How do our cells "know" which type of cell to differentiate into?

15 Questions and Answers

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Natalie Kalos, Science nerd, engineering major
Answered 2 years ago · Author has **3.8K** answers and **2.6M** answer views

How do our cells "know" which type of cell to differentiate into?

Ah, stem cell biology…

First thing to know that it truly varies. Differentiating into the cells of a nephron is not necessarily too similar to differentiating into cardiomyocyte cells in the heart in many of the specific details or even the broader paradigm, for example.

Now, there are some broader concepts behind cell fate decisions like differentiation that typically apply in one way or another and possibly in some combination. Here are some examples, since I think this might be more what you're looking for.

- Mechanotransduction. This basically means the mechanical environment for the stem cell in question is ultimately triggering some portion of the signalling pathways leading to differentiation. This can even include the cells being physically constrained
- Chemical signalling onto or through the cell membrane from outside ligands. Commonly in cell biology, receptor-ligand binding ends up leading to a much more important signalling cascade within the cell leading to more dramatic behavior, and differentiation isn't an exception to that broader theme. This can also include interaction with the extracellular matrix, essentially a meshwork of molecules cells anchor themselves to.
- Innate genetic expression of the relevant genes. Some of our genes are meant to specifically guide portions of this process and even broader embryonic development as a whole. For example, the shortness of many Turner's syndrome girls is generally thought to go back to the underexpression of just a single such regulatory gene behind bone growth due to the presence of only one X chromosome.
- The idea that genetic expression and signalling pathways can lead to constant, long term, effects on a cell and its behavior (such that differentiation doesn't reverse itself without another nudge) because the overall relevant pathway stabilized itself at a steady state point, as opposed to other processes that may lead to oscillatory or transient behavior instead. This is admittedly more of a dynamical systems viewpoint rather than a biological one, but it turns out to be a powerful way of understanding biology to apply mathematical understanding to it as well.

It is indeed a fascinating topic that biology is only beginning to unravel, but it already shows those basic patterns.

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How do cells know what to become?

How do cells know where to go?

How do cells know?

Which is the first type of cell to differentiate?

If all the cells in our body have the same DNA, then why aren't they all the same kind of cell? How can there be different cell types, shapes, and functions?

Ajit Rajasekharan, Looking at life from a computational perspective
Updated 1 year ago · Author has **801** answers and **2.1M** answer views

How do cells know what to become?

Arjun's answer gives a clear overview of how cells know what to become.

At the molecular level, the answer to the question "how do cells know what to become" is largely dependent on the answer to the question, "how do cells know where they are?" for the following reason.

divides making multiple copies (*with all copies containing the same code*), knowing where each cell is relative to other cells is a critical driving factor to decide what a cell's fate is and its role in the growth process - particularly what parts of its code gets executed.

- For instance, in the case of a fly, a single cell rapidly divides yielding about a 1000 copies with each copy carrying the entire code to make a fly. At that point, driven by cues that establish their positions, cells begin to execute different parts of their code. This selective code execution leads to the development of distinct regions that in turn serve as precursors for further "location specific code execution" ultimately yielding a fully developed organism with eyes, wings, legs etc. This whole process, from a single cell to a fully developed functional fly with all its body parts, happens in 15 hours with very little errors in most cases (*one has to tamper with the program code to make a leg grow where an antenna should be, for instance*). [2]
- In the microscopic world of cells where development and growth happens, measurement of position is typically made over spans of a few 100 micrometers or less. [1]

So how do cells know where they are?

- The simplest way cells appear to know where they are is by measuring the concentration of molecules of a certain type that has settled on a steady state concentration gradient and using that concentration as a metric for distance. **Figure 1**
- There appears to be multiple ways to establish a concentration gradient, but the simplest mechanism observed is the gradient formed by diffusing molecules of a certain type that are typically destroyed/cleared by cells sensing them. It is the removal/clearing of the diffusing molecule that helps form the gradient - pure diffusion without removal would eventually yield only a uniform distribution of the diffusing molecule. **Figure 2,3** [9], [11]
- While the mechanism to determine location appears to be very simple, the reliability of determining position with the accuracy and precision that is required for proper development to occur makes this a challenging problem. For example, the variability in production of the molecule forming the concentration gradient, the variability in the binding of the molecule to receptors with which cells measure concentration, variability in activation of signalling paths that ultimately turn on execution of specific portions of the code, etc. can all be high making position measurements both inaccurate and imprecise. **Figure 2**
- There appears to be no perfect solution to this problem other than an engineering solution of making the right trade-offs. Nature seems to do just that - evolve trade-offs specific to each circumstance. For instance, embryos that develop in eggs laid on land need to accommodate unreliability from temperature fluctuations more than mammalian embryos or those that develop in marine environments.
- While we do know diffusing molecules serve as "rulers" to measure distance and help cells know where they are, other mechanisms appear to play a role too in determining position and shaping development, particularly at length scales that exceed those that can be generated by diffusion alone. For instance, long range mechanical forces appear to play a crucial role in the shape of a developing fly wing. Active transport driven by motor proteins appear to play a role too at length scales exceeding diffusion impact lengths. [11], [12] Recently biolectric signals have also shown to play a role in patterning and development The Levin Lab, Department of Biology: Home
- The role and mechanisms of these other types of rulers that shape development, such as mechanical signals, migrating cells,electric fields etc. remains to be fully studied [11], [12]

How do cells become different from the knowledge of where they are?

- Typically, the positional cue (*be it from concentration gradient, or any other "rulers"*) either directly or indirectly triggers location specific code executions in cells (*i.e. transcription/translation of genes in a location specific manner*), making cells different from each other.
- The positional cue also plays a role in locking a cell into a differentiated state, executing only certain portions of its code. This locked state is preserved even across cell divisions. For example, a cell that becomes a skin cell produces only more skin cells from division (*recently we have found ways to reset a cell's locked state*). [14]
- There are exceptions, however where cells locking into a state is purely stochastically driven independent of their surrounding environment. Nature appears to have evolved this strategy due to its advantages in certain cases. [13]

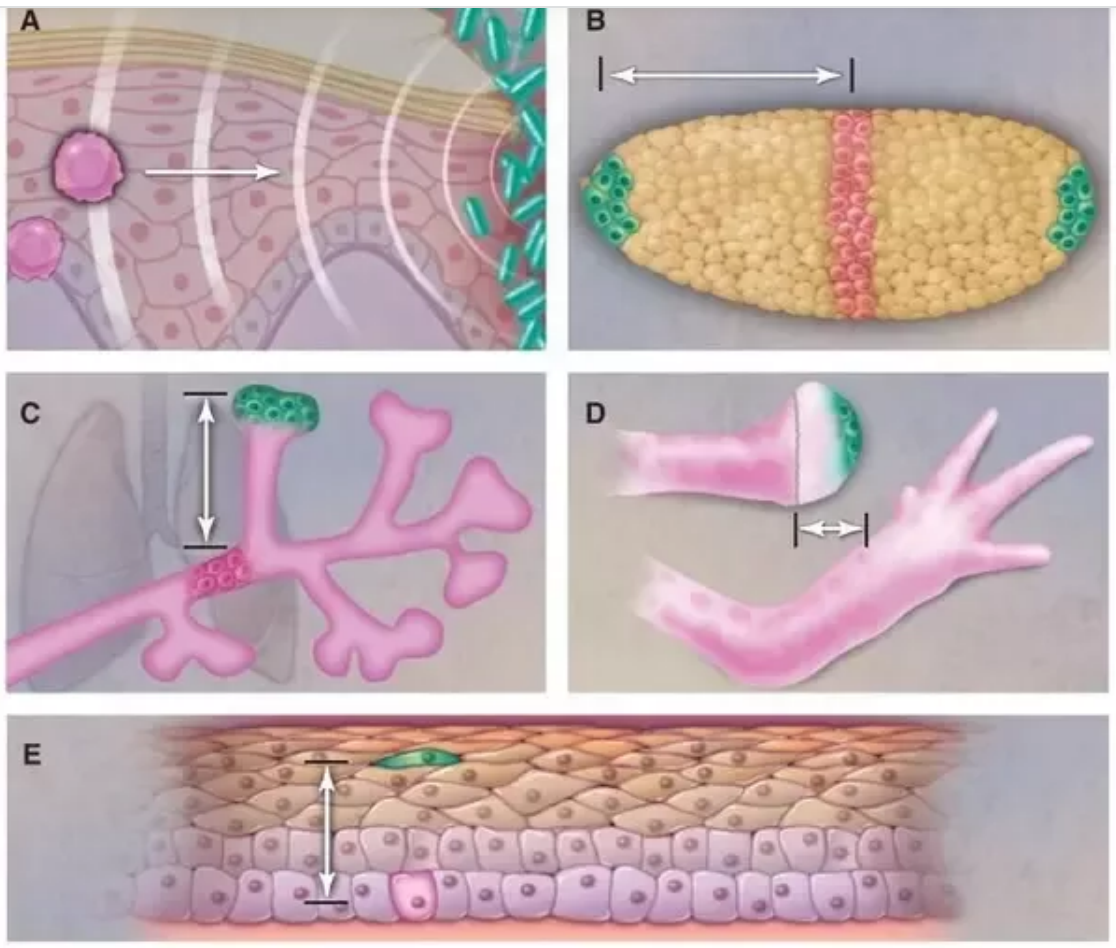


Figure 1. *A gallery of positional tasks. A leukocyte (A) may need to know in which direction to head to find the site of an infection but not the absolute distance to it. A cell in an early embryo (B) may need to know absolute location with respect to one or the other end of the embryo so that it differentiates into a spatially appropriate cell type, whereas a cell in a tissue undergoing branching morphogenesis (C) may need to know only the rough location with respect to the nearest branch point or vessel. In regenerating tissues (D), cells need to know their position with respect to a site of injury or amputation, whereas in tissues or organs with laminar structures (E) cells may need only know whether they are in the appropriate layer.* [1]

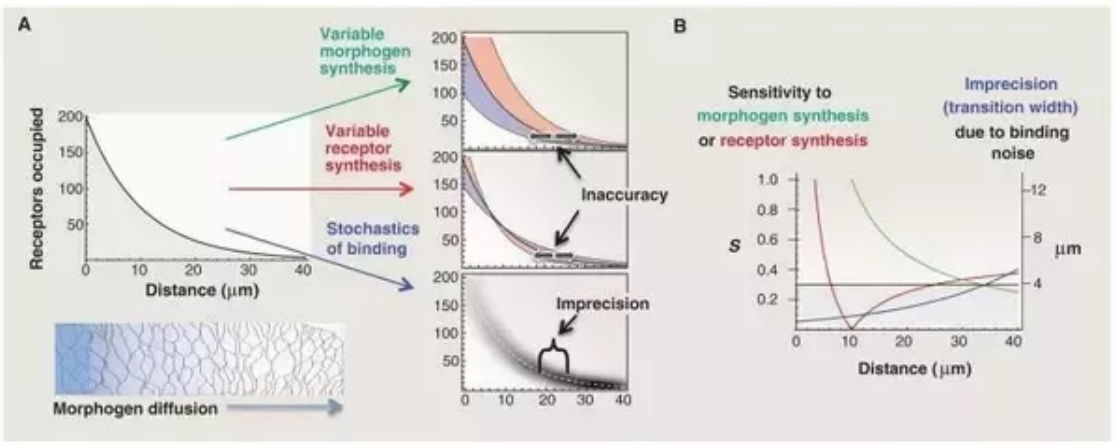


Figure 2. *Effect of input variability on the reliability of diffusion gradients. (A) Diffusion of molecules through intracellular spaces, when coupled to receptor-mediated uptake, produces steady-state gradients from which cells can ascertain their positions. But variability in processes that contribute to gradient formation or interpretation will necessarily lead cells to make mistakes. Their errors may be classified as either inaccuracy, whereby the average cell at a given location obtains an incorrect positional value, or imprecision, whereby there is cell-to-cell variability in the positional information obtained by cells at equivalent positions (the latter effectively converts the gradient of positional information into a probability cloud, rather than a sharp curve). (B) The most important potential sources of unreliability are different at different locations along a gradient [values shown are based on the gradient in (A)].* [1]

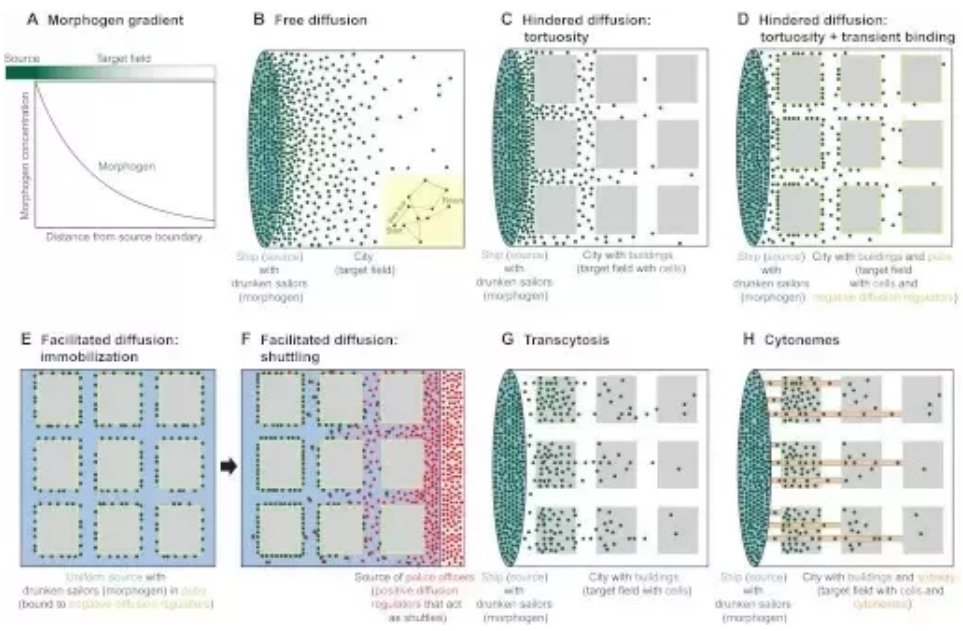


Figure 3. ***Morphogen transport and the drunken sailor analogy.*** *(**A**) The transport of morphogens from a source establishes a gradient in the target field. (B-H) Five major*

*molecules are represented by sailors and cells are represented by buildings. (**B**) In the case of free diffusion, sailors (green dots) leave the ship (blue oval) and disperse into the city (white square). Inset: sailors take steps of the indicated fixed size and the direction of each step is random. This 'random walk' describes the diffusive behavior of molecules in solution. (**C**) In the tortuosity-mediated hindered diffusion model, buildings (gray) act as obstacles that sailors must move around, thus increasing the tortuosity of the environment. (**D**) In the case of diffusion that is hindered by tortuosity and transient binding, the sailors stop in pubs (negative diffusion regulators, yellow) located at the periphery of buildings. Note that, in contrast to effects from tortuosity alone, sailors congregate at the periphery of buildings, and there are relatively few freely moving sailors. (**E**,**F**) The shuttling model does not require a localized source of sailors. Instead, sailors are initially present mostly in pubs (negative diffusion regulators, yellow) and uniformly distributed in the city (E). Police officers (positive diffusion regulators, red) disperse from a source on the right side, pick up sailors from pubs and escort them through the city by preventing further pub visits (F). When police officers disappear (not shown), sailors can re-enter the pubs. Over time, this results in the concentration of sailors on the left. (**G**) In the transcytosis model, the sailors travel through the buildings. (**H**) During directed transport mediated by cytonemes, the sailors travel through subway tunnels (orange), which deposit the sailors in buildings.* [9]

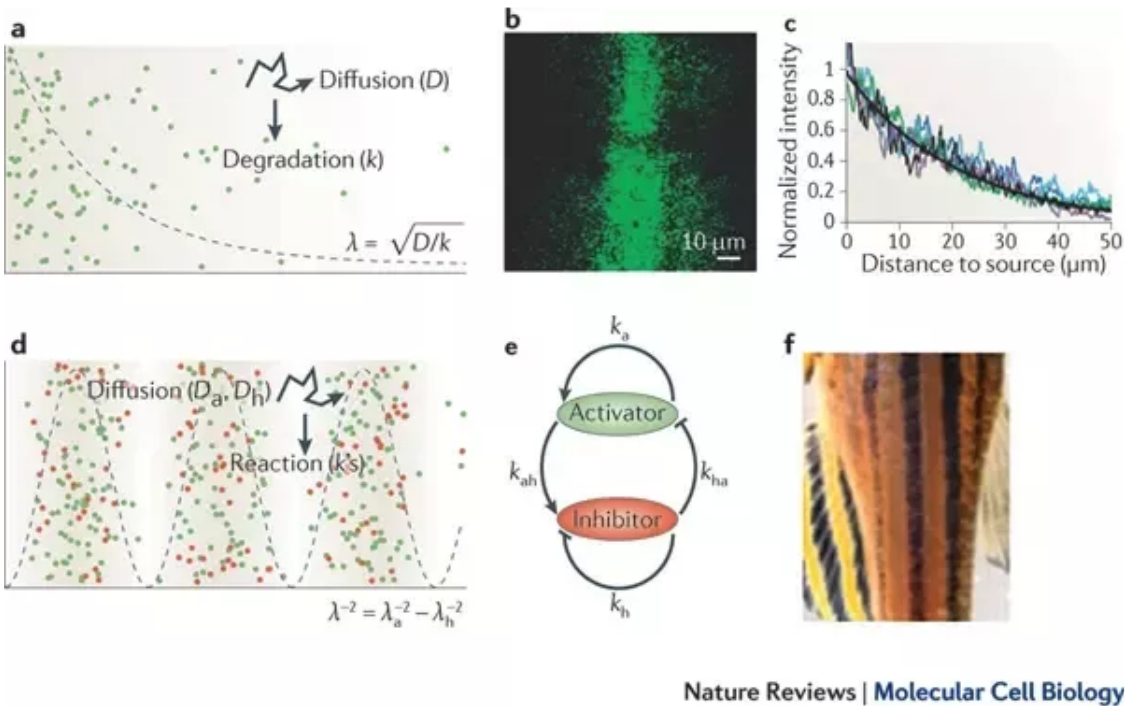
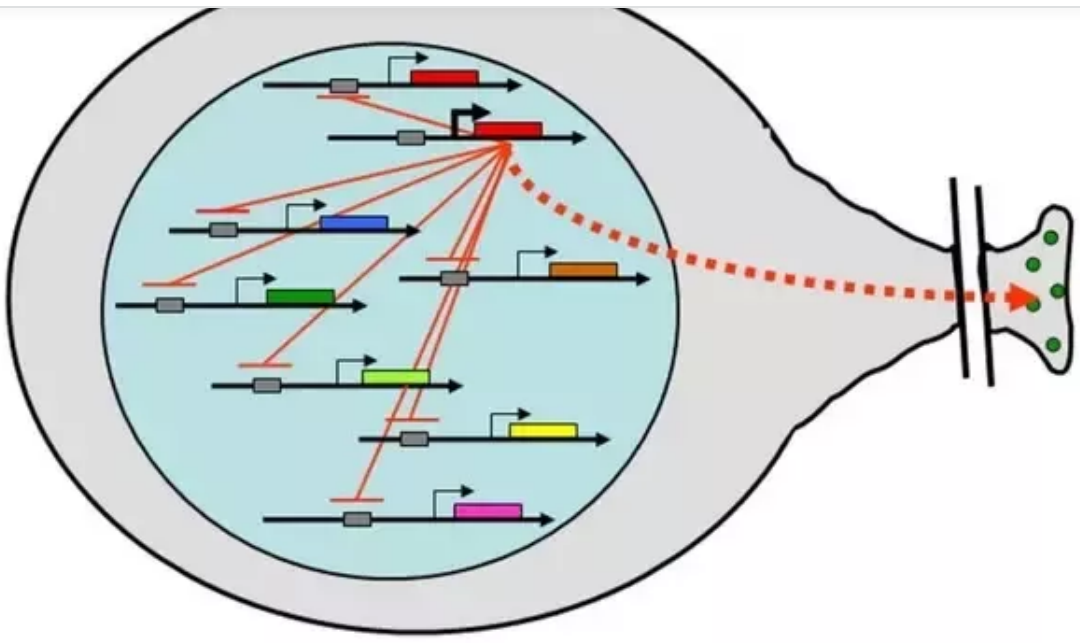


Figure 3. *a | Schematic of a local source–global sink mechanism. Morphogens (green dots) are released at a point and degrade as they diffuse away. The steady-state concentration of the molecule decreases exponentially, with a length constant given by λ = √(D/k), in which D is the diffusion coefficient and k is the rate constant of degradation. b,c | Green fluorescent protein (GFP)-tagged Decapentaplegic (DPP) patterning in a developing fly wing (b). DPP diffuses away from the source, the vertical line along which the intensity is highest, and is degraded in the tissue to give an exponential gradient32 (c). d,e | Schematic of a 'Turing pattern' (d) featuring two chemical species (activator shown in green and inhibitor in red), with the reaction scheme in e. As a result of self-amplification, a peak in activator and inhibitor concentration grows. Because the inhibitor diffuses away from a peak more quickly than the activator, it has higher concentrations relative to the activator on either side of the peak, thereby restricting the width to which the peak may spread. The distance between the peaks in the pattern, λ, is a complicated function of the diffusion coefficients and rate constants defined in e. At the onset of pattern formation, λ is given by the formula shown in d, in which λa = √(Da/ka) and λh = √(Dh/kh); 'a' represents the activator and 'h' represents the inhibitor. f | The stripes on a zebrafish are thought to be generated by a Turing mechanism* [11]



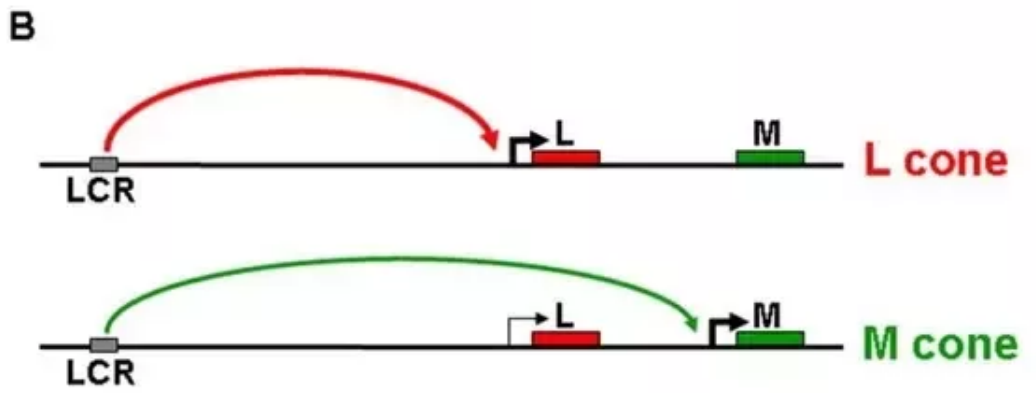


Figure 4. ***Cell-autonomous cell fate decisions***

*Panel **A** illustrates cell-autonomous stochasticity in a mouse olfactory neuron. The neuron expresses one olfactory receptor gene (red) to the exclusion of all others (blue, brown, dark or light green, yellow or pink), including the other allele of the 'red' gene. The olfactory neuron somehow instructs its target neuron in the olfactory bulb of its choice (dashed arrow).*

*Panel **B** illustrates cell-autonomous stochasticity in an old world primate color vision cone photoreceptor. The choice of a cone photoreceptor to become M (green-sensitive) or L (red-sensitive) depends on the ability of a single Locus Control Region (LCR) located upstream of the L and M genes to contact one of the two genes. If the LCR contacts the M gene, the cone becomes an M cone, and similarly for the L gene. This ensures that only one gene is expressed in each cone. As the LCR-M-L cluster is located on the X chromosome, only one copy is present in males and only one is active in females, due to X-chromosome inactivation.* [13]

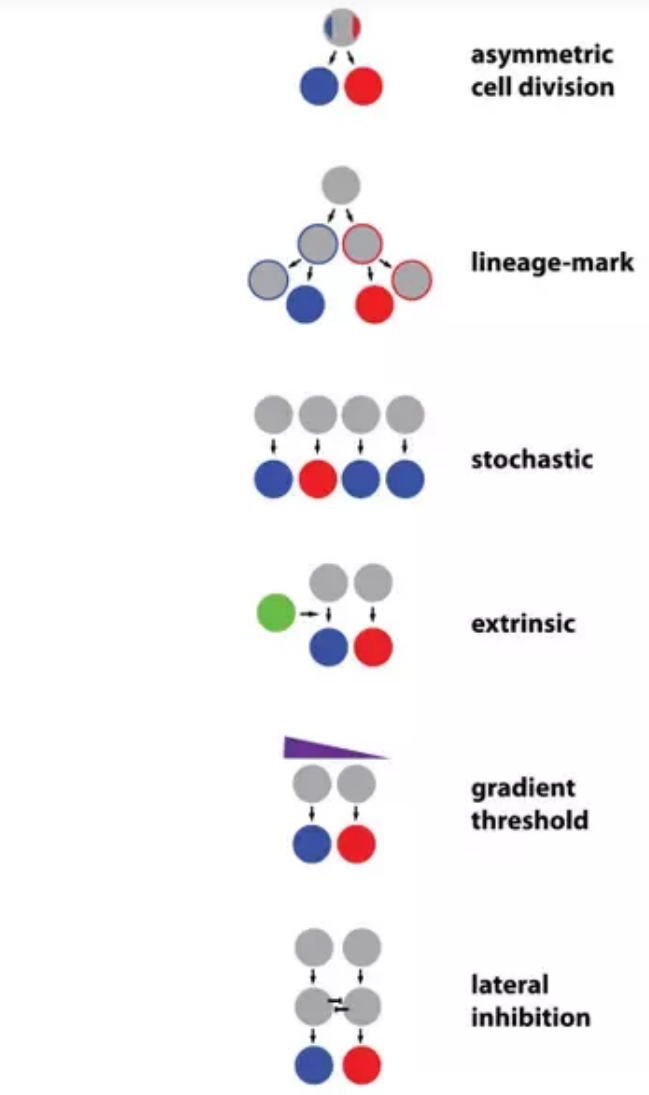


Figure 1. General Modes of Binary Cell Fate Decisions
Gray circles represent undifferentiated cells prior to fate choice; Blue and Red circles are differentiated cells that have acquired fate subtypes.

Figure 5. Binary fate decisions in differentiating neurons.

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15. Binary fate decisions in differentiating neurons.

Update 2019

Biolectric signals seem to play a role in pattering and development. Voltage gradients created by all cells (not just neurons for signaling) seem to regulate development. Deciphering this bioelectric code could perhaps give us a deeper understanding of development which is still very incomplete to date. The Levin Lab, Department of Biology: Home

A recent talk (Dec 2018) on this topic by Dr. Michael Levin

David Belair, PhD Biomedical Engineering
Answered 5 years ago · Author has **861** answers and **1.9M** answer views

How do cells differentiate into different types?

Originally Answered: How do cells differentiate?

Trafalgar did a good job identifying *why* cells differentiate, so I will attempt to broadly explain *how* cells differentiate.
Cells are in constant communication with each other and their environment *via* proteins and small molecules. Cells have receptors on their cell surface allowing them to respond to particular signals, but not all cells have the same types of receptors (and therefore not all cells can respond to the same signals). In the blastocyst stage of development (a few days after fertilization of the egg), there exists an epiblast layer of cells that can essentially become all the tissue types of the body. These cells from the epiblast are known as embryonic stem cells, and they are pluripotent in that they can differentiate into the three germ layers (ectoderm, endoderm, mesoderm) making up all the tissues and organs of the mammalian body. The pluripotent stem cells in the blastocyst must differentiate during gastrulation (during development), in which there are 3 different germ layers in the developing embryo (which represent three tissue types that will eventually develop). This is perhaps the single most important event during mammalian development, and it is at this stage that the cells of the developing embryo begin to differentiate and form organs and tissues [1] .

Differentiation in general (during gastrulation and later on during mammalian development) is driven by mechanical cues (gradients of mechanical stress in the embryo as it changes shape), by cell adhesion cues (from the extracellular matrix and with other cells), by soluble cues (proteins or other molecules that can bind to receptors on the cell surface), by oxygen tension (the gradient of soluble oxygen), or other soluble or insoluble signals. These cues can signal a cell to change its phenotype and differentiate [2]. Differentiation in general begins with a cue that can transduce its signal inside the cell. Cues can be transduced in the cell by receptors on the cell surface (that transverse the cell membrane) that are activated and change their shape upon binding of the cue to the receptor [3]. In some cases, the cue can directly pass through the cell membrane and signal to the nucleus or to other intracellular proteins or molecules, but most cues are too large to pass through the membrane and require a cell surface receptor to transduce the signal to the inside of the cell.

Once a receptor is engaged by a cue at the cell surface, intracellular proteins and messengers are recruited to the part of the receptor on the inside of the cell. These intracellular proteins and messengers bind to the receptor, recruit other messengers, and eventually activate a sequence of events that brings the signal to the nucleus of the cell (where all the DNA is stored). Once at the nucleus, these intracellular signals can activate transcription factors, which are proteins that are specialized to bind to DNA at specific sites and turn on the expression of certain genes. Conversely, signaling from cues outside the cell can also turn off particular transcription factors and repress the expression of certain genes by similar transduction pathways. The transcripts (mRNA) of the genes that are turned on or off by the signaling cue at the cell surface can then be translated into proteins that either are sent to the cell surface (as receptors or cell-secreted proteins) or stay inside the cell (as transcription factors, signaling proteins, structural proteins). Additionally, cell signaling and signal transduction can affect the genome by chemically modifying the histones that wrap the DNA (more details can be found in my previous answer on histones, What is histone acetylation?).

Differentiation can be thought of as a cellular process that begins with an initiating event and leads to changes in gene expression that cause a stem or progenitor cell to specialize its function.

References:(forgive me for citing Wikipedia - please look at internal citations for more information).
[1] Gastrulation
[2] Cellular differentiation
[3] Signal Transduction at Cell Membranes: Protein Kinases and Phosphotases

Related Questions

How do cells know what to become?

How do cells know where to go?

How do cells know?

Which is the first type of cell to differentiate?

If all the cells in our body have the same DNA, then why aren't they all the same kind of cel…

Stephen Thomas Blume, Dentist, writer, engineer
Answered 3 years ago · Author has **413** answers and **241.4K** answer views

How do cells know?

Originally Answered: Do cells "know" what they are doing?

This is a great question and science has absolutely no answer. We probably never will since all of the internal parts of cells and their functions have been identified. There is no known part of a cell that can direct its unbelievably rapid and complex processes. Each cell in a human body produces 2,000 protein molecules per second. What could possibly direct that hyper-speed and uber-complex formation? The nucleus can be removed from a cell and the cell will continue on doing all of its functions such as taking in nutrients, converting those nutrients to usable energy, and ridding itself of waste products. Except it cannot make new proteins. Cells can live for months without their nucleus. So the nucleus isn't the director of cell function, or the "brain" of the cell. I find it amazing that biology students are taught about the functioning of cells, how proteins are formed, how cells convert nutrients into energy, etc. without addressing how all of this is controlled and directed. How do non-living molecules "know" where to go inside and outside of a cell so they can perform their functions? What makes them "swim" from one place to another, and what controls that "swim"? How does mRNA swim through tiny pores in the nuclear membrane, and then swim their way to and lock on to a ribosome, like a living snake with eyes and a brain? The fact that this is a complete unknown is never mentioned in biology texts and classes. What could be a bigger mystery? Maybe the mystery of what entity directs the formation an infant from an ovum. The mysteries still left to solve are far greater than the ones science has solved. In this field, we are scientifically still babes in the woods.

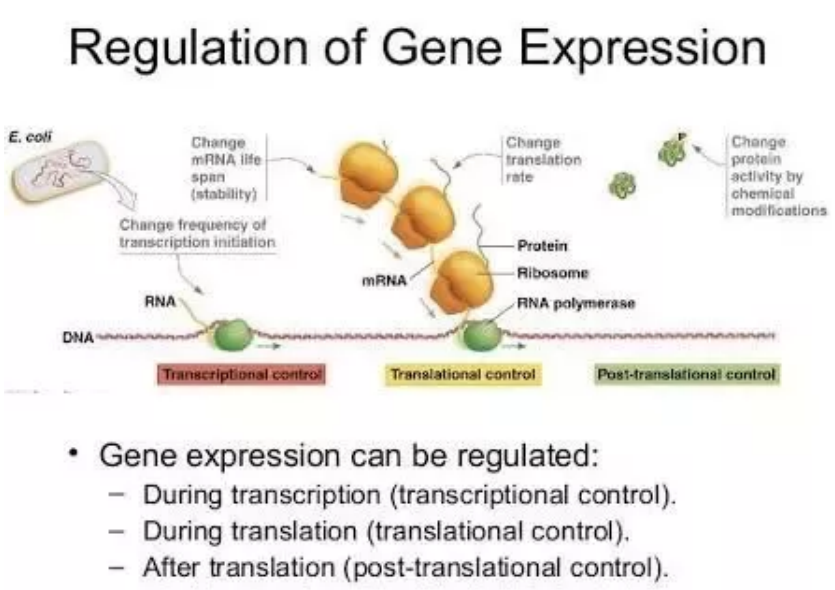
Ravi Tej, Have seen it and have read about it.
Answered 5 years ago · Upvoted by Roger Morton, PhD. In Plant Molecular Biology, ANU 1994 · Author has **219** answers and **956.1K** answer views

If all the cells in our body have the same DNA, then why aren't they all the same kind of cell? How can there be different cell types, shapes, and functions?

Originally Answered: If all cells have the same DNA, then why can't all cells do the same functions?

You are right when you say that all the cells have the same DNA (same set of genes).

But what differentiates one cell from an another is the **selective expression** of the genes. Agreed that brain too has the same gene for insulin synthesis as does the pancreas. That doesn't mean that the brain produces insulin, because either the brain cell is *regulated* in not translating the gene to the protein (insulin) or the produced protein is inactivated so as to turn it non-functional. And this process of *repression/inhibition* is the gamut of **regulation of gene expression.** Which is a huge topic unto itself.



This process of regulation of gene expression is not a peculiarity to humans but is found in all living cell. It may be either simple as can be seen by the *lac operan* concept for

be its proteins (posttranslational), RNA (translational), the DNA beside the gene in question (promoter sequence concept).

For example, when a gene is methylated it stops expressing (commonly). And thus the cell can *regulate* specific sets of genes to be expressed, *which defines the identity of that cell.*

Charles Low, B.A. Biology, Gordon College, MA (1967)
Answered 2 years ago

How do our cells "know" which type of cell to differentiate into?

By interacting with other cells. Cells produce chemicals that other cells sense and react to. Even nothing more than a simple clump of cells, each cell giving off just one chemical, could tell surface from interior based on the concentration gradients in the clump. Then surface cells can react differently, perhaps folding , causing a new gradient and turning on a new chemical. Now there are more ways cells can distinguish their locations compare to others and more chemicals can be turned on or off. In a few months a tiny clump of cells has produced all the myriad parts of a new living animal. All a complex orchestration of chemical signals.

Of course it took billions of years of evolution for animal cells to reach this kind of complexity.

David Wright, PhD Life Sciences & Developmental Biology, University of Dundee (2011)
Answered 2 years ago · Author has **782** answers and **344.4K** answer views

How do cells respond to contact with other cells?

There are two ways to interpret this question: “what cellular behaviours result from contact with other cells?” or “what mechanism allows cells to respond to contact with other cells?”

The answer to the first question is bewilderingly complex. There probably as many ways in which cells react to cell contact as there types of cell (and potentially more, as one cell type might react differently to different types of cell contact).

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Subham Sarkar, studied at The University of Burdwan (2017)
Answered 1 year ago

How do stem cells know what type of cell to become?

They don't.

Here is an analogy. When I was a young school student, I could choose whichever career option I wanted. Sportsman, academician, singer, writer etc. So that was my totipotent stage (potent to become anything). As soon as I chose academics (pluripotent), I had my other career options closed. Next I took science (multipotent). Which means options for arts or commerce are not there anymore. Then I opted for Graduation followed by

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1 1 1

Peter Morrison, SynBio PhD candidate; M.Eng; OURC half-blue
Answered 2 years ago · Author has **60** answers and **55.4K** answer views

How do cells know where to go?

A cell doesn’t really ‘know’ anything: there’s no cognitive processing going on there.

Fundamentally, DNA makes RNA’s, and RNA’s make proteins. Some proteins interact with the cellular environment; some proteins interact with DNA; and some proteins interact

Sound simple? Here's the thing: each cell has thousands of different proteins floating about in it. The number of interactions that are going on at any point in time is mind-

John Moorhead, former Professor of Immumology, Assoc. Dean Research at University of Colorado Anschutz Medical Campus (1970-…

Answered 2 years ago · Author has **1.6K** answers and **1M** answer views

How do our cells "know" which type of cell to differentiate into?

How cells "know" or "learn" what cell to become starts with an undifferentiated stem cell. These undifferentiated "stem" cells have the capacity to become any type of a cell in the body. This is a complex process which is influenced by both the environment the stem cell is in and by soluble growth and differentiation factors which turn stem cell genes off and on to iniatiate the process of growth and differentiation into specialized organ and tissue cells.

Beginning with pluripotential stem Cells, i.e., cells that can become any type of differentiated cell, and cocktails of growth and differentiation factors this whole process can now be replicated in vitro. This has opened a whole new field of study and research for the re-growth and/or repair of damaged organs such as the spinal cord.

1

Vigneshwar S, works at Institute of Genomics and Integrative Biology

Answered 3 years ago · Author has **177** answers and **443.7K** answer views

Why do cancer cells not differentiate?

Oncogenes.

Does it ring a bell? Ever heard of it before. If yes, you know where I'm going with this answer. If no, then let me explain further.

Oncogenes are tumor causing genes. They are the genes which are responsible for cell division. And yes you're right, if you thought they're presen in all dividing cells. They're normally called proto oncogenes. That is, their expression is tightly regulated and after a certain point in a cell's life they get down regulated by apoptotic signals and the cell dies.

8 2

Annaya Khan, MBBS At Baqai Medical University

Answered 2 years ago · Author has **58** answers and **56.2K** answer views

How do our cells "know" which type of cell to differentiate into?

The process you're referring to is called "Differentiation", which in biology refers to stem cells becoming other cell types.

Chemically: The chemical properties of the surrounding the cell and available nutrients play a factor. These are things like pH, oxygen levels, CO_2 levels etc.

Physically: Certain cell types are receptive to different mechanical stimuli and surface properties. If you're trying to grow stem cells on a certain material you can alter it at the nanoscale to promote differentiation into a certain cell type. Another example is

Lois Cronholm, former Former University Administrator, Retired (1965-2009)

Answered 2 years ago · Author has **5.5K** answers and **831.2K** answer views

How do our cells "know" which type of cell to differentiate into?

An accurate summary can be stated in a sentence. The details of how this works would take up pages if we were to include all of the current research on this question with

Here is that sentence: The genetic information in that one fertilized egg includes regulator genes that sequentially direct the differentiation into different cell types and structures.

59 views

Hugh Miller, Professor of Biology at East Tennessee State University (1988-present)

Answered 3 years ago · Author has **1.5K** answers and **330.8K** answer views

Why do stem cells differentiate into different types of cells?

Basically a stem cell is a cell that has not undergone any genetic selection process. Conversion of a stem cell into a different cell type involves selected switching on or off of gene networks. It is this switching that provides the genetic selection to become a specific type of cell. The term differentiation is used to describe this gene switching process.

53 views · View Sharers

2

Tatiana Nikolskaya, Retired CEO of Biotech company

Answered 6 months ago · Author has **200** answers and **14.5K** answer views

How do our cells "know" which type of cell to differentiate into?

Originally Answered: How do cells know what to differentiate into?

If you modify your question to ""How do cells know what to become?" - you'll get at least 8 answers. And all you need to do is to read. Good luck!

40 views · Answer requested by Efrayim Bulka

Related Questions

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How do cells know where to go?

How do cells know?

Which is the first type of cell to differentiate?

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How do cells differentiate into different types?

How do cells respond to contact with other cells?

Why do stem cells differentiate into different types of cells?

How do stem cells know what type of cell to become?

Why do cancer cells not differentiate?

Are there any human cells whose functions are currently unknown or poorly understood?

Could we manipulate cell's microenvironment to induce cancer cells to differentiate into normal body cells?

How can Cells be seen? What are some examples?

How do individual cells know they are a part of a system and whether or not to stop or start producing new cells?

Besides cancer cells, how many cell types are there in tumors? What are the "good" cells and "bad" cells?