Extracellular Matrix

Shelden, Chapter 19, Basal Lamina.

**Audio:**
The extracellular matrix is the only topic in this course where we’ll be discussing something that’s fundamentally not a cell or part of a cell. Instead, the extracellular matrix, or ECM, is mostly made up of a material known as ground substance, along with a variety of types of imbedded protein fibers. Cells are the third and least abundant component of the extracellular matrix. However, since the extracellular matrix is made by cells and plays a significant role in determining the behavior of cells in it, we’ll discuss the cells of the extracellular matrix briefly. Every distinct tissue in an organism expresses characteristic extracellular matrix components, which gives the tissue its physical characteristics and also gives the cells imbedded in it signals that they have to interpret correctly. As a consequence, the composition of the extracellular matrix is highly variable, and we’ll be looking at some of the molecular mechanisms that give rise to this variability. However, there are only two major types of extracellular matrix materials, which are shown in the cartoon image at the top of this slide. Most of this picture is filled with the first type, which includes the grey shaded material and the red and green imbedded fibers. This tissue, which is called connective tissue, forms most of the extracellular matrix material in our bodies. It has a variety of roles, including the formation of conduits for nerves and blood cells. It also provides supporting material for cellular organs, such as the liver and kidney and it performs a variety of mechanical roles in our bodies, including the formation of the skeletal system and things like tendons and ligaments. The layer that is shown in yellow in this cartoon is the other type of extracellular matrix material. This is a layer that’s found at the base of all epithelial and endothelial cell layers and it’s called the basal lamina, or sometimes people call it the basement membrane. The electron micrograph on this slide gives you a feel for what a basement membrane looks like. It’s a dense fibrous sheet of material that separates an epithelial tissue from the underlying connective tissue.

Connective Tissue

Images

**Audio:**
Here’s what connective tissue looks like. The image on the left shows that there is an abundance of pink-stained protein fibers. These particular fibers are made of a protein called collagen type 1. You can also see blood vessels in this connective tissue, which may reflect the role of this particular tissue in forming conduits for blood vessels in our bodies. There are a very small number of purple-stained nuclei, which are the fibroblasts, scattered through this tissue and these are the cells that are responsible for making the extracellular matrix. The electron micrograph shows a scanning EM of connective tissue. The material that was colored in grey on the previous
slide was extracted during the fixation and staining process, and so it’s gone. This helps to see the dense network of fibers that the cells both have to produce and move around within. In order to move within this type of material, fibroblasts and other cells that navigate through the extracellular matrix secrete proteases which digest the fibers and other components of the extracellular matrix.

### Slide #3

**Formation: produced by specialized cells: fibroblast, chondroblasts, osteoblasts**

**Images**

**Audio:**
This slide shows everything we’re going to learn about the specialized cells which are part of the extracellular matrix and produce the extracellular matrix. The majority of cells we’re going to talk about are on the left hand side of this image, which are fibroblasts. Fibroblasts are the cells that produce collagen fibers. The shape of the cells is a reflection of their attachment to extracellular matrix fibers and gives the cells a sort of characteristic spindly or pointy appearance. On the right hand side, at the top, is an image showing chondroblasts. Chondroblasts are the cells that make cartilage and when they become imbedded in the cartilage material they’re called chondrocytes. The image on the bottom, right hand side of this screen shows bone forming cells which are called osteoblasts. The dark pink material at the bottom of the picture is the bone. The layer of darkly stained cells are the osteoblasts, which are depositing bone on the outside of the existing bone material, in much the same way that the trunk of the tree grows by adding layers to the outside. You can also see some fibroblasts in the upper part of this image and the osteoblasts that become imbedded in the bone material are then called osteocytes. The newest material that’s been deposited by the osteoblasts lacks the mineralization that is characteristic of more mature bone and that new material is called osteoid, which I’m not going to ask you to remember. In addition to these cells, there are a number of other types of cells that are found in the extracellular matrix, such as cells of the immune system. However, these other cell types are not actively engaged in creating the extracellular matrix and so I’m not going to talk about them further.

### Slide #4

**Composition**

- Ground substance with embedded fibers. Ground substance: glycosaminoglycans (CAGs), glycoproteins, and proteoglycans
- Ground substance does not stain with normal stains and appears white. Collagen Fibers are pink

**Audio:**
Here’s another image of connective tissue, which once again shows the proteinaceous fibers. The white spaces that are present in this image would normally be filled with ground substance and so we’re going to start by talking about what ground substance is. Ground substance is the material that would fill these spaces and it’s comprised of three major components. The first is glycosaminoglycans, or GAGs, and the second is glycoproteins, and third are proteoglycans and
we’ll be looking at what each one of these components is in just a second.

**Slide #5**

**A. Glycosaminoglycans:**

Most simply a long sulfated polysaccharide composed of linked disaccharides

- Highly negatively charged molecules which attract sodium (Na+) and thus water. This forms a gel which resists compression forces.
- Major types are hyaluronan, chondroitin sulfate, dermatan sulfate, heparan sulfate and keratin sulfate
- The only simple GAG is hyaluronic acid – a single linear molecule

**Audio:**

Most of the ground substance that’s present in extracellular matrix materials is in the form of glycosaminoglycans. In their simplest form, glycosaminoglycans are simply long chains of sulfated polysaccharides, which consist of a disaccharide of some type, strung together in a long row. The types of sugar disaccharides that are used to form these chains determine what type of a glycosaminoglycan it is. Examples include hyaluronan, chondroitin sulfate, which is found primarily in cartilage, dermatan sulfate, which is found primarily in skin, keratan sulfate, which is found in epithelial tissues, and so on. This image also shows one of the major characteristics of glycosaminoglycans, which is that they have many negative charges. These negative charges attract sodium ions, which is a positively charged ion, and in turn, sodium will attract water. This causes these materials to form a gel-like material when they’re swollen with water, and it’s this gel material, which gives extracellular matrix its physical characteristics. In their simplest form, glycosaminoglycans are simply a long linear chain of linked disaccharides. However, only one category of glycosaminoglycans actually is a simple linear chain of linked disaccharides and that one is called hyaluronic acid. All the other glycosaminoglycans we’re going to look at are more complicated and we’ll look at this complexity on the next two slides.

**Slide #6**

**Proteoglycans**

- GAG side chains linked to a protein
- Formed by a tetra-saccharides linked to a protein core serine which nucleates a GAG side chain
- There is enormous diversity of GAGs

**Audio:**

The majority of glycosaminoglycans are not present as a simple linear chain. Instead, they form more complex structures. The next complexity in this hierarchy are proteoglycans, which are depicted on this slide. Proteoglycans are formed by linking a simply glycosaminoglycan to a protein core. There are a variety of proteins that can form the core and a variety of glycosaminoglycan side chains can be linked to the core, and this is part of what gives the extracellular matrix its molecular complexity. The side chains are linked to the core protein via a special tetra-saccharide, in other words, it has four sugar moieties, which forms an adaptor link between the glycosaminoglycan side chain and the core protein. There’s tremendous variability
in the configurations that proteoglycans can take, and that’s shown at the bottom of this slide. Some proteoglycans have just a single glycosaminoglycan side chain linked to their core protein, and the core protein is relatively small: decorin is an example of that. Other proteoglycans can have hundreds of glycosaminoglycan side chains, linked to a very long core protein and an example of that is shown on the right hand side of this image and these can be very huge molecules.

**Slide #7**

**Proteoglycan aggregates are formed by linking core proteins to a GAG core with linker proteins.**

Images

**Audio:**
The final level in this hierarchy of complexity is the proteoglycan aggregate, which is shown on this slide. Proteoglycan aggregates are proteoglycans which are then linked back to a central hyaluronic acid molecule. So the hyaluroic acid molecule, which is a glycosaminoglycan is shown in blue in this diagram and the proteoglycans which we were looking at on the previous slide have a protein core are shown in green and red. The proteoglycans are linked to the hyaluronic acid molecule core using what are called, linker proteins, and those are shown in black in this diagram. The electron micrograph on this slide shows a single proteoglycan aggregate, and have a look at the scale bar on the image. The scale bar is one micron, so the length of this macromolecular complex is fifteen or more microns long, which is twice the diameter or more of a red blood cell. So, you can see that these are fantastically large molecules. They’re also a favorite structure for cell biology professors to put on exams for students to know about.

**Slide #8**

**Function of GAGs:**

Space filling, water and salt balance
Regulate extracellular protein functions:
- Immobilize proteins, limiting range of activity
- Bind proteins and prevent their activity
- Store proteins for later release
- Protect proteins from degradation and prolong their activity
- Concentrate proteins. For example mediators of inflammation (chemokines) are concentrated near an infection

**Audio:**
The functions that glycosaminoglycans perform in the extracellular matrix are as variable as the molecules are. The most obvious function is simply to fill up the spaces that are not occupied by other cells or fibers. This is a function that’s obvious when you consider their size. In addition, I’ve already pointed out that these molecules attract salt ions and water, and so they play a major role in maintaining the salt and water balance of tissues. Deregulation of this balance can cause metabolic abnormalities, tissue edema, which is the filling of tissues with free water, and other
problems. In addition, glycosaminoglycans can perform a variety of functions that serve to regulate proteins found within the extracellular matrix and some of these are shown here. For example, a variety of hormones and other signaling factors are secreted by cells into the extracellular matrix, where they can interact with glycosaminoglycans. The interaction can immobilize the proteins and therefore limit their range of activity or protect them from degradation, thereby prolonging their activity. In some cases, the binding or association of the proteins or signaling factors with glycosaminoglycans may inactivate them and they may become active only later when they’re worked on by other cells in the extracellular matrix, and finally, the effect of the glycosaminoglycan ground substance can serve to concentrate proteins in a limited area. A good example, where all these things come into play is the example of inflammation in response to a local infection. Cells in the region around an infection site release signaling molecules like inflammatory cytokines, and other cells of the immune system need to hone in on these signals in a directional manner, and so the signaling has to be present at a high concentration in the area of the infection and then the concentration has to dwindle as you move away from the infection site. If the inflammatory cytokines were able to move freely and rapidly throughout the entire body, the information contained in this concentration gradient would be spread out and lost.

Slide #9

Molecular Seiving (perlecan in basal lamina of the kidney glomerulous)

Images

Audio:
Because glycosaminoglycans interact so strongly with water molecules, they are also able to form barriers that influence the movement of fluid across a tissue. This slide shows a really good example of this, which is the filtration apparatus of the kidney. The primary filtration site in the kidney is a structure called the glomerulous, which is shown on the left hand top of this slide. The core of the glomerulous is a knot of permeable capillary tubes, which is shown in this image, and surrounding these capillaries is a unique cell type called a podocyte, which wraps the capillaries with a finger-like protrusions. A cross section through this interface is shown at the bottom of this slide. The finger-like protrusions which are now cut in cross section, are shown at the top of the image and the walls of the capillary cells, which are very leaky, are shown at the bottom. In the middle is a dark, fuzzy material called the basement membrane and it’s filled with a glycosaminoglycan called perlecan. In healthy individuals, fluid which contains metabolic byproducts will leak through this filter, but the filter excludes things like red blood cells and even large proteins. If you get defects in this barrier, then proteins and even blood cells will begin to show up in the urine.

Slide #10

Cell Signaling

- Interaction with some GAGs alters cell development or proliferation

Audio:
Finally, I’ve been mentioning as we went along how the extracellular matrix variability serves as environmental cues to cells that are present in the extracellular matrix, which tells them, either they are in the right place in the body or tells them something about what they should be doing, and this is one experiment that shows this. The image on the left is a section of cartilage tissue, found at the end of a growing bone. At the bottom of the image, bone-forming osteoblasts are moving into the cartilage matrix and replacing the cartilage with new bone, which appears orange in this image. The osteoblasts are responding to cues from glycosaminoglycans in the cartilage matrix, which they are looking for to determine where they’re supposed to be going. On the right is an image of the same type of tissue which was treated with an enzyme that degrades glycosaminoglycans, called hyaluronidase. Hyaluronidase is produced by cells in our bodies under some circumstances and it’s also produced by bacteria, which helps them invade tissues of the body. After treatment with hyaluronidase, the bone-forming cells no longer get the right signals from the matrix, and their activity stops, and that’s shown by the absence of the orange coloration on this image.

**Slide #11**

**B. Glycoproteins**

- (Fibronectin and Laminin) are large proteins with many adhesion sites for fibers, GAGs and cell surface receptors

**Audio:**
The last molecular component of the ECM we’ll discuss are the glycoproteins. Glycoproteins are primarily proteins, which are decorated with small amounts of polysaccharides. However, these polysaccharides are much smaller than the long chains which form glycosaminoglycan side chains. There are many different glycoproteins, but we’re going to discuss two major ones, which are fibronectin and laminin. These proteins have multiple binding sites for all the components of the ECM and their function is to link all of these components together physically. The diagram on this slide illustrates the glycoprotein laminin, acting as a coupling agent between transmembrane integrins collagen IV and the glycosaminoglycan perlecan.

**Slide #12**

**Laminin**

- Abundant in and helps form basal lamina. Recognized by epithelial and other cell integrins

**Audio:**
Here’s what laminin looks like. The diagram shows that laminin is actually a trimer of three subunits, known as the alpha, beta and gamma chains. The trimer forms an extended coiled coil domain and is also characterized by numerous globular domains that serve as binding sites for cells or components of the ECM. Laminin is a glycoprotein that is most commonly found in the basal lamina that underlies epithelial cell monolayers and that’s why it’s called laminin.

**Slide #13**

**Laminin**
Laminin supports and promotes cell attachment and migrations

Audio:
This video illustrates one of the functional roles of laminin. There’s a nerve cell at the top of the screen which is sending out a neurite, such as what happened during formation of nerve connections in embryos or the brain. The upper portion of the surface shown in this image was coated with laminin and the bottom was coated with a charged molecule called polylysine, which sticks to cells, but in a non-specific manner. During the course of the video, the neurite moves out, along the laminin-coated portion of the slide, but although it’s capable of attaching to polylysine, it prefers not to and instead executes a turn at the interface between the two coatings. This is one of the ways that bioengineers are using, in efforts to get neurons to form experimentally defined networks, such as those that might be useful for interfacing silicon computer chips with nerve endings.

Slide #14

Fibronectin

- Abundant in connective tissues
- Recognized by integrins expressed by mesenchymal and neuronal cells.
- The recognition signal is Arginine-Glycine-Aspartate (RGD), and it is found on many other proteins that regulate cell adhesion including clotting factors.
- Fibronectin deletions are embryonic lethal mutations.

Audio:
Fibronectin is the other glycoprotein I want you to know about. Unlike laminin, which is primarily found in the basal lamina, fibronectin is found in all connective tissues, where it mediates the attachment of fibroblasts to ECM components. The laminin molecule is a branched dimer, which is held together by two disulfide bonds. Like laminin, fibronectin contains a number of globular domains, which form binding sites for components of the ECM, as well as the fibroblasts themselves. These include the heparin binding site, which attaches to the glycosaminoglycans and a collagen binding domain, which links fibronectin to collagen fibers. There’s also a self-association domain that allows fibronectin to form larger complexes, and finally, the cell binding domain contains a region which is attached to by integrins, expressed on the surface of fibroblasts. This region contains a short peptide loop, with three amino acids: arginine, glycine and aspartate, which are abbreviated RGD. The RGD domain is a classic cell attachment motif which is present in many other proteins that have to interact with the extracellular surface of cells and so I do want you to remember this specific sequence, the RGD polypeptide. You can do experiments with RGD peptides. For example, attaching proteins that contain an RGD motif to a surface will facilitate the attachment of fibroblasts to that surface. Alternatively, if you treat cells with a soluble form of a protein that contains an RGD motif, the RGD motif will bind to integrins on the cell surface and therefore block the ability of the cell to attach to its surface.

Slide #15

Fibers
- A. Collagens: 25% of the dry mass of vertebrates is collagen
- Collagen fibers have the tensile strength of steel.
- There are about 20 types of collagen
  - Type I forms strong fibers in connective tissues and bones
  - Type II is found in cartilage
  - Type III forms reticular fibers
  - Type IV is found in basal lamina underlying epithelial cells

**Audio:**
The fibers that are found in the extracellular matrix are the final component that we’ll talk about and there are two types of fibers: the collagen fibers and elastic fibers. Collagen fibers are the more diverse and they’re formed by the assembly of over 20 different types of collagen proteins, each with different physical characteristics and expression patterns in our bodies. Collagen is the most abundant protein in our bodies and it’s the basis of the structural integrity of our tissues. For example, tendons and ligaments are essentially just collagen fibers. A collagen fiber is as strong as a steel cable of the same weight, although there are a large number of types of collagens, I’m only going to ask that you know four specific collagen types. Collagen I is the most abundant type and it’s found in connective tissues, which include bone, tendons and ligaments. It forms very thick, unbranched linear filaments that are easy to see in microscope slides. The image on the lower left of this slide shows what collagen type I fibers look like in a tendon. Collagen type II makes relatively fine fibers which are difficult to see and they’re the ones that are found in cartilage. So cartilage, which we looked at on a previous slide, looks relatively homogeneous because the fibers are very fine. Collagen type III forms what are known as reticular fibers. Reticular fibers are highly branched fibers found in organs that have a large density of cells, such as the liver, spleen and kidney, and similar organs. The image on the right shows liver tissue, stained with a dye that binds to the collagen type III fibers and you can see how the fibers form a three dimensional net that’s helping to hold the cells in place. The final type of collagen I want you to know about is collagen Type IV and that is found characteristically in the basal lamina. It forms the dense, felt-like mat that was shown in slide one of this lecture.

**Slide #16**

**Synthesis and assembly**

Fibroblast next to much bigger extracellular collagen fibers

**Audio:**
This electron micrograph illustrates the biological problem faced by fibroblasts when they produce collagen fibers. The cell is quite small, but it’s responsible for producing these very large, strong and insoluble collagen fibers that are filling up the rest of the image and we’ll be discussing how the cell does this in the next couple of slides.

**Slide #17**

**Synthesis and assembly:**
- Collagen is synthesized as a linear monomer called pro-alpha-collagen
• In the ER, pro-alpha-collagen is hydroxylated and glycosylated. (Hydroxylation requires vitamin C)
• Modified pro-alpha-collagen forms a trimer. The trimer is soluble and called procollagen. Procollagen is secreted.

Audio:
The formation and synthesis of collagen fibers is a multi-step process and you need to understand the process in detail. The first step is the synthesis in cells of a protein monomer known as pro-alpha-collagen. This protein is soluble and it’s moved into the cell’s endoplasmic reticulum, where it’s modified by hydroxylation and glycosylation. It’s this step which requires vitamin C. Vitamin C deficiency prevents the synthesis of collagen fibers, including those which are important for anchoring teeth into the jaw. Tooth loss is one of the symptoms of scurvy, which is caused by vitamin C deficiency. The modification of pro-alpha-collagen in the ER, leads to formation of a soluble trimer, which is now known as procollagen. Procollagen is secreted by the cells into the extracellular matrix where it is still a soluble component.

Slide #18

Synthesis and assembly

• After secretion, peptides at the ends of procollagen molecules are cleaved.
• Resulting collagen molecules are no longer soluble, and they aggregate into collagen fibrils.

Audio:
Procollagen is a soluble protein. It has a central core, which is shown in red on this slide and two flanking ends which are shown in green and the green ends are what makes the trimer soluble. Once procollagen is secreted, enzymes that are found outside the cell, known as procollagen peptidases, cut off the ends of the molecules and the remaining insoluble core trimer becomes known as a collagen monomer. Collagen monomers are not soluble and they assemble spontaneously, with no other factors, into collagen fibrils, which are between ten and three hundred nanometers in diameter. The subunits are linked together in a staggered arrangement and as I mentioned during the discussion of intermediate filaments, this organization makes the filaments strong because it avoids weak spots, which would be formed at the ends of molecules if they were all lined up across a filament, and an analogous structure that you might think about are bricks in a brick wall, which are generally laid down in some sort of a staggered fashion, not in linear rows. The regular arrangement of the collagen monomers gives collagen fibrils a really characteristic banding appearance which is shown in the electron micrograph on this slide and it’s easy to pick out collagen fibers as a consequence of this in electron micrographs of tissues.

Slide #19

Collagens

• Other types of collagens do not form fibers themselves, but instead bind to and can crosslink or bundle other forms of collagen.

Audio:
Finally, the large collagen type I fibers you’ve been seeing in the histological slides in this lecture are actually bundles of individual collagen fibrils and there are several types of collagen molecules which don’t form fibers, but bundle other fibers into bigger structures, or can cross-link them into three dimensional mesh works, such as are typical of, for example, collagen type III molecules. I won’t ask you to know specific collagen types that do this, but I want you to be aware of their existence and their function.

**Slide #20**

**Elastin**

- Another fibrous extracellular matrix protein that forms elastic fibers. It is secreted in a process much like of collagens. Elastin is abundant in tissue that stretches (skin, heart, arteries)

**Audio:**
Elastic fibers are the other major fiber type that’s found in the extracellular matrix, and elastic fibers are formed from the protein elastin, which is synthesized by mechanisms similar to those involved in collagen fiber synthesis. Elastic fibers have the appearance of rubber bands when they’re found in tissues and they’re primarily found in tissues that have to undergo repetitive deformation without losing its shape.

**Slide #21**

**Elastic Fibers**

- Aorta (left) and skin (right) stained for elastic fibers

**Audio:**
Skin and tissues of the cardiovascular system are good examples of tissues where elastic fibers are common. Here, these tissues have been stained with a dye which shows them in black. The tissues are relaxed, and so the fibers are wavy. If the tissue was stretched or distended, the fibers would look like stretched rubber bands or they’d be linear lines.

**Slide #22**

**Cell Biology of the Extracellular Matrix**

- Organization of the Extracellular Matrix can organize associated cells

**Audio:**
There are a number of ways that the extracellular matrix regulates the function of cells and we’ve already discussed the molecular diversity of the extracellular matrix and some of the ways that the cells can interact with it through integrins. On the last four slides of this lecture, I want to discuss a few other aspects, one of which is shown here. So, first, the structural arrangement of the extracellular matrix can influence cell behavior and the arrangement of the extracellular matrix fibers is also generated by cells. This slide shows an example of how this can occur, In which an initial cell produces orientation cues within the extracellular matrix. Other cells migrating in to this area will read those cues and replicate them in more of the extracellular
matrix and therefore, this process can self-propagate to form a large mass of oriented tissue. The right hand side of this slide shows a couple of images where this principle is being applied by bioengineers who are trying to generate replacement muscle tissues out of muscle stem cells, and what they’ve done is to artificially create a pattern of extracellular matrix molecules on a surface and then seed muscle stem cells onto that surface. The cells then respond to the cues that are embedded into the extracellular matrix material by lining up and eventually, the hope is that these cells will then produce their own extracellular matrix, which will allow the formation of larger and larger masses of tissue which are functionally organized.

Slide #23

Cell Biology of the Extracellular Matrix

- Organization of the Extracellular Matrix alters cell survival

Audio:
In addition to regulating cell shape, the arrangement of the extracellular matrix can also regulate cell survival. This slide shows an experiment where cells were allowed to attach to a pattern of fibronectin deposited on the surface of a cell culture chamber. The same total amount of fibronectin was deposited in both patterns, but their organizations are different. The pattern at the top allowed cells to attach, but the cells don’t develop a normal morphology and they eventually die. The same total amount of fibronectin, deposited in the orientation shown at the bottom of this image, allowed cells to adapt a normal morphology and they survived.

Slide #24

Fibroblasts

- Fibroblasts can remodel fibronectin, providing surface cues for cell adhesion and migration.

Audio:
Here’s the reverse situation, which shows that cells can influence the orientation cues in the extracellular matrix. These images show how fibroblasts can deposit fibronectin on a surface in an oriented manner. The image on the right shows fibroblasts that were stained with a probe for the actin cytoskeleton and the image on the left shows fibronectin that was deposited by these cells on the surface they’re attached to. Notice that there’s a striking correlation between the two, indicating that the cells are using their cytoskeletal system as a model for organizing the deposition of fibronectin on the surface. Other cells migrating into this area after these cells have left would be able to read the information contained in the fibronectin pattern and respond appropriately.

Slide #25

Remodeling of extracellular matrix (collagen) fibers by fibroblasts

Video

Audio:
Cells can also rearrange the fibers found in the extracellular matrix. This is a video from my laboratory showing a single fibroblast, cultured in a three dimensional collagen fiber matrix. As you watch the video, you should be able to see that the cell is able to pull on the fibers and rearrange them as it moves.

Slide #26

Cell Biology of the Extracellular Matrix (cont)

- Degradation of Extracellular Matrix by matrix metalloproteases and serine proteases assist cell migrations.
- Hyaluronidase is produced by some very virulent pathogens
- Matrix proteases are important potential targets for antimetastatic therapies

Audio:
Finally, I’ve already mentioned that some bacteria are more virulent than others because they can produce enzymes which degrade the extracellular matrix. Cells also produce these enzymes in order to move through the ECM normally and cancer cells do this as they metastasize. On the left is a diagram of a tumor cell, showing the secretion of proteases which degrade the ECM and their attachment to cell surface receptors which forms a functional enzyme complex. It’s these complexes which allow the cell to migrate through the ECM. On the right is a diagram showing how methods that cause cells to produce inactive proteases could block this from happening, and consequently, inhibitors of protease activity are important potential targets for anti-tumor therapies.