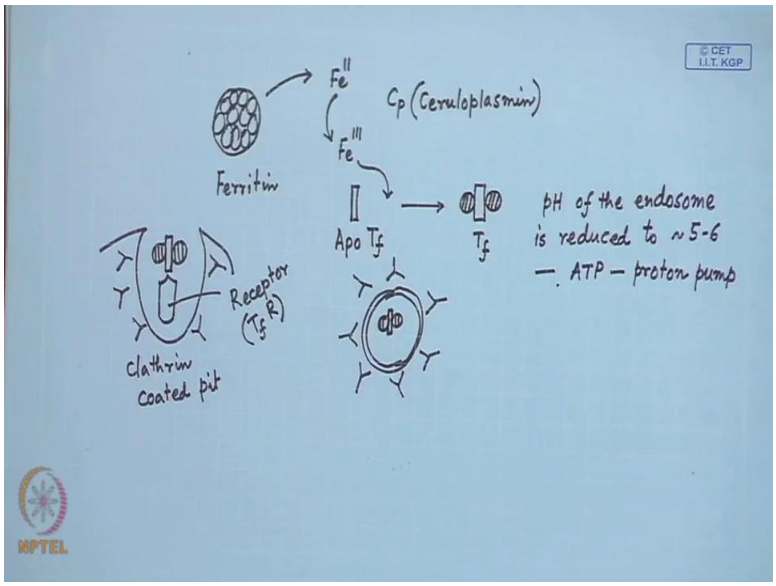

So, what we have in our hand, is that you have to transfer the iron centers present in the ferritin molecule. So, this is your store house for iron in the ferritin, and these particular iron when it is coming out as Fe 2, and this Fe 2 can be oxidized to Fe 3 by ceruloplasmin C p. It is a copper barring protein molecule is available there,

ceruloplasmin, and once it is oxidized, this particular ferric ion goes to apo transferrin moleculehm.

So, this apo transferrin molecules has two identical iron binding sites, and extra structure has proved that; that it has two typical iron binding site. So, when it is taking this iron, it is transferring from apo transferring to iron loaded transferrin molecule, and you have two such pockets what we just discussed for this iron site for transferrin molecule, so you get that. And when this particular thing is forming, so accumulation of this particular iron site within the apo transferrin is further stabilized by a system, where iron binding site, and one biological part is playing some important role there, within a cavity type of arrangement, which is known as clathrin coated pit.

So, these are basically the clathrins. These are nothing but you know the name, which are the receptor for transferrin. So, how we designate that, this is designated as T f R; receptor for transferin. So these receptors are playing some important role, because when this particular apo transferrin molecule is loaded with iron, they are sitting on this particular clathrin coated pit, because the clathrins are there. So, these some protein type of molecules are there, so these are basically the clathrin, and these clathrin's are responsible for closing of this pit and opening of the pit. So, when this particular iron is entering. So, within this particular pit they are forming. So, at one hand, you have theapo transferrin your taking of the iron, and that iron loaded systems is there, and this particular thing when its forming a circular form.

So, ultimately when iron is getting entered, so you get the corresponding. So, you have the clathrin. So, it is basically a it is giving a cell like structure, and within that you have the iron loaded transferrin molecules are sitting inside. Now there is something; that means, which basically transfer this to the endosome, so and the p H of the endosome. We are just looking at how the carbonate binding is important, for your iron binding as well as the iron release, and how it is being checked by controlling the simple p H. So the p H of the endosome, is next reduced to; say roughly 5 to 6 by a ATP dependent proton pump. So, because we all know that the ATP can control the p H of a particular medium. So, when ATP dependent proton pump is involved and this particular proton which is available there is responsible for the protonation of the bound carbonate.

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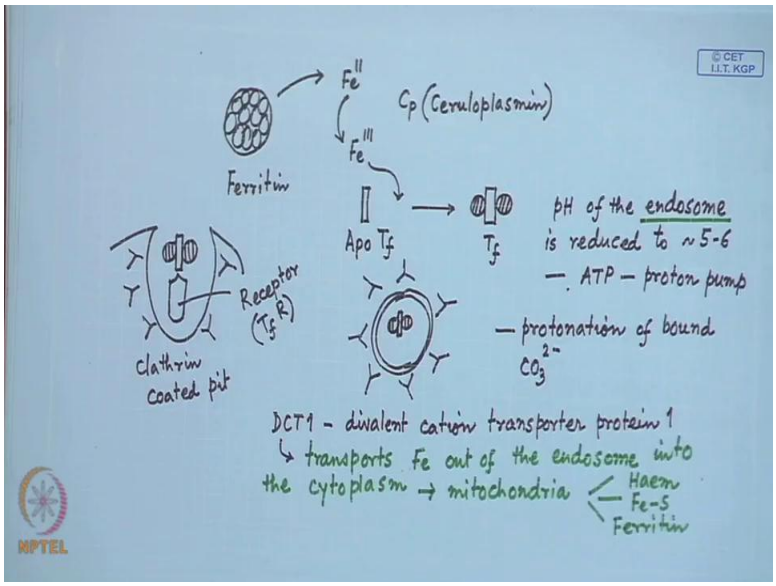

So, one transporter protein is now coming into the picture, just you know the name. Do not worry about this name, its name is also very simple, which is divalent cation transporter protein. One; there are several of them present, so D C T 1 is coming into that picture. So, these D C T 1 will transfer this iron out of the endosome into the cytoplasm. So, endosome was there, so these are though not very complex biological term, but you should all know now, that this particular D C T molecule then transports, iron out once the carbonate is getting protonated, out of the endosome into cytoplasm.

Then it goes to mitochondria, and mitochondria transferring that iron to again back, to the synthesis of heem type of molecules. This is so how you utilize the particular iron now, or where we have started our discussion, or iron sulphate proteins for the synthesis of iron sulphur proteins. And if we find that immediately those iron centers are not required, for the synthesis of heem molecules, or this typical ferritin molecules.

The excess of this iron can next be stored in ferritin. So, these particular mechanisms, which is solely dependent on iron coordination to the several donor atoms, and the corresponding binding of the carbonate group, and the corresponding control from the ATP; that means, ATP proton pump can control the corresponding protonation of the carbonate group, and it is getting released. So, p H is utilizing for the binding of the carbonate, and sometime this iron we are generating in our system, so it is also in C2 produced. The carbondioxide what we are producing, those carbondioxide during

protonation giving you the bicarbonate anion, as well as the carbonate anion. So, this particular ligand is playing that particular role; that it is utilized for iron trapping and binding within the transferrin molecule. Then if you just simply from one particular part to the other, if you can control the p H of the medium and that p H control can be utilized further release of the iron, in higher animals.

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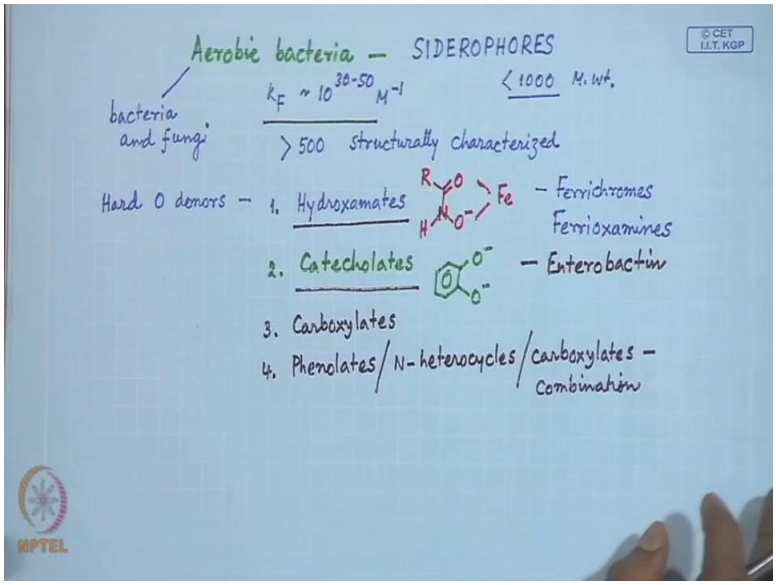

But what is the case for this iron transport for bacteria and small molecules, which we will find that in case of aerobic bacteria. We use some interesting molecules, which are known as siderophores. Compared to your transferrin molecules which are pretty complex, this siderophores molecules are low molecular rate compounds, of say about less then thousand molecular weight, but they have very high affinity for iron. Sometimes they are formation constant for complexation is, varying from one source to the other to 10 to the power 30 to 10 to the power 50 mole inverse. So, these aerobic bacteria are present, or they are originating from the different bacteria and fungi. So, this mechanism is useful for the microbes; that means, the microbials cell to take up this iron, and so far a huge number of these which is greater than 500. So, 500 such species have been structurally corrected, because they are low molecular weight species.

So, molecular weight is less than 1000, because they are low molecular weight species .These particular siderophores molecules had this possible to determine their structures. So, they are structurally characterized at the same time, for their iron utilization. So like

your transferrin molecules, they also have the hard oxygen donors. So, once you identified the hard oxygen donor groups are available for iron binding and their irongilation, for the transferrin in all these bacterial gilating agents, which are siderophores, and one group of these molecules are; that typical hydroxamates, driving from hydroxamic acids. They are hydroxamates and hydroxamates are C O N H O H hydroxamic acid from hydroxamic acid. So, you get. So, when these two groups are binding to iron.

So, you get a o o donor bidented part. So, all these molecules are very beautiful, because they are all providing very good organic ligands, to bind your iron, and these hydroxamates when they are present, and those molecules which have been characterized, are ferrichromes and ferrioxamines and another category contains catecolates.

So, you have at the end point, you have the catecolls; example of that group is enterobactin. Also we can have carboxylates and points and phenolates, together with other nitrogen bareingheterocycles, or carboxinates; that means, a combination of these true. In first case when we have hydroxamates, all the three groups which are available for octahydral iron center; that means, you need three such groups, to bind iron site. In case of catecholates also, you have three such catacholate groups which are available for binding your iron site, and we get a corresponding octehydral iron site; that is why your corresponding formation constant is also very high. So, these particular molecules are isolated during 1952 or so.

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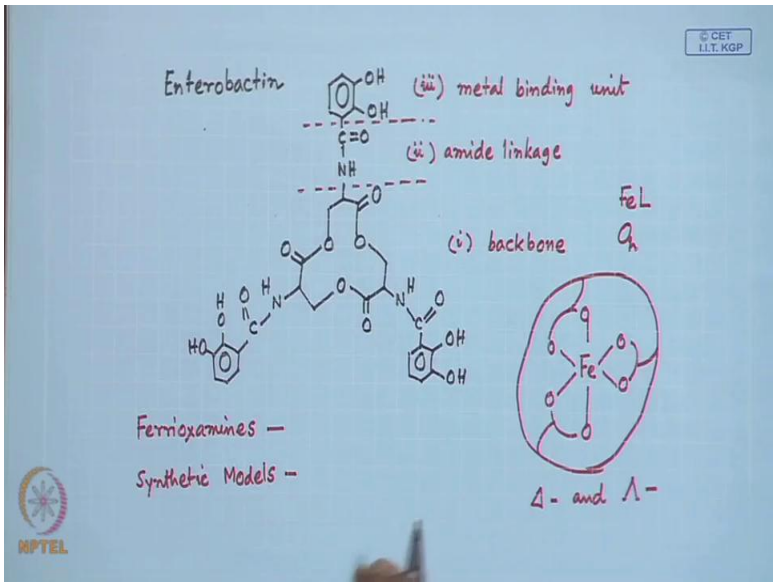

And one such very important molecule is your enterobactin, and which has a. In most of this cases, either they are linear in structure or cyclic in structure till this is repeated on three sites. So, this is your whole structure, it has three parts; first word is your back bone, which is nothing but a trimester, it is a cyclic trimester, and which is very important to know that, because for binding of iron you have these catecol units are important, and this catechol units are important, and this catechol units forming a compound which is your FeL. The composition for the compound will be f el. So, you have the tirester part at the cover and you have three pendent groups basically. So, it is a basically caping one. So, three pendent groups are there, so this pendent group, the second pendent group, then the third pendent group forming a octahydral iron complex. So, this backbone is important, then the second part is your amide linkage, and third part is your metal binding unit.

So, this particular form how they are forming is a very interesting molecule, and it has seven part of so many synthetic studies on these type of molecules. So, this is one part one o part, this is another o opart, and this is the third o part. And if you consider the entire tri cyclic, the cyclic triester part at the top. So, which is basically connected, which is basically connected from these, and which is basically connected from this; from the top. So, you have three pendent groups are there. So, basically it is anchoring, is a like a crane is anchoring. So, it is when they are, you have a very high a formation constant, it is immediately taking up this particular iron from there, and when they are forming, so

depending up on the corresponding orriation. It can form two forms, what we know, the delta form as well as the lambda form. When you few along the C3 axis of the octahydral. So, both these two form sites are forming there, but for some of the metal ions, because it is not only true for iron, but it is also true for benedium and for some other systems, and marine organisms.

So, these bacterial thing is also very important to know, because how we are competing with bacteria for iron, because bacteria also need iron for their regular survival, and when one form is forming; that means, in some cases the delta form is forming, and in some other cases the lambda form is forming, and if we are able to hydrolys the triester form. So, that can immediately give us the corresponding iron, like the way we are getting the corresponding carbonates for the iron release from the transferrin molecules, because these trimester backbone is not so stable for this siderophore molecules.

So, all these things, next day we will see some other groups, which are like ferrioxamines and some synthetic models, how good they are for iron gilation, and what type of this linear molecules, if we can have some medicinal importance, because if we can have some iron overload in our body. If we accumulate large amount of iron, not only in our heart, splin, liver, or brain weather we can take out those irons, and some of these groups, because they have very high binding affinity for iron. If they can become consumed as medicine, they bind iron and they can go out from our body. So, that will see in our next class.

Thank you.