Course Name: I Think Biology

Professor Name: Dr. Ramray Bhat (IISc)

Department Name: Biology

Institute Name: Azim Premji University

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W4L22_Cancer Biology (Guest Lecture)

Hello, my name is Ramray Bhat. I am an associate professor in the Department of Developmental Biology and Genetics in the Indian Institute of Science, Bangalore. In this talk, I will discuss what constitutes the pathology of cancer, what are some of the interesting features that that make cancer a unique disease with respect to other non-communicable diseases. I will also give a brief introduction about the kind of work that are we are doing to try and understand the pathogenesis of this disease as well as attempts to understand it so as to tackle cancer. Cancer can be understood to be a disease in which there is loss of control over the proliferation of cells within the tissues and organs in our body.

So, here I have a section of an organ which has been stained with dyes that allow one to understand the nuclear and cytoplasmic architecture of that particular organ. Each organ has its own unique pattern in which cells are arranged among themselves. In this particular section, one can envisage the arrangement of cells in a particular manner which makes this organ unique from all the other organs. You have the section of the same organ but the organ is now in a disease state.

So, the arrangement of cells in this particular section of the same organ is altered. Therefore, one can understand pathology of a particular organ as a condition in which the arrangement or the pattern of cells is disrupted. In this section which is has again been taken from the same organ, there is a further disruption of cellular arrangement which gives us a sense of disease progression. In other words, as the arrangement of cells gets further and further disrupted, the organ starts becoming more and more diseased and also its functions start getting disrupted. In other words, the organ now does not function in a manner in which it is used to doing so.

This is the narrative of cancer in which due to an excess proliferation of cells as well as their movement, the patterns of the cells in that particular organ get disrupted and one gets cancer. Therefore, one can understand cancer in a broader context as a condition in which there is pattern deformation. Typically, the development of organs are understood to be through a process of pattern formation where cells have now come together and have given rise to these unique patterns that make our livers different from our spleen and

our spleen different from our kidneys. Each organ has a unique pattern of cells and therefore cancers of all these organs can therefore be understood to be a process of reversal of this pattern or a pattern deformation. Now if one were to therefore look at this process and ask what leads to the deformation in patterns of cells, one therefore has to understand the structure of these patterns, the grammar of this pattern.

And this can be best understood by looking at the components within the cells that that allow for these cells to come together and form a cooperative entity. So in this slide, what we are showing is the cellular cytoskeleton. The cellular cytoskeleton is like the underlying scaffold within a cell that interacts to build the cellular shape, the cellular size and it also allows the cells to interact with other cells in its milieu. This cartoon depicts how cells are arranged with respect to each other and you can see that as cells are placed side to side, they have set the cellular cytoskeleton which we spoke about in our previous slide, connecting them together, belting them together to form this unique arrangement. Below the cells, one can also see certain connections that are being made with sheet-like structures.

These sheet-like structures are proteins on which the cells are sitting and therefore the cellular cytoskeleton also connects the cells with the sheet underlying them. This is what builds patterns. This is what builds what we also called the organ architecture. In this slide, we see the specific structures that these cytoskeletons are connecting to that allow cells to connect with each other as well as to their underlying protein sheets. The junctions have specific names depending on their functions as well as their structure as well as the the their locations.

At the very top, you have what are called the apical junctions. In the middle, you have adherens junctions and at the bottom near the sheets, you have gap junctions. The cells also connect with the underlying basement sheets or what are called basement membranes through structures called hemidesmosomes. So these structures allow the cells to come together in an organized fashion and build a tissue, build an organ. In this slide, we see each of these junctions shown where one can appreciate that these junctions allow the cells to now come together and perform certain functions.

So for instance, the the gap junctions allow transmission of cytoplasm or transmission of signals within the cytoplasm to move from one cell to another cell. Adherence junctions on the other hand allow the cells to tightly connect with each other and give the tissue resilience. You have the apical junctions at the very top near the apex of the cells and these junctions allow the cells to tighten up the and compartmentalize their front end from their back end or the apical side from the basal side. Finally, the hemidesmosomes allow the cells to connect with their underlying basement sheets or basement membranes thus giving rise to a proper tissue scaffold that allows the tissue to be built up from scratch. Tissues are not just composed of cells arranged in whatever fashion.

I was talking about the basement membrane. The basement membrane is part of a larger set of agents called the extracellular matrix. This is basically a collection of proteins that have been secreted by these cells and these proteins house the cells by coming out of the

cells. They create a scaffold that acts as a very active entity to house the cells, pattern the cells, and even provide mechanical and chemical cues to the cells. Collectively known as extracellular matrix, it consists of different proteins with a variety of functions and properties both chemical and mechanical.

The extracellular matrix also is secreted by other cells that travel between different organs. These cells are known as the connective tissue cells, cells such as fibroblasts. They create the extracellular matrix that then surrounds the native cells of these individual organs, the cells that make up make each organ unique with respect to each other and they build the extracellular matrix around them. This in turn sort of constitutes the two parts of an organ, the parenchyma and the stroma. The parenchyma is made by the cells that are native to the organ as well as the extracellular matrix that is made by these cells.

The stroma on the other hand is made by cells which travel from one organ to another as well as connect one organ with another and therefore constitutes the connective tissue as well as the extracellular matrix that is made by these cells. The extracellular matrix or ECM of the stroma and the parenchyma as well as the cells that connect different tissues, the connective tissue, and the native parenchyma tissue collectively make an organ. So the extracellular matrix as I mentioned consists of different types of proteins which are conjugated with lipids as well as glycans. The extracellular matrix is mostly though made up of fibrillar proteins known as collagens, one of the most abundantly found proteins present within animal bodies. The collagen is made in the stroma and within the stroma the collagen acts to space organs, to shape organs, and to provide mechanical resilience to these and mechanical structure and protection to the different organs.

So now that we understand what is an organ, how is an organ patterned in terms of cells that make it up, one can therefore understand cancer as basically the loss of all these instructional principles that go into forming the organs. In other words, cancer therefore can be understood as the loss of control over cell division that keeps the cell number in check once it has formed this organ and prevents this organ from basically exploding. Cancer also represents the loss of control over movement of cells. In an organ, one typically has cells once they are arranged in a particular pattern, the cells don't move. That is the reason why cells from the liver don't travel to the brain and cells from the brain don't travel to the liver at least in a functioning state.

So cancer therefore represents the loss of control over this restriction of movement. Cancer also represents the loss of these junctions that allow the cells to come together. The same junctions that we see in functioning organs are now lost. Cancer also represents the loss of adhesion to the underlying basement membrane matrix. Therefore cells which are arranged on this on this sheet now are no longer held there and therefore are free to move.

Cancer also therefore represents the loss of this epithelial or parenchymal stromal compartmentation. So there is no more of these boundaries that allows organs to be built properly. The grammar of pattern is lost. And this represents, this loss of architecture is

what cancer is. What I have described is the loss of architecture at the cellular level.

At the same time within the cells as well as on the cell surfaces as well as outside, there are multiple molecular changes that are also taking place which lead to these disruptions and the breakdown of cell pattern formation. So for instance, the cells which are working physiologically within an organ are constantly in a state where they are trying to inhibit the signals that allow the cells to divide or that allow the cells to move. And this signal is also coming from the underlying extracellular matrix. The matrix instructs the cells to keep what is called quiescence which is the state where cells are not dividing as well as not to migrate. However, in cancer what one gets is that there are cues that come out of the cells which break the extracellular matrix.

The extracellular matrix is no longer able to instruct the cells not to move, not to divide. Hence, the consequence of this is that you have loss of the extracellular matrix and you have a gain in the ability of the cells to now divide, move, and hence break the pattern. The cells in turn also secrete enzymes that are able to cut through proteins, proteins that are part of the extracellular matrix. So this leads to further loss in mechanical properties and protections. Therefore, allowing the cells now to move out of the organ and move to other parts of the body.

This process, the movement of cells from one organ to another organ is known as metastasis. And this is the process that is responsible for the morbidity of cancer. In other words, the reason why people die from cancer. Newer understanding of how cancer spreads can be understood not just to the point of understanding that cancer represents a loss in the original pattern of the cells as it forms an organ. But one can turn this concept around its head and therefore also posit that cancer represents a gain of new patterns.

The reason for doing so is because when one typically gets cancer and cells cells start spreading to other parts of the body, they don't do so necessarily in a chaotic manner. There is also certain principles that go into understanding how they spread, how they branch out, how they move, why do they move at a particular velocity. Do they move together or do they move as single cells? All of these also involve understanding a grammar of interactions of cells with themselves as well as with their matrix. Therefore, one can now consider cancer migration, cancer invasion or what is also called cancer metastasis as a gain of new set of interactional properties of cells and their external matrix. And therefore understand cancer as gain of a new pattern.

Next slide. So, in our laboratory, we try to understand the process of cancer spread. We break it down into a few interesting locales, into a few theaters where interesting interactions take place. The cancer metastasis can be understood to be a process where cancers move out of their local organ, seek a blood vessel, enter the blood vessel, move through the blood, reach a new site where they now move out of the blood vessel and enter a new organ and start spreading within that organ. We try to understand each of these locales and each of the interactional properties that occur in each of these locales and that would then allow us to try and understand the process of metastasis and also ultimately to attack this process. In this slide, what we see is what we have done in the

laboratory is to take cancer cells, put them within the extracellular matrix that is typically in that organ and put it under a microscope and essentially videography this process.

In this manner, we are now able to look at the cancer cells as they are spreading out. We are able to measure displacements and velocities of these cancer cells as they spread in a three-dimensional environment. This allows us therefore to understand how fast in some individuals does cancer grow and in some other individuals why does it grow more slowly. Getting these numbers is incredibly important to understand the pathology of cancers as well as to manage each individual or each situation as it warrants it. In the next slide, what we are showing here is our our certain model systems that we have developed in our laboratory which are called organ on chips.

These essentially reproduce aspects of anatomy of individuals but again in a miniaturized version and combine this with fluids using microfluidics. So what we have here is a blood vessel-like structure which has been connected with a cancer-like structure and this allows us to now understand how cancer cells spread out of the cancer, break that pattern that we discussed, and move into blood vessels. In other words, enter blood vessels. We try to use these systems to understand what are the various cues that allow us to understand how the blood vessel environment affects the entry of cancer cells into the blood. What are the different processes that cancer uses to break through the natural cells that are present within our blood vessels and how does the cancer cell survive within the blood vessel.

In the next slide, what we show is how cancer cells exist within blood vessel-like environments or fluid-like environments. Here we have combined again the aspects of microfluidics with cell biology to to put cancer cells or what are called spheroids which are collective of collectives of cancer cells as they flow through these fluidic environments. We try to understand what makes them withstand the various shear pressures and mechanical forces that are typical of these blood vessels. How are cancer cells able to tide over these processes? What makes them stronger in this process? What might lead to disintegration of these cancer collectives? And this allows us to study how metastasis occurs within an individual.

Next slide, We then also try to understand how and why does cancer spreads eventually to specific organs.

Is it that those organs secrete certain cues, secrete certain agents that make cancer cells become more friendly? This is similar to the metaphor of seed and soil where not just the seed but also the soil determines whether the seed will eventually become a plant. In other words, we try to combine two different organs which are which are shown here through two different fluorescent proteins, and try to see whether certain properties of the normal non-cancerous organ also makes it a better site or in other cases a worse site. For

cancers to ultimately spread. So with this, I will end my talk and and thank you for paying attention. Thank you.