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PROFESSOR: The thing we have to talk about here is multicellular life. Cells, although we can think of them as entities, are generally not the unit of a whole organism. There are many organisms whose unit is a single cell, but the really interesting ones are the ones that have got lots of cells. And so life has developed in a way that most organisms are multicellular.

And we can pose the question of why that might be. My trite phrase, while it's more interesting, is actually a very poor answer. There's a much better answer. And that is if you have something made of lots of cells, different parts of that organism can specialize and do different things.

And so you can get a diversification of function, which allows the organism to colonize new parts of the earth, interact with its environment in different ways, interact with other members of its species in different ways, and it does become-- allow a much greater complexity of life. So I would say-- the answer I would give you is it allows new functions to evolve and greater complexity of life to develop.

If we consider the human adult, and look and see what we're made of, we contain about 400 different kinds of cells. We can call those cell types where each cell type has a specialized function. Those cells are organized together, and they're located in specific places.

So the cell types are organized into groups. They are organized into three dimensional structures. One of the things that is most interesting about living organisms is that they're 3D. Think of it if we were all sitting there as flat sheets, you know, you get the idea. The 3D-ness is extraordinary. And it's one of the things that being multicellular allows you to do.

So cells are organized into groups, they are organized into 3D structures, and this notion of groups of cells and structures is that they work together. Groups of cells arranged in a certain way work together to form a whole, an organ, that has got an even greater specialized function.

So these work together to make organs. And in particular, as we'll talk about next time, it's the groups of cells and their 3D structures which makes the organs. And the organs themselves can be organized into super structures called organ systems. And we'll work on all of these things over the next couple of lectures.

Today we're going to talk about cell type. Here is-- before-- I'm thinking if I should show you a slide first, or if I should write this on the board. Let me show you a slide first because I want these next two boards to follow one from another. All right.

Different cells. Oh! There we go, OK. Different cell types. These are micrographs of different cell types. Here are red blood cells, which regulate oxygen transports for metazoa involved in reproduction, and neurons involved in communication. Each of them has got the basic cellular functions that we've talked about over the last lectures, but each of them is obviously morphologically different. They look different and they carry out different functions.

The cell types get organized in specific ways. This is a really extraordinary example, which is the retina of your eye, the light sensitive part of your eye, which contains a number of different kinds of cells. And these cells are organized in layers, and so they're color coded here. And you can see the different layers are grouped together, but then the different layers communicate with one another.

And this communication, and this organization is key. You can have all the different cell types in the retina, but if they're not arranged in this rigid structure, or in this specific structure, the retina doesn't function.

3D structures. We'll talk next time about engineering structure out of cells. And the heart is one thing you have to think about engineering. The only raw material that you have to use for the engineering is cells, and so how do you get something that looks like a human heart, and carries out the exquisitely regulated pumping function of the heart.

And here's another one that I'll touch on, which is the question of position. It's not that we just are made up of lots of different kinds of cells that are grouped together in organs. It's that they're also positioned in the correct place.

And in this plasticized human-- actually, I think it's a fully plastic human-- if you open up the cavity and look into the abdomen, you can see these organs that are arranged packed so beautifully like this. It's no accident. They get there, because they're told to get there. There is a process that positions the organs in the precise way. And if they're positioned incorrectly, there are medical consequences, which are very severe.

All right, so all of these things we need to think about. But let's go back to the board, and you

will recognize this diagram, which is pivotal for what we're going to talk about today. Here is a mantra that I've mentioned before. And you need to know and really need to understand this. All cells contain the same set of genes.

Professor Jacks will give you one exception to this rule, but it's the exception. All cells in your body contain the same set of genes, but not all those genes are used in every cell type. But each cell type uses-- and you know the word expresses now-- each cell type expresses a subset. And it's a unique subset-- well, let me put unique in parentheses, and you'll see what I mean-- a unique subset of the genome. And this set of genes and the products of those genes make the cell type what it is.

The products of those genes, usually proteins and some RNAs, give the cell type it's function. So there are two corollaries here. One, you have to understand how the expression of genes is controlled, and that is pivotal to this list. And two, this set of genes that makes each cell type, the set of active genes that makes each cell type what it is, forms a kind of a combinatorial code for a cell type.

So let's just write this down. So control of gene expression is crucial. And there is a combinatorial code of gene expression for each cell type. A combinatorial code of expressed genes for each cell type.

You will not find this notion of a combinatorial code in your book. But I think if you talk to any life scientist who's doing research right now, they would agree that that is the correct way to be thinking about cell type. So let's explore this a bit more. And let's write out three different cell types.

And I'm going to introduce the word here cell fate. And both cell type and cell fate can be used interchangeably with the term function. And let's pick neurons, muscle, and the epidermis, which is the outer layer of the skin. And let's consider the genes that are present in each cell type. And let's consider the genes that are expressed in each cell type.

The genes that are present in each cell type as I've just told are the same. And so let's make them A, B, C, D, and E. And each of those genes is present in each of these cell types, but only some of them are used. And so let's say in the neurons A, B, and E are used, in muscle A, C, and D and A, B, and C in epidermis.

So look at what I've written there. And you can pick out some patterns. You can pick out a

gene that is expressed in all of the cell types. So gene A is expressed in all of the cell types. And gene A exemplifies a gene that we term ubiquitously expressed, sometimes termed a housekeeping gene. I really dislike that term, but you will see it.

So ubiquitous expressed, maybe you'll see housekeeping. You can come to office hours, and I'll tell you why I hate that term. And then you can pick out a gene, which is expressed in some of the cell types, but not others.

So let's look at B. Here's B expressed in the neurons in the epidermis, but not in the muscle. And B would be referred to-- and actually C is the same way, isn't it? C is in muscle and epidermis. B and C would be referred to as genes with restricted expression.

So B and C would have restricted expression. And then there's two genes there E and D, which are only expressed in one of their own cell type, in neurons or in muscle. So D and E would be cell type specific genes. And from this simple example, you can see a number of things.

Firstly, you can get a combinatorial code that is specific for a cell type without any genes that are specifically expressed in the cell type. If you look in the epidermis example, A, B, and C are expressed. None of them are a cell type specific. But nonetheless, they give the combinatorial code that is the epidermis. And then the other examples, they each got a cell type specific gene.

What is a combinatorial code really look like? Well, to be honest we don't actually know. There is no cell type for which the combinatorial code is being worked out. But you know now there were about 20,000 human genes. And probably about half of them are expressed in most cell types.

So the combinatorial code for any given cell type is going to be thousands and thousands of genes, which are expressed or not expressed and which are also expressed at different levels. And we have to take that into account. So really finding the combinatorial code is incredibly difficult. And we don't know any for any cell type, but the notion is exactly the same.

I want to remind you here with this diagram that the control of gene expression to give you the final expressed product can be anywhere all the way from chromatin structure through transcription all the way through protein processing modification and localization. Good. All right, so now we have a framework by which we can think of what a cell type is. And the

question, of course, that you're asking is, so how does that combine tutorial code get expressed in each of the cell types?

Let's pose that question. How does a cell type express its code? And there's a couple of answers. The global answer that I'm going to give you to this question is stepwise. And let's have stepwise answer one.

The idea-- and we can do this-- I'm going to do this two ways. I'm actually going to do this-- no, I'm not going to do this two ways. Before we get there, this is a great slide, which will show you two things. One, it will show you the expression patterns of two different genes in the whole organism.

So here is a gene called myoD. I've shown this to you before that is cell type specific. It's just expressed in these kind of chevron shape things, which are the developing skeletal muscles, the voluntary muscles. And here are a couple of genes that are expressed in large regions of the developing animal. And you can see they're expressed, because of these colors that are there and the colors are indicative of where the RNA for that gene is.

The technique that allows you to look in a whole animal and ask where the RNA is for particular genes are found, is called in situ hybridization, up here at the top of the screen. And the idea is that you take animals-- here, I've said embryos-- developing animals, and you fix them, which means you kill them and you permeabilized them. You make holes in them, and then you use the principles of base pairing, where you look and see where the RNA is using a probe, which is an antisense RNA for a particular gene of interest. And you label this antisense RNA.

You mix it with the embryo that's got holes in or the animal that's got holes, where the RNA for gene x is. It will base pair to your antisense probe. You then wash out the extra. And you look and see where the color that comes from the label is. And that color tells you where the RNA for a particular gene is.

So these colors in the developing animal tell you where particular RNAs are. It's a very powerful technique. And it allows us to figure out which genes are cell type specific and which genes are more generally expressed.

Let's look at your first handout. And I'm going to write it on the board, as well, because this is really important. And you're going to need to know this for this lecture and when we get to

stem cells, as well.

So you can look on the screen. You can look on your hand-out. And I would suggest you write it, as well. The notion when we're thinking about cell type is that we start off with cells that don't know who they are. And they're called uncommitted cells. They're undecided.

And as they go through life, they get some inputs. We'll be vague about those. They're up there. I'm not going to write them here.

And at that point, they become committed cells. They are sometimes called determined cells. And at this point, the cells have decided what they're going to become. And later on, those committed or determined cells will go on. And they will become differentiated cells, where they have their final fates or their final function.

There's a time metric on this progression. And the notion really is that as cells go through this decision making process, they change which genes they are expressing, such that at the culmination-- but if you think about this or come and talk to me, you'll find it's more complicated. At the culmination, they will be expressing their combinatorial code.

Uncommitted cells, as they transition to committed cells, activate a set of genes that I'm going to call regulatory genes. They're the transcription factors, the translation factors, the protein processing factors. And these regulatory genes will then go and activate a set of genes that I'll call effector genes.

And the effector genes are the ones that are actually carrying out the function of the cell. They are the globin that's carrying the oxygen around the body. They're the neurofilaments that are making the neurons long and strong and able to transmit a signal. They are the cartones, which make hair cells able to secrete the hair that actually you see.

So the effector genes are the functioning, the functional mediators. And it's this mix of regulatory genes, which I've written as R, an effector genes, which I've written as E, which form the combinatorial code for a cell. So that's one answer. And you have more up there, which we'll come to in a moment. But let me give you another answer.

It's also the same answer stepwise, but this answer has to do with the history of an organism. I've avoided talking about embryos, until now, because I wanted you to think about the outcome, the cell types. But actually, all of this starts-- cell type formation starts right at the beginning of an organism's life, when two haploid cells, the egg and the sperm, magically get

together and join to form a diploid cell, the zygote.

This zygote, which is also a single cell is itself a magical cell, because it contains all the information necessary to form whatever organism is going to be the outcome. The zygote goes on to form an embryo, also diploid that contains many cells. And the embryo goes on to form the diploid adult, also with many cells. And in humans, there are about 10 to the 14 cells in the human adult.

And during this process of two single cells, two dying cells, the egg and the sperm are with a very finite lifetime, when those cells fused with one another-- and we're not going to talk about this any more than that then this discussion because of time constraints. When they fuse to form the zygote, there is an extraordinary process where the zygote is now resurrected in its life, and it has the capacity to give rise to the whole organism.

What happens during this process? Well, firstly, I've pointed out, cells divide. There's a lot of cell division. And that's really key to getting different cell types. You have to have something to work with. And as they divide, they become different.

According to the list on the screen and on the board above, the egg, the sperm, in fact, are differentiated cells, but let's start with the zygote, which is undetermined or uncommitted and undifferentiated. And I'm using determined and committed deliberately interchangeably so you get the idea that the terms are interchangeable. So the zygote is undetermined and undifferentiated. And as it goes through its embryonic stage, determination starts, continues into the adult. And later during late stages of embryogenesis and into the adult cells differentiate and become their final thing.

So determination starts in the embryo and sometime later the process of differentiation starts and continues. And so that's a second way of actually writing out the stepwise phenomenon of how cells become different from one another and how different cell types are formed. Let's take a look at some slides here. And let's take a look at a couple of movies.

This is a movie of the first few weeks of human development. And what you will be able to see from this is the enormous increase in size of a human embryo that's coupled with cell division and also with cell determination. And it's going to play again.

And what you can see, up until about day 56, we all had very nice tails, and then they disappeared, unlike other animals. But all of these are taken at the same scale. And so you

can get a sense of the huge amount of cell division that's going on during these first few weeks of life.

Here's a second one. This is a zebrafish embryo. And I want you to watch this embryo as it develops very rapidly much more rapidly than a human during the first 19 hours of development.

The fish embryo is kind of like a chicken embryo. There's a big cell called a yolk cell. And on top of this yolk cell sits a little other cell, which is the embryo itself. And it's this little top cell. Here it's already divided to give rise to two cells from which the embryo is going to arise.

And so as you watch the movie, you'll see these two cells dividing into four, into eight, and so on. And then you'll be able to see the beginnings of the fish emerge. And I'll play it a couple of times and point out some things to you.

Here's the cell division, taking place. It's not as rapid as this, but it's of course, a very rapid process. And now you have a little cap of cells on the yolk, and watch what happens. That cap of cells spreads out to cover up the yolk. And a lot of cells move to that side of the embryo, the right hand side of the screen.

Here's the eye emerging in the brain. And here are the muscles of the fish. And let's watch it again. Isn't that cool? So let me stop it.

Here at this stage, you have got several hundred cells that are sitting on top of this yolk cell. This pointer seems to have died, but they're sitting on top of the yolk cell. And you will be able to see when I start the movie again how those cells spread out to cover. And they are actively doing it. They know to do it.

They actively spread out to cover the surface of the embryo. And then actively a group of them moves to one side of the embryo to form most of the embryo, including all the nervous system, the muscles, the intestines, and so on. So let's start it again. There you can see these cells spreading out. They've spread it out to this-- they've spread out to this point. Let's let them spread out some more.

Here they are. They've completely closed up the yolk. And if we stop now, you'll see on the right hand side of the screen. There's a much thicker group of cells. They're thousands and thousands of cells now that are there.

Now at this point, if you look at gene expression in the embryo, you can pick out many different regions of the future brain. You can pick out the future intestines and the future muscles, but there is no differentiation at this point. The cells do not know. The cells have not finished becoming what they are becoming.

And here as we go on a bit more, here is the eye up front. And these bumps of the brain. And then these little chevron shape things there are the future muscles, your fish fillet. And there is the fish moving on. It's really a fantastic process. Very good.

Let's go back to the board and talk about this more theoretically. We have sort of answered a question here. How does a cell type express it's code? Well, not all at once, over time and over a series of many steps. But that's not actually the whole on answer.

And so let's rephrase the question to make it a little more precise. And I've rephrased it by asking, what tells a specific cell type to express its code? What tells a specific cell type to express its code?

And the answer is-- it's just not going to be really helpful to you, but it will in a moment. The answer is that there are a bunch of inputs. There are a bunch of instructions that the cell gets.

And let's write this out in a kind of theoretical way. We'll get to the molecules in a moment. Here again are our uncommitted cells. And they can be exposed to a number of different molecules. The inputs-- let me just come clean here. The inputs are specific molecules. And as you'll see in a moment, they all have got something to do with cell signaling or regulating gene expression.

These uncommitted cells can be exposed to many different inputs. Let's take three different inputs. We'll call them input 1, 2, and 3. And these inputs through many steps and changes in gene expression. And the inputs can be composite. They don't have to be a single thing.

We'll take those cells into differentiated cell type 1, cell type 2, or cell type 3. And cell type 1-- you know, to belabor this, we'll express code 1, cell type 2 code 2 et cetera. As these decisions are made similar to the kinds of decisions we've looked at in biochemistry previously.

There can be interactions. And so it may be that as cell type 1 develops, it's actually inhibits the formation of cell type 2. And cell type 2, in turn, might be an inhibitor of the formation of cell type 3.

So there are interactions between cells. So the inputs can be composite. They can composed of several molecules factors if you like. And there's crosstalk, just like the crosstalk between the receptors that we talked about in cell-cell signaling.

And that's not surprising, because in fact the inputs includes cell-cell signaling molecules. So there's ligands and receptors that we spoke about previously. So what are the inputs? And there are two.

One are signals that act between cells, just like we've been talking about in cell biology, cell-cell signaling. And wherever you talk about cell-cell signaling, it is implicit that you're talking about interactions between cells. Ligands, which in development are sometimes called inducers, acts on the receptor. And the outcome is to change cell fate.

This is a subset of the signaling interactions we talked about previously, where the response here or the response previously was manyfold, the response here would be to change cell fate. But there's a second kind of input. And those are the molecules that are cell autonomous, also referred to as being inherited factors and referred to in development as determinants.

And these determinants-- this is what cell autonomous means-- act within cells. And so they're not going to be ligands some receptors. They will be things, for example, like transcription factors. Furthermore, both determinants and inducers can act in a concentration dependent way so that a small amount would give you one cell fate and a larger amount would give you a different cell fate.

So it can be concentration dependent. And in the cases where a signal or a determinant is concentration dependent, it gets a special name. It's referred to as a morphogen, for historical, not particularly logical reasons. But if you see the term you'll know.

And finally, before we go to some slides, one can find groups of these inputs, groups of these regulatory molecules. So all of these inputs, all of these other regulatory molecules or regulatory factors. And they can act spatially in groups.

So you can find regions of the developing embryo, where there are groups of these molecules acting together. And where you find these groups, that particular region of the embryo may have a powerful effect in influencing the cells which form around it. And that region, that group of factors in one region that can influence its surroundings is called an organizer.

So groups of signals, which are localized, that is in one place, in one group of cells can

influence the surrounding cells and is termed an organizer. And there are many organizers in the body both in the embryo and in ourselves as we'll discuss when we talk about stem cells. Examples of organizers, I'll show you in a moment.

There's something called the Spemann organizer, which is very famous. And some of you may have learned about that previously. And then there are regions, for example, in the forebrain, the developing cerebrum, where there is an organizer that actually tells the different parts of you developing higher cortical function to form.

So let's look at some slides and some of your handouts. And I drew these for you, because I thought it was really important that you got them. Here is localized determinants, localized regulators called determinants.

And you see the idea here. This is important. This isn't on the board.

Here's the mother cell with these boxes, where these boxes represent some kind of regulatory factor. And you can see I've drawn them on one side of the cell, such that when that cell divides one of the daughters doesn't get them and one of them does. And if the boxes are regulatory factors, the daughter's cell that gets them will go on to do something different than the one that doesn't. And you can get two different cell types coming out of this.

And I've listed examples of the many different kinds of factors that can be determinants. Here's a real example. This is an early worm embryo.

Remember, I told you about Professor Horvitz, who got the Nobel Prize for discovering cell death processes. This is the same animal he works on. And on the top panels are nuclei stained in blue with this dye called dappy.

Here's the zygote. Here's the two cell embryo and the 32 cell embryo. And you can see that there's a nucleus in every cell. On the bottom are some determinants that are called pea granules.

Pea granules are composites of protein and RNA. And they are regulators of where the future germ cells will form, the future egg and sperm. Look how these germ-- look how these pea granules segregate during development.

Here they are on one side of the embryo, even in the zygote, and then the zygote splits. Look, one of the two cells gets them more and the other does nothing. And at the 32 cell stage,

there is one cell out of 32 that has all of the pea granules. And they've been excluded or degraded from the rest of the embryo. And that is a really beautiful example, perhaps the most beautiful example of determinants segregating.

Here's another one, the signaling factor secreted by neighboring cells. Uncommitted to cells over time will do something. There's enough transcription factors and regulatory factors in all cells that over time they'll go on to differentiate into something if they're normal cells. But there's a signaling cell telling an uncommitted cell to activate a signaling pathway and go on and make cell type 2.

And these are the inducers, which are ligands binding to receptors and changing sulfate. These signaling pathways can act in a concentration dependent way, as seen on that screen. And here is the notion of a morphogen, where a high ligand concentration will give an output of cell type 2 and low ligand concentration and output of cell type 3. And we touched on how this works molecularly, previously, it's not well understood and is complicated.

This is the most famous example of cells that can go on and tell other cells what to become. It's a group of cells that was termed the organizer before it was clear that there were actually lots of organizers. And they organized was defined by a graduate student Hilde Mangold, together with her advisor, Hans Spemann.

Mangold, unfortunately, went on and was killed in an explosion. Spemann went on to get the first Nobel Prize for developmental biology in 1935. It's never seemed fair. It isn't fair, anyway. That is a sad story.

Spemann was the preeminent developmental biologist in the 1920s. And this is the finding that Dr. Mangold made. She took an embryo and she removed from the embryo-- so you not only do you see my calendar-- you get an insight into the rest of my life. My husband is a professor over at that other university.

So we have competing teaching schedules today. So Dr. Mangold took a group of cells from the future back of the embryo-- we'll talk about this next time-- and she transplanted them into another embryo. She transplanted them into the belly. So she took back cells and put them in the future belly of a host embryo.

So there's a donor and a host. And she could see the difference between these embryos, because they had different pigmentation. They were different colors.

And then she let them go on and develop. And this was a hugely difficult experiment in those days for technical reasons. But over a period of a couple of months, these embryos developed. And what she found was this peculiar embryo, which is a conjoined twin.

And she could show by looking to see where the cells she had transplanted in were, that there was this host embryo that was made of all the original host tissue. And there was another embryo joined to it in this orientation, but that only a little bit of the second embryo actually came from the donor cells. Most of the second embryo came from the host cells. And this was epiphanal, because she could understand that those donor cells had told the host tissue to make another embryo.

It was an extraordinary unprecedented finding, and it gave the notion that cells can tell other cells what to become. Does this happen in other animals for sure? This is from a colleague of mine Jerry Thompson, who made these conjoined twin frog embryos by organizer transplants.

Does that happen in humans? It does. Conjoined twins come from, we believe, organizers that have split and have given rise to two embryos, which don't separate properly from one another. And we will stop there and continue on Monday.