Tissue Engineering
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Lecture - 04
Scaffolds: Extracellular Matrix

So today, we will talk about the Scaffolds. We looked at the three different arms of the Tissue Engineering triad; we saw materials, cells, and signals. So, we looked at a brief introduction of all of these things. Today we will start with aspect, which I work on, which is the designing of scaffolds. We will talk about different materials that can be used for scaffolds and what are the desired properties and so on.

The first type of scaffold we are going to talk about is the Extra Cellular Matrix itself. As you know, ECM is present all through your body, and that is where the cells attach and grow. So, there are two aspects to be gained from this lecture; First is to understand what the ECM is? And how it is relevant for tissue engineering?

First, we need to know what the components of ECM are? How it is structured and so on? So that we can try to mimic it. So, that is a crucial aspect which we need to start with, and then we will talk about how ECM is currently being employed in tissue engineering, and there will also be a small reading assignment, which is just a research article, which you would have to read, which talks about using extracellular matrix for tissue engineering applications. So, before we go into details of the extracellular matrix itself, what are scaffolds, and what are their roles?

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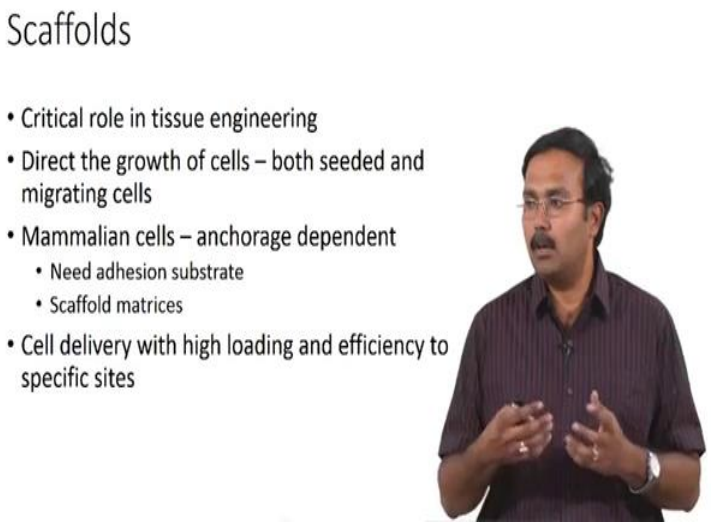

Scaffolds have a very critical role in tissue engineering because they actually can direct the growth of cells; it could be either seed the cells on the scaffolds and use this cell-seeded scaffolds as a tissue-engineered construct, or you could use only the scaffold, then you might have cells migrating towards this or away from this. So, it can regulate these factors.

Mammalian cells as I had already mentioned are anchorage-dependent, they are actually adherent cells. So, they need some substrate on which they can attach and then grow. So, scaffolds are the matrices, which provides this type of surface. Also, they provide mechanical support for the tissue. Depending on the tissue, the mechanical properties and other physical properties can be imparted by the scaffold.

So, the cells which are delivered, you might want high loading, and you might want specific cell attachment to the sides of which you are interested in. So, for these types of things, you need a scaffold, which needs to be appropriately engineered.

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So, having said this, what are the desired properties of a scaffold? Can you think of properties, which you would want in a scaffold? I will write down as you shout out the answers you think of.

Student: Compatibility.

Ok.

Student: Mechanical properties.

Ok, Compatibility, mechanical properties.

Student: Biodegradable ability.

Student: Biodegradability.

Ok, Biodegradability.

So you had something?

Student: Same.

Ok, What else?

Student: It should not be immunogenic.

Ok, Part of compatibility ok.

Student: Higher cell adherence.

Ok, Cell adhesion.

Student: Porosity, high surface area.

Porosity ok, why porosity?

Student: Nutrients.

So, the other ones are more direct you know why, but porosity why?

Student: Because we will be adding molecules that should diffuse and reach the tissues.

Ok, so, it will help in diffusion that is one reason. Can you think of any other reason?

Student: Cell infiltrate nutrients.

Cells will infiltrate.

Student: Oxygen; oxygen, and nutrients.

Oxygen transfer, ok.

Student: Toxic byproduct. So, the cell also.

So, all these are diffusion. So, diffusion in and out that is one aspect, and then cells in infiltration are one aspect ok. Porosity also will give you the real structure of an ECM. It is closer to what an ECM would be, ECM has these porous matrices in which the cells can adhere and grow ok, anything else?

Student: Nontoxic.

Again part of compatibility. Ok, is that all, can you think of anything else?

Student: I do not know the word for it, but like there is a possibility that scaffolds can be infected by bacteria or foreign pathogen so.

Ok.

Student: The that property I do not know what is the word?

So you want the scaffolds to be.

Ok, to be bacteriostatic or bactericidal.

Student: Yes.

Ok, so that could be a desired property, but again that can be part of compatibility right. So, it will again, just like how your own cells rejecting it, having some infections can also come as part of compatibility, but you can lessen it as separate property as well. So, we will just call it antibacterial; how that antibacterial property is given can be discussed, and it might also depend on what type of tissue you are talking about right.

So, if you are talking about wound dressing, which is for skins, then you might want a very antibacterial material, whereas if it is going to be for something else it might not be that crucial. Ok.

Student: Interaction with growth factors like adherence with growth factor with the ECM.

So, the ability to deliver signals, can I say that way, signal delivery.

Anything else.

Student: Lightweight.

Lightweight. Ok, why? So, it is.

Student: So, what if it is an implanted in long; like, it won't restrict our movement or something?

So, I would say it needs to be of similar density as your natural tissue. So, saying lightweight is probably not the best way to describe it. Because see, if you are going to talk about a bone tissue, that is obliviously going to be heavier than soft tissue and weight is not the parameter you are looking at a density which is more uniform. So, what is the fundamental difference from properties standpoint between density and weight?

Student: Weight is volume-based and density is material based.

Correct, what is that property.

Student: intensive.

Intensive properties and extensive properties. Intensive properties are ones, which do not depend on the size and extensive properties depend on size. So, when you are talking about something like this, you are talking about the property of the material itself, it should not vary with the size. So, if you are replacing a large tissue, it is going to be heavier anyways, ok, what else? Ok.

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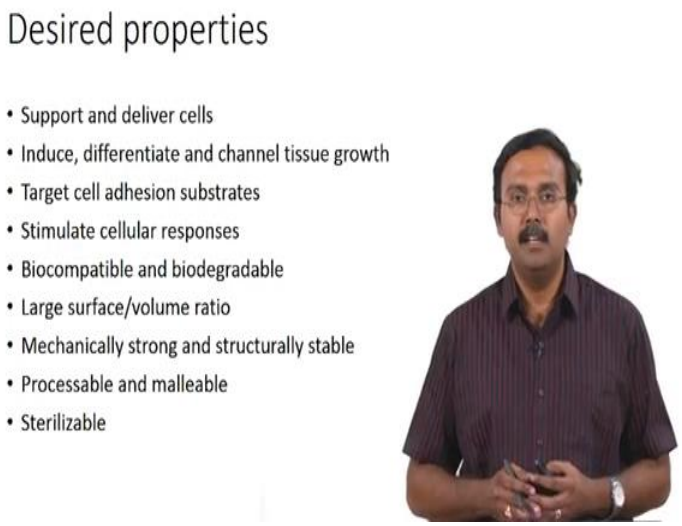

So, let us look at what I have; so, many important things you have given; support and deliver cells, induce, differentiate and channel tissue growth, target cell adhesion substrate, and stimulate cellular responses would all come under providing signals. So, these are just different signals which we are looking at. Biocompatible, biodegradable; so again, compatibility is crucial, because you need to make sure there are no immunogenic responses and so on.

Degradability depends on the type of application. So, how fast or slow it needs to degrade will depend on the rate of regeneration of the tissue we are talking about. And then you have to talk about the large surface to volume ratio, which is one of the aspects, which porosity will provide you. When you have a large surface to volume ratio, for the same volume of the implant, you can actually have a lot of surfaces on which the cells

can attach. The cells are only seeing surfaces; they are not going to see the scaffold as a whole right. So, when you provide a lot of pores or if you make it into nanofibrous matrices, then you have a lot of surface area for the same volume. So, this will help the cell adhesion and growth.

Mechanically strong, structurally stable. So, these are all the properties which we think of from a biological standpoint. From a final production and manufacturing standpoint, we need the material to be processable and malleable, and it should also be sterilizable. So, there are different techniques which you can use to sterilize, but whatever technique you use should not affect the properties of the material right. So, if you are going to use protein on top of these scaffolds or like collagen; it should not get denatured, while you are processing, while you are sterilizing it.

So, these are important factors which you need to account for and choosing the technique used for sterilization would also matter, and you can design things appropriately. Ok so, these are the desired properties, you are looking for. How you provide these desired properties is the challenge. So, you need to look at what materials can be used, what chemistries can be used for crosslinking. So, depending on the level of crosslinking, your mechanical strength can actually vary and so on.

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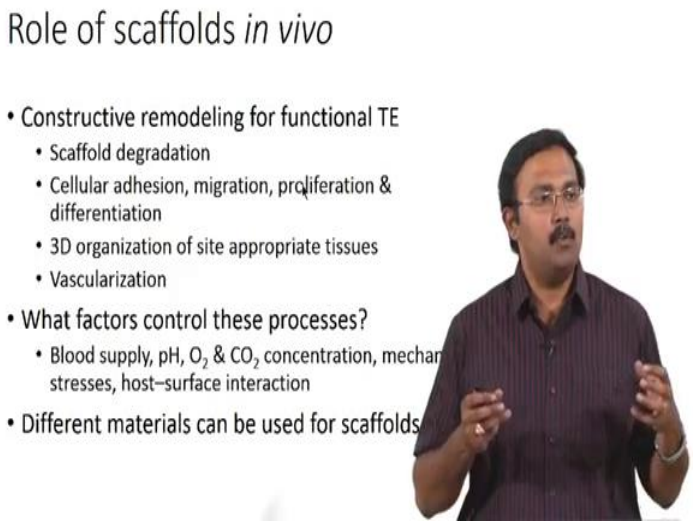

Student: Might be a silly question, but do optical properties matter, when it comes to scaffolds?

Depends on which scaffold, right. So, the optical property of a scaffold would matter if you are trying to engineer a cornea right. If you are going to engineer a liver, I do not think optical properties matter. If you are going to engineer nerve tissue, then your electrical properties would matter. So, depending on the tissue you would have to design the properties. Physical properties will primarily be driven by the type of tissue you are trying to engineer. Mechanical properties; bones are going to have different properties, muscles are going to have different properties, and so on.

So, what is the role of scaffolds in vivo? It helps in the constructive remodeling of functional tissue, engineered tissue. So, this scaffold has to degrade, and cells have to adhere, migrate, proliferate and differentiate. 3D organization of the site to form appropriate tissues should happen, and it should also help in vascularization.

So, this is what would happen when a scaffold is placed in vivo ideally, right. So, if these things happen, you know that the scaffold is doing its job. So, what factors will control these processes; blood supply, pH, oxygen, carbon dioxide, concentration, mechanical stresses, host surface interaction are all some of the parameters which can regulate these things.

For getting this type of scaffolds, people use different materials. So, we will talk about some of the major classes of materials, and we will also look at how materials can be processed to get these types of materials. First today, we will talk about the extracellular matrix.

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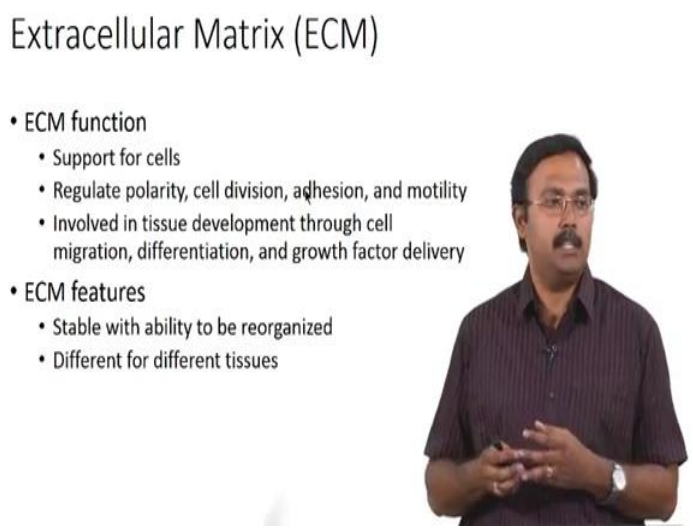

The extracellular matrix would be the gold standard because that is what is there in your body. So, if you can get the extracellular matrix to do its job and use that directly for tissue engineering; that is what you would do, but what would be the limitation of doing that? So, if you want to use the extracellular matrix, what do you think could be the limitation?

Student: Availability.

Availability is one problem; ok, can you think of something else?

Student: Compatibility.

Compatibility why?

Student: For immunogenic reasons, you have to get from the same tissue, or it elicits immunogenic responses.

So, that is true for cellular ECMs, when you decellularize it, it would not be a problem that is what I wanted to get to. So, if you actually have removed all the cells and cell debris, then the matrix itself will not be immunogenic, because all these proteins are reasonably well conserved. So, they are conserved across species ok. It will not cause any problems.

Student: Sir, so how will it is, we developed in vivo.

What do you mean?

Student: So, I have.

In vitro or in vivo?

Student: In vitro.

In vitro, how would you create a decellularized ECM? So, there are techniques for it. So, the last few slides on this lecture will be that we will talk about it, and the reading material will talk about that extensively.

ECM function is to support cells, regulate polarity, cell division, adhesion motility. It is also involved in tissue development through cell migration, differentiation, and growth factor delivery. So, ECM features which we need to understand are, they are stable with the ability to be reorganized right.

The extracellular matrix can get reorganized by activation, by the action of enzymes, like metalloproteases. We will talk about them, but we also need to understand that the features of the ECM are going to be different for the different tissues, it is not going to be the same. Even though we just call it as collagen, there are actually different types of collagen and which collagen is present in which part of the tissue matters, ok.

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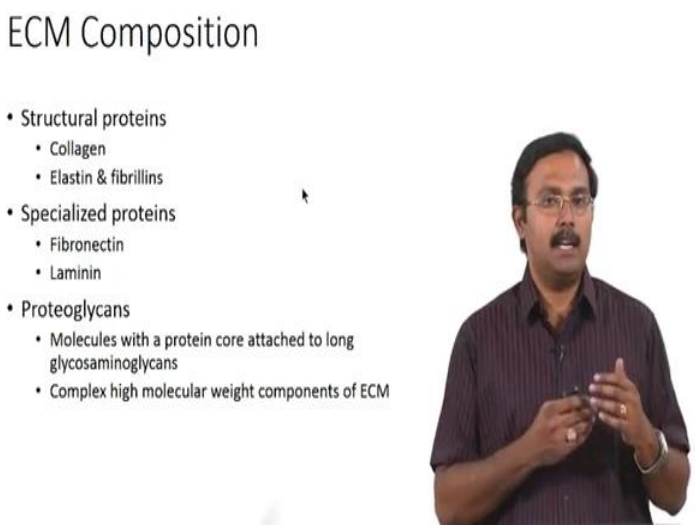

So, ECM composition can be broken down to three major classes; Basically, two major classes; proteins and proteoglycans. Amongst proteins, there are actually two things; one is a structural protein, which provides support for the tissues to grow, and the other is specialized proteins, which have special biological functions. So, the structural proteins also have some biological functions, but for simplicity, we will classify them as only structural proteins.

Proteoglycans are basically, molecules where you have a protein core to which long glycosaminoglycans are attached. These are complex high molecular weight components present in the ECM. They provide the viscosity and the fluid-like nature of the ECM itself. Amongst the structural proteins, the common ones are collagen, elastin, and fibrillins. Amongst specialized proteins, the common ones which you see are fibronectin and laminin. So, we will talk about these in little more detail.

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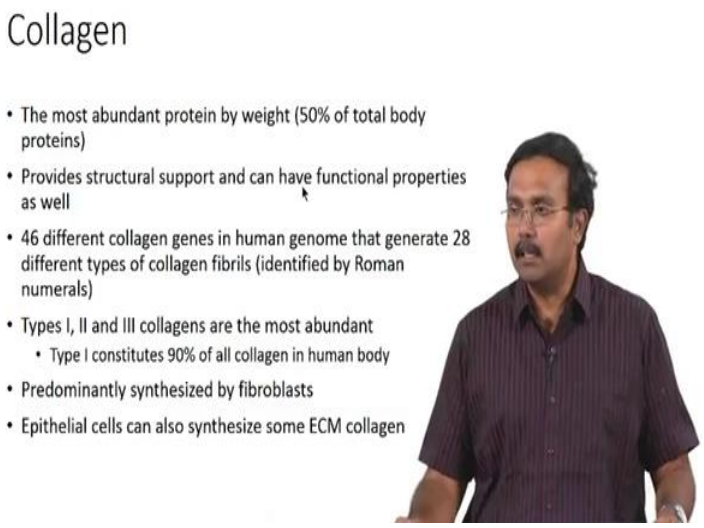

Collagen is the most abundant protein by weight. This is a very common question, which is asked in many places, what is the most common protein in the body? And inevitably, most people say hemoglobin, which is not correct, ok.

The most abundant protein in your body is collagen ok. This is the structural component; it provides the support; it also can have some functional properties. There are actually 46 different collagen genes in the human genome, and it generates 28 different types of

collagen fibrils. These are just identified using Roman numerals. So, you would have Type I, Type II, Type III, and so on.

The collagen fibrils are the ones which provide the strengths. The fibrils assemble to form collagen fibers and these bundles which are the collagen fibers actually impart the mechanical strength. So, they are very strong structures. Types I, II, and III are the most abundant; amongst which Type I is by far the most abundant. Type I, actually constitutes about 90 percent of all the collagen in your human body. So, primarily Type I is present in all the tissues.

These are predominantly synthesized by fibroblast. If you culture fibroblast and maintain certain environment, you can make these fibroblasts secrete collagen. So, there are labs, which actually do that, and in our institute, Professor Verma's lab does that. They culture fibroblast to secrete collagen.

And the yield of it is always a problem. Depends on the cultural condition, you would not know whether how much of a matrix you would get. So, this is one way to get the ECM type of a scaffold. Epithelial cells can also synthesize some of ECM collagen.

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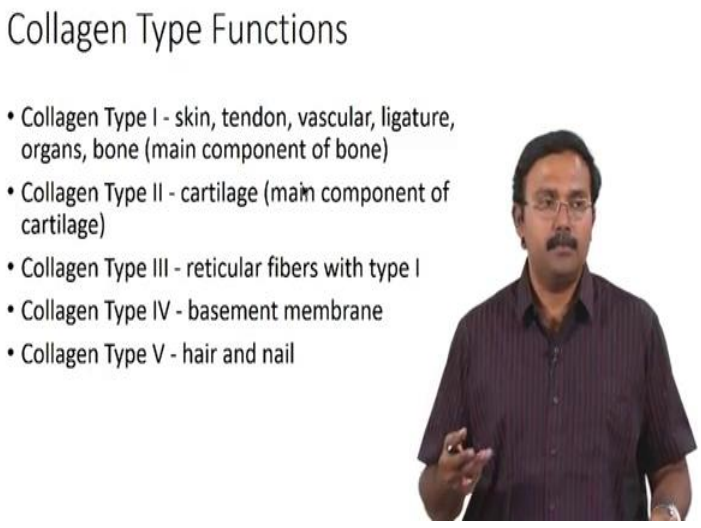

As I said, there are 28 different types of collagen fibrils, and these are some of the major ones. Type I collagen is seen in skin, tendon, vascular, ligature, organs, bones. This is the main component in bones. The collagen component of bone is primarily Type I.

And you have Type II collagen, which is mainly seen in cartilage, and Type III collagen is seen in reticular fibers along with Type I, and Type IV is seen in the basement membrane. The basement membrane is the one which separates the tissue from the matrix. So, you would have that in the basement membrane, and Type V is seen in hair and nail. They have different mechanical properties, they have significantly different physical properties, and they are seen in different tissues.

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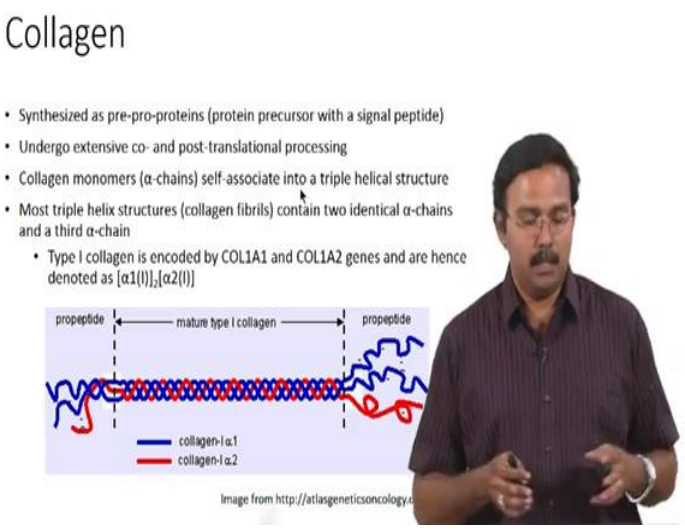

So, this is what the collagen fibril looks like. This is a triple helix which you see. So, this is a matured type I collagen. Basically what happens is they are initially synthesized as pre-pro-proteins. So, pro-protein is one which, a protein precursor, when these come along with a signal peptide, and they are called pre-pro-proteins. You have pre-pro-collagen, which is usually synthesized. From this, there are actually a lot of co- and post-translational modifications, which happen for the collagen to form the fibrils.

Collagen monomers, which are called the alpha chains; self-associate into a triple helical structure. Collagen has a triple helical structure, which is called the collagen fibrils contain two identical alpha chains and a third alpha chain, which is different.

So, the type I collagen itself is encoded by COL1A1, and COL1A2. There are actually two alpha-helices from COL1A1 and one from COL1A2. These three form the triple helix, which is shown here. The two blue ones are the collagen 1 alpha 1, and the red one

is the collagen 1 alpha 2. So, from this, they form the triple helix, which forms the collagen type I fibril.

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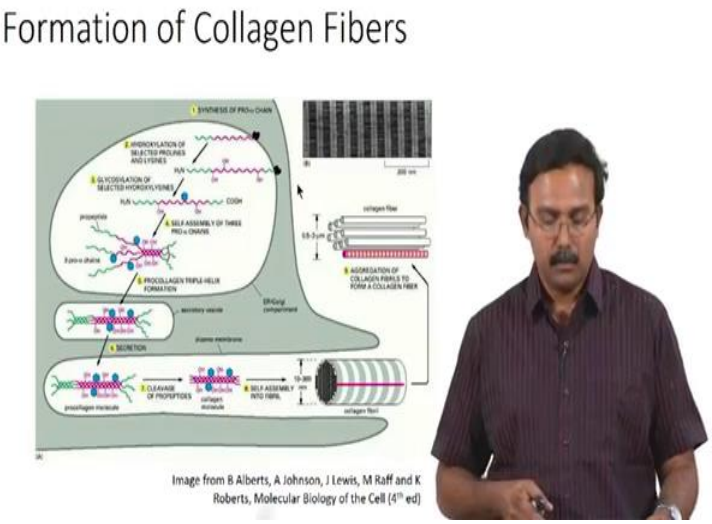

This process actually shows the synthesis of collagen. What you have is collagen fibers are produced from a pro-alpha chain. This pro-alpha chain, some of it is done intracellularly, and some of it is done extracellularly. So, the once you see after secretion, after the sixth step is the all extracellular.

So, until then it is intracellular; so you have the synthesis of pro-alpha chains, which is the first step and then you have hydroxylation of selected prolines and lysines. Collagen primarily has glycine, as the amino acid, and the next to that is proline and then hydroxyproline. So, you have hydroxylation of certain prolines and lysines.

So, the prolines are actually hydroxylated and some lysines are hydroxylated. And these hydroxylysines are then glycosylated. Once these glycosylated hydroxylysines are present, you have the self-assembly of the three pro-alpha chains to form a pro-collagen triple helix.

This pro-collagen triple helix is secreted and outside what happens is the pro-peptides are cleaved, and finally, you have self-assembly to form the fibril. So, these fibrils are about 10 to 300 nanometers thick. What happens is these individual collagen molecules, or triple helix molecules are crosslinked, using the activation of an enzyme.

Anyway so, by the action of an enzyme, you have a crosslinking, which is done. Depending on the crosslinking, you would actually have the strength. Once more and more collagen triple helices are crosslinked, you would have very thick fibrils, and these fibrils all aggregate to form a collagen fiber. So, this collagen fiber is what forms the matrix.

This is the typical process for the Type I collagen, and you can actually find a similar process for other collagens as well. Depending on the initial pre-protein; initial alpha chains which are used, you would get different types of collagen. So, this is from basic cell biology. You do not need to know the process or this biosynthetic pathways of collagen; however, what you might want to know is what are the molecules, which are the precursors for collagen, ok.

If you have that, you could probably try to use them for your tissue engineering applications, or you can try to understand some of the pathways where we can push towards the generation of collagen. You could try in vivo secretion of collagen as a way of regenerating tissues.

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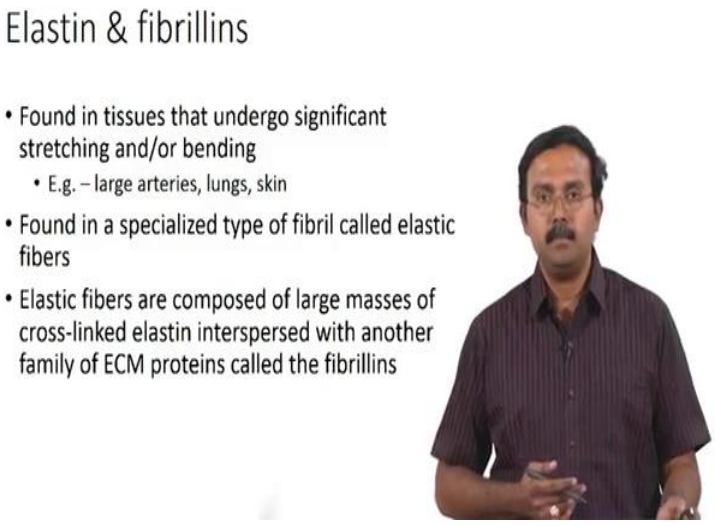

Elastins and fibrillins are found in tissues that undergo significant stretching or bending. As the name suggests, they have elastic properties. So, examples would be large arteries, lungs, and skin. These actually go through a lot of the stretching and bending right. Also, some physical, mechanical stresses are experienced by this. So, you would have a lot of

elastin or fibrillins. There are specialized type fibrils, which are called as elastic fibers. The elastic fibers contain large masses of crosslinked elastin, interspersed with fibrillins. The elastic fibers primarily contain elastin, and there is some amount of fibrillins as well.

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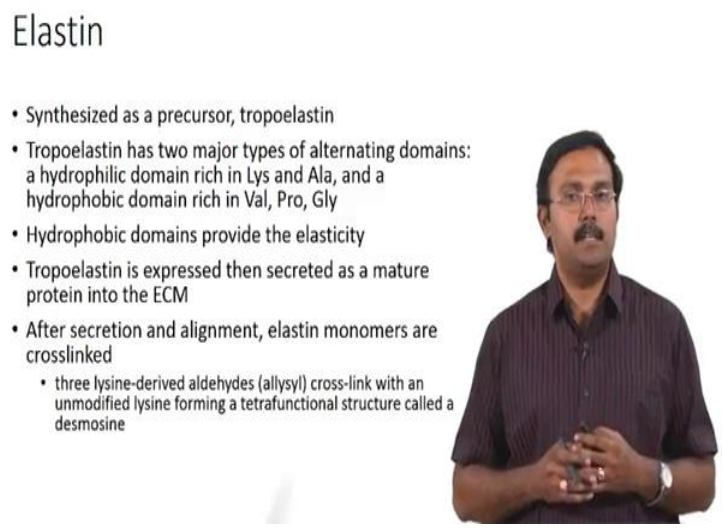

Elastin is basically synthesized as a precursor called tropoelastin. Tropoelastin has two major types of alternating domains; one is a hydrophilic domain, which is rich in lysine and alanine, and the other is a hydrophobic domain, which is rich in valine, proline, and glycine. The hydrophobic domain provides the elasticity. If you are going to design polypeptides to prepare scaffolds, then using these types of amino acids will give you the elastic property, which you are looking for.

Tropoelastin is expressed and then secreted as matured protein into the ECM. After secretion and alignment with the ECM, elastin monomers are crosslinked. And this three lysine derived aldehydes, crosslink with an unmodified lysine to form a tetrafunctional structure which is called as the desmosine. So, this is the elastin fiber which you would have.

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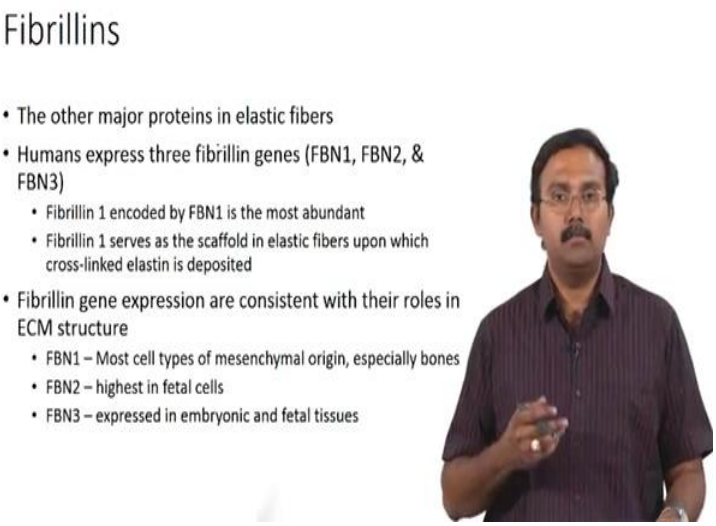

The other major component in the elastic fiber is the fibrillin. There are actually three fibrillin genes in humans, and fibrillin 1 is the most abundant, and it serves as the scaffold for elastic fibers after crosslinking with the elastin itself. So, this gene expression is consistent with the role in the ECM.

FBN1, which is fibrillin 1, is secreted mostly by cells from the mesenchymal origin; it is seen a lot in bones. FBN2 is secreted highest in fetal cells, whereas FBN3 is expressed in embryonic and fetal tissues. Some of these are not seen as very common in adult tissues.

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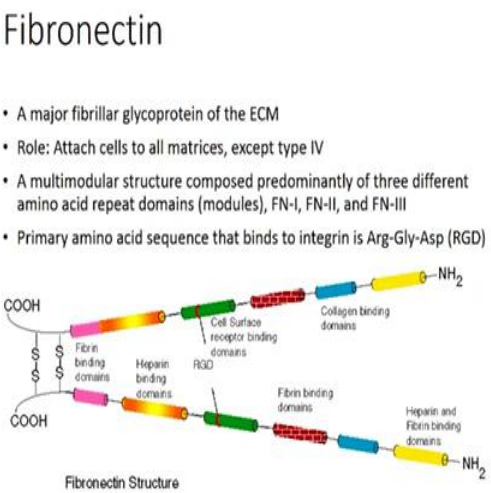

So, those were the structural components. You also had a couple of functional proteins, which we had mentioned, fibronectin and laminin. Fibronectin is a major fibrillar glycoprotein in the ECM. It has a role in attaching cells to all matrices, except for collagen Type IV; when you have a Type IV matrix, laminin is involved in the cell adhesion.

So, what happens is, these have a multimodular structure with three different amino acid repeat domains, and these are called FN-I, FN-II, and FN-III. In the primary amino acid sequence that binds to the integrin, which is expressed in the cells are the RGD domain, arginine, glycine, and aspartate. The fibronectin provides this type of a motif on which the cells can attach. So, that is why fibronectin is even used for coating of cell culture plates and other things, where you can ensure cells are attached to the surface.

People also use RGD domains. You can create these tripeptides and use them along with your scaffolds to promote cell adhesion. If you cannot use all of the fibronectin, you can create these short peptides, which can be used and that will help in cell adhesion.

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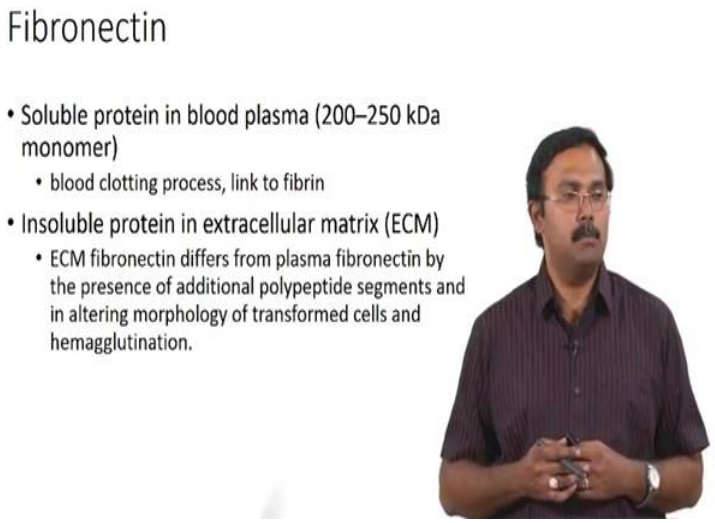

Fibronectin exists as a soluble protein and insoluble protein. Soluble protein is present in the blood plasma; it is involved in the blood clotting process and links to fibrin during that process. You have insoluble protein in the ECM, where ECM fibronectin has the polypeptide segments, which alters morphology and helps in the cell attachment.

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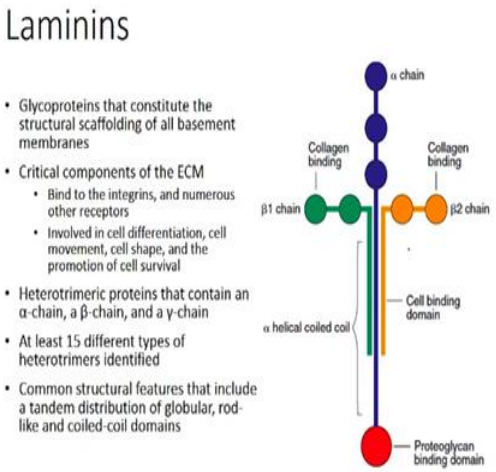

So, you have laminins, which are another set of glycoproteins. They constitute the structural scaffolding for all basement membranes. If you remember, we also said that collagen type IV is involved in basement membranes right. Along with collagen Type IV, you would have laminin existing. So, that it can help in cell attachment.

This is a very critical component of the ECM because it has a lot of functions; it can bind with integrins and many other receptors. And it is involved in cell differentiation, cell movement, the shape of the cell, and promotion of cell survival even.

Because of this, it plays a crucial role, and it is present in reasonable abundance. It is a heterotrimeric protein that contains an alpha chain, a beta chain, and a gamma chain so, which is what I have shown here. It can also be called as beta 1 chains and beta 2 chains, which is the traditional way it was represented.

There are at least 15 different types of heterotrimers that have been identified. The common structural features, which you would see, are having a tandem distribution of globular and rod-like and coiled domains. So, that is what is laminin, and this is the general representation of the laminin structure.

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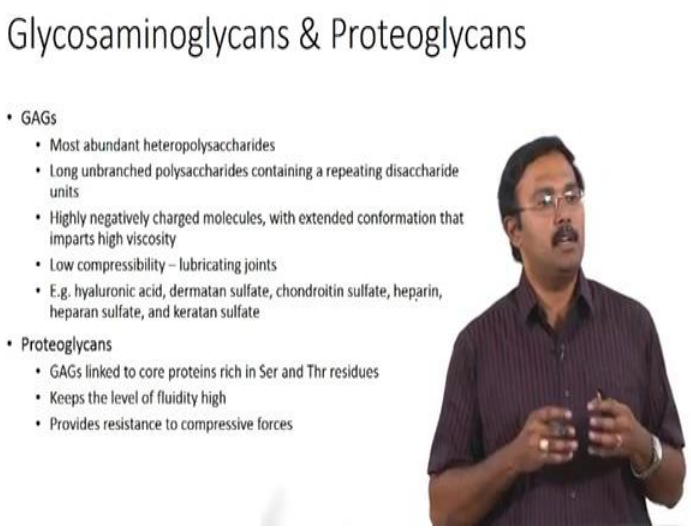

Other than these, we also have proteoglycans and glycosaminoglycans. Glycosaminoglycans are the most abundant heteropolysaccharides, which are basically long unbranched polysaccharides with repeating disaccharide units. Instead of having a random chain, you would have disaccharides, which are repeated. And these are highly negatively charged with extended conformation that can impart viscosity.

They also show very low compressibility. Because of these properties, they are used as lubricating agents in the joints. You would see these materials like hyaluronan and so on, chondroitin sulfate in the joints. And, all of these occur in different tissues, you can actually look it up on the net, and you would see that the tables which explain where these can be found. Some of the common glycosaminoglycans are hyaluronic acid, dermatan sulfate, chondroitin sulfate, heparin, heparan sulfate, and keratan sulfate. These are all commonly seen in your body.

Proteoglycans are basically, glycosaminoglycans that are linked to core proteins which are rich in serine and threonine. They make sure that the fluidity of the tissues maintained and they provide resistance to compressive forces.

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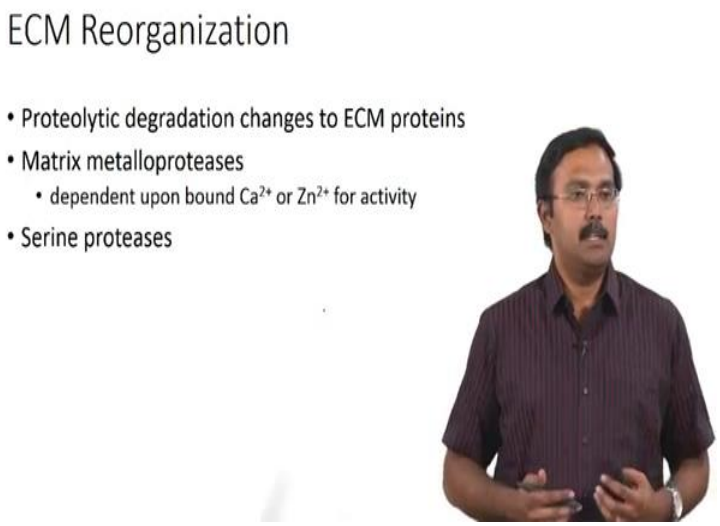

They play a crucial role in making sure the tissue maintains the gel-like feature. When we talk about ECM, we also need to understand that ECM is not a static matrix; it is getting reorganized. You can have proteolytic degradation to remove the ECM.

Some of the enzymes, which are involved in this are matrix metalloproteases and serine proteases. They will degrade the tissue, and as I already said, many different types of cells are involved in secreting these ECM matrices to continuously remodel this tissues.

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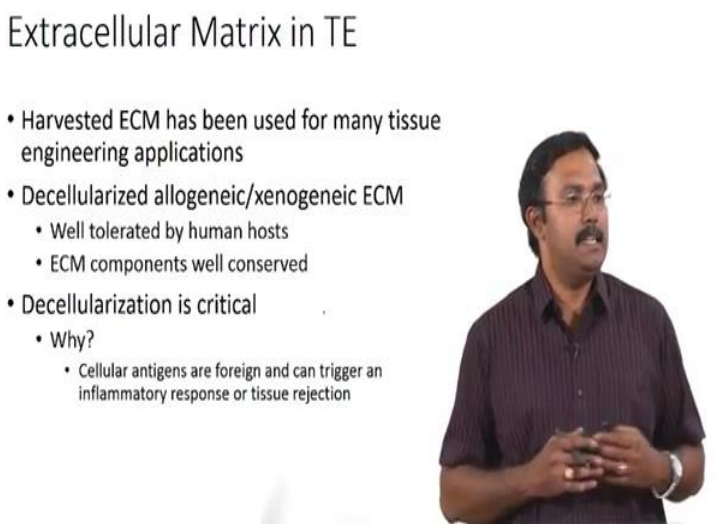

When we talk about ECM in tissue engineering what people are doing is; harvesting ECM for tissue engineering applications. So, they take the tissue and either it can be allogeneic or even xenogeneic ECMs, and they decellularize it. It is well tolerated by human hosts because ECM components are well conserved.

Decellularization is very crucial because cellular antigens are actually foreign. Even if you get it from an allogeneic source, you would have to make sure that there is proper tissue type matching, if you are going to have the cells along with it.

If there are no cells, then it cannot trigger immune responses or inflammatory responses. So, for that reason, you have to carefully decellularize it. There are many techniques to do it, to remove all the cells, ok.

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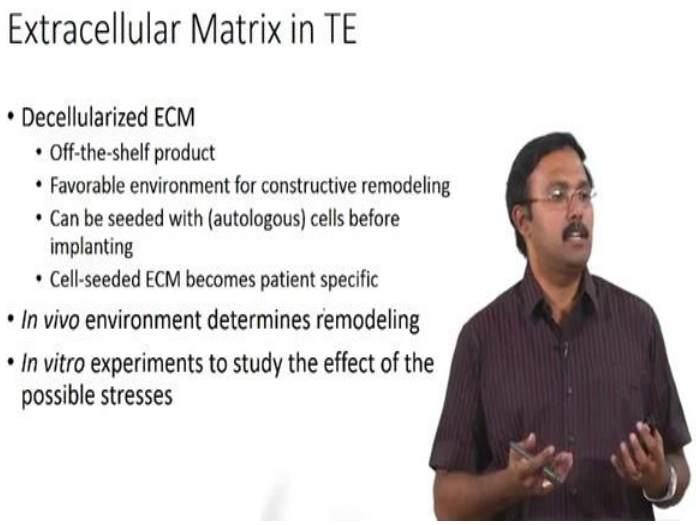

Decellularized ECM can actually be an off-the-shelf product. This can provide a favorable environment for constructive remodeling. These can be seeded with autologous cells before implanting if you want, then you have a patient-specific personalized medicine right. Because ECM is common for everybody, then you do not have to worry about that.

Now, the cells which can create the immunogenic response are from the patient himself, which means there is no risk of rejection. You can tailor it that way. Once you have it inside, then in vivo environment will determine the remodeling of the ECM. People have

done in vitro experiments to study the effect of the possible stresses that decellularized ECM can go through.

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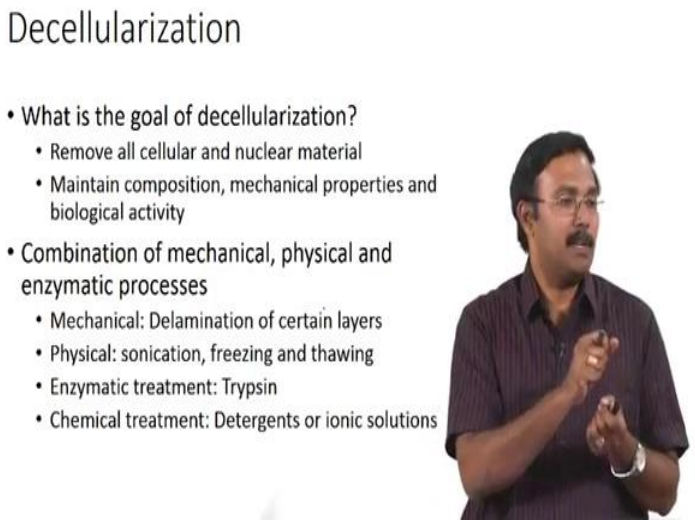

There are different techniques to do it, but what is a fundamental goal of decellularization? What do you want to accomplish, I said, why we want to accomplish that, but what do you want to accomplish? What are all the things which you want to remove when you are talking about decellularization? So, you want to prevent any immune response, for doing that what are all that you should remove? Removing cells is the general thing, but.

Student: receptors

There can.

Student: Cell receptors.

Cell receptors, ok.

Student: Antibody.

So.

Student: Antibody.

Antibodies so.

Student: Cell debris.

Any cell debris. So, that is actually what you want to do. But specifically, what you are trying to do is; you want to remove all cellular and nuclear material. While you are doing this, you want to maintain the composition and mechanical properties and biological activity of the ECM.

That is the challenge. Removing all cells is not too difficult. See, I can always take an ECM and dip it in the sulfuric acid right. The idea is to remove the cells, without damaging the ECM. So, how you go about doing that is the process impart, which makes it unique.

There is a combination of mechanical, physical, and enzymatic processes which are done. Mechanical process would be the simple delamination of layers. So, this is nothing, but just stripping off layers.

You take out one layer and then strip out the first layer, which might contain too many cells, and you take that out. And then you can have physical things like sonication, freezing, and thawing and so on. Sonication will destroy the cells, will just rupture the cells, and you can do freezing, and thawing, that also does the same. So, these are just cell disruption techniques.

And then you can use an enzymatic treatment like trypsin. Trypsin can remove the cells from their adhesion sides, and trypsinization is done even when you do cell culture procedures. And then you can also use chemical treatments like; detergents and ionic solutions. You need to be careful with what exactly you are doing, and how exactly you are processing it.

The mechanical process of delamination needs to be done with reasonable care. It could just be physical brushing of things, could be as simple as that, people actually do that, but it could also be a lot more complicated with designing well-controlled equipment. It depends on how you want to design the process.

These are general technique. You can go into the great details of the techniques, when you read the reading assignment because if I were to describe materials and methods for each of these, it might be too much information ok.

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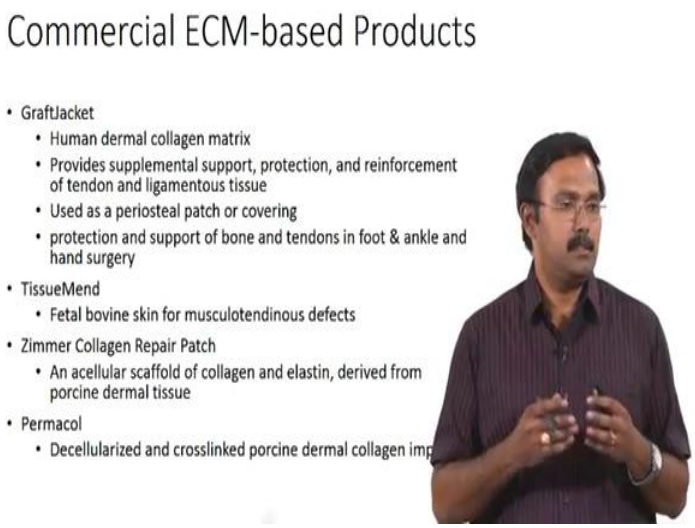

These are some of the commercial ECM based products which are currently available. GraftJacket is a product where a human dermal collagen matrix is used. This provides supplemental support and protection and reinforcement, reinforcement for tendon and ligamentous tissue.

This is also used for covering the periosteal patch, and it acts as a protection and support for bone and tendons during foot, ankle, and hand surgery. This is just a collagen matrix which is crosslinked. From the skin, they take the collagen and create a crosslinked matrix which can be used for these applications.

TissueMend is from fetal bovine skin, and this is used for musculotendinous defects. Zimmer is a collagen repair matrix which is an acellular scaffold of collagen and elastin derived from porcine dermal tissue.

Student: Sir ECM from other animals cause an immune reaction?.

As I was saying, these proteins are very well conserved ok. They do not cause any immune reaction mostly, as long as you remove all the cells and cell debris; the chance of immune responses are very low. So, that is why most of the times when people work

with collagen, it is not that they are using human collagen. If you go back and look at literature, people used collagen from so many different sources it could be from fish, rats, chicken, bovine, just take it from anywhere, and you can start using it. Because collagen is collagen, it is just a protein, and it is reasonably well conserved to ensure there is no effect.

And as far as the glycosaminoglycans, these are carbohydrates. These are just molecules which are going to have the same structure, does not matter where it comes from. So, because of this reason, you can actually use it from xenogenic sources as well. Zimmer collagen patch is from pigs, and so is Permacol. This is again decellularized crosslinked pro-porcine implant, which is being used for different applications.

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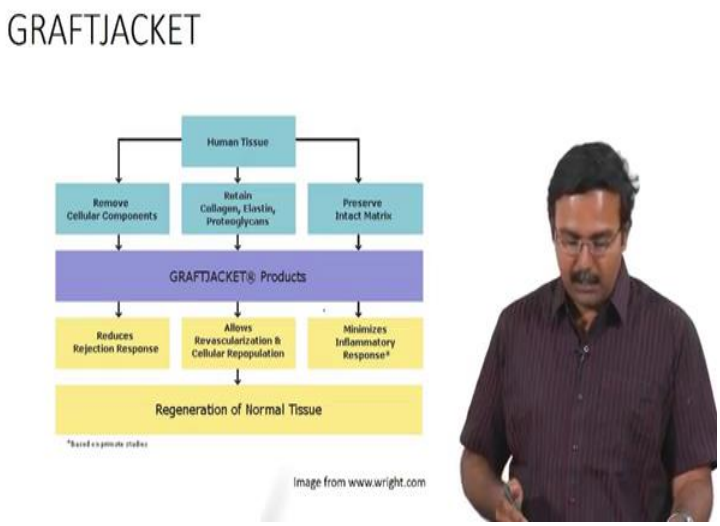

These are all some of the commercial products, and as for as GraftJacket goes, they actually have nice representation of what it actually is, how they prepare it, and what they expect to have.

They take a human tissue, which is basically, the dermal tissue here. And they remove all the cellular components and retain collagen, elastin and the proteoglycans and make sure that the matrix is intact. This creates the GraftJacket products, which they commercialize, and this is by a company's name Wright;

This reduces the rejection response because the cellular components are gone. This will also help in revascularization and cellular repopulation because you have all the pores and all the structures necessary for the vascular network to be created. This will also have a minimized inflammatory response, based on primate study that they have shown. They hope this will regenerate normal tissue. So, this is a commercial product which is available for different applications.

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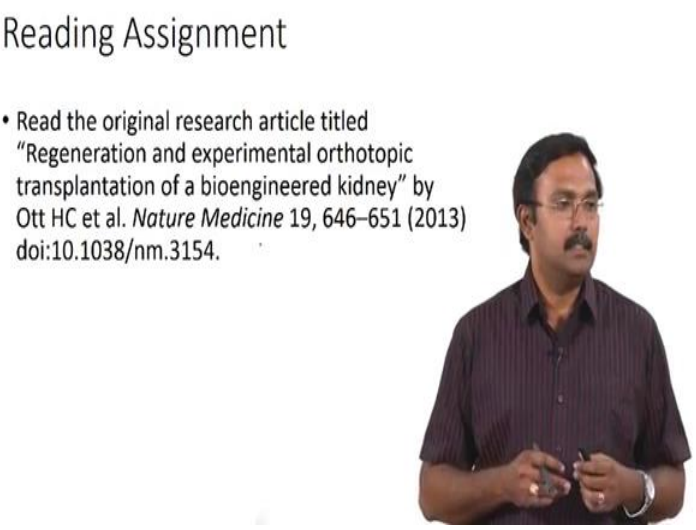

With that, we conclude this lecture on this topic. This is the reading assignment, which I was talking about. There is actually multiple kinds of work which has been done. Here, what they have done is regeneration and experimental orthotopic transplantation of a bioengineered kidney. They have taken a kidney and decellularized it and seeded it again to create a functional kidney, which they have placed it in the different position that is what orthotopic transplantation is.

They keep it in a different position and see how exactly the kidney functions. They have done it in vivo, small animal studies in this paper, I believe. So, go back and read this paper, there are many other papers as well. This is a paper where people have done for the entire organ, unlike a just a small patch or something. The other commercial materials are just patches, you take the skin, and you take the collagen to crosslink it and use it as a patch. So, unlike that, this is slightly different, ok.