WHAT IS THE MATRIX OF LIFE?

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Life develops and evolves through several complex cellular interactions. These interactions are supported by a matrix in the cellular microenvironment. How is this matrix put together? How do cells bind and respond to it? Does it influence cell function in disease?

Almost all living organisms are made up of cells. For e.g., the human body is composed of trillions of cells that live and work together. These cells are very similar in how they are put together, but differ significantly in their size and shape. This, in turn, could affect how they function (see **Fig. 1**).[1]

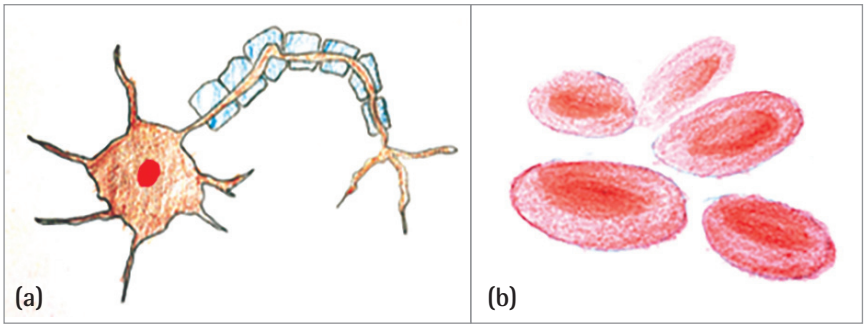

Fig. 1. In all shapes and sizes. Multicellular organisms, like humans, have cells of many different shapes and sizes. Cells like **(a)** neurons can grow up to 100 microns in length (0.1 mm). They are very different to **(b)** red blood cells (RBC) which are shaped like vadas and are about 8 microns in size.

Cells in **multicellular** organisms tend to self-assemble into tissues, organs and organ systems (see **Fig. 2**). The size, shape and ability of cells to self-assemble into more complex structures may depend not just on the kind of cells in a tissue, but also on how their tissue **microenvironment** is organised.

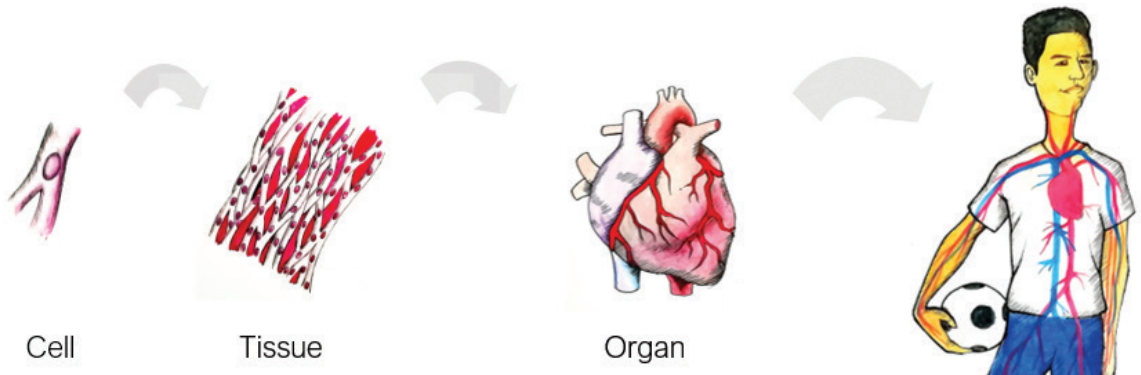

Fig. 2. Cells to tissue to organ. Individual cells come together to form the beating tissue that makes the organ that is our heart. The beating heart now works as part of the complex circulatory system that carries blood (nutrition and oxygen) throughout our body.

The architecture of a cell is shaped by both biochemical and biophysical (mechanical) cues from the microenvironment, and their downstream effects inside cells.[1] For e.g., animal cells derive their structure and shape from forces exerted by:

a. the **cytoskeleton** inside the cell that pulls at and pushes on its membrane,[2,3]
b. the binding of the cell to components of an **extracellular matrix** (ECM) that surrounds the cell and pushes against the cell boundary,[4,5] and
c. cell-cell interactions.

Communication between the cytoskeleton and the ECM are mediated by receptors, like **integrins**, on the cell membrane that bind to components of both these structures (see **Fig. 3**). Similarly, cell-cell interactions are mediated by **cell adhesion molecules** (CAM) like cadherins on the cell membrane that bind cadherin molecules in neighbouring cells.[6,7]

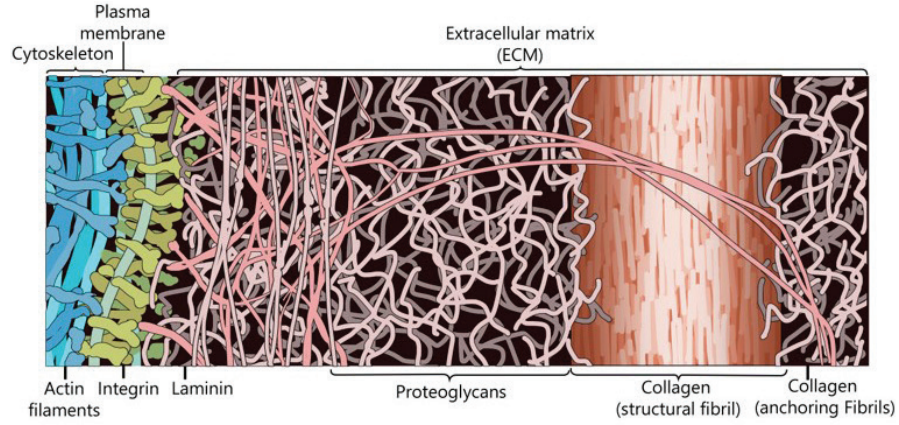

Fig. 3. The plasma membrane boundary of the cell. It is lined on the inside by the cytoskeleton (in blue) and on the outside by a mesh of ECM proteins (such as collagen and proteoglycans). Receptors are proteins inserted in the cell membrane that talk to both the ECM and cytoskeleton.

The cytoskeleton is a network made up of protein subunits that attach themselves to the cell membrane, cellular organelles, and the nucleus. It has two major components:

a. The **microtubule cytoskeleton** (see **Fig. 4a-b**) is a hollow tube that arises from the centre of the cell and spreads to cover it, acting as railroad to move things around the cell.[3,8]

b. The **actin cytoskeletal network** (see **Fig 4c-d**) supports the cell structure while helping generate forces that can change cell shape and drive cell movement. Actin also plays a vital role in responding to mechanical cues and converting them to biochemical responses in the cell.[2,3,9]

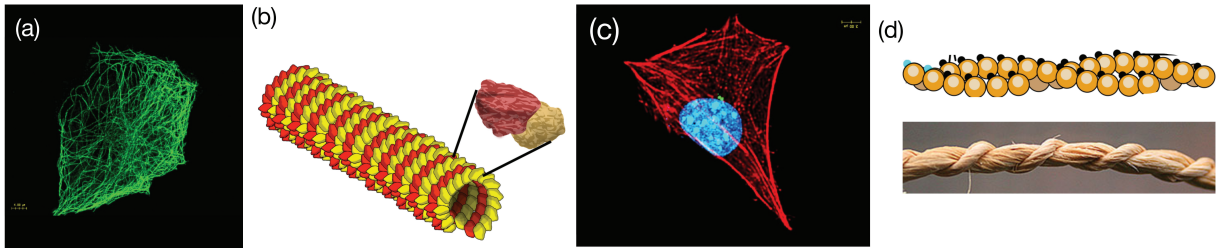

Fig. 4. The cytoskeleton. The microtubule network in green **(a)** is made up of individual tubulin pieces (alpha: yellow, & beta: red subunits) assembled into a tube **(b)**. The actin network is seen in red around a blue nucleus **(c)**. Each actin thread is composed of identical pieces assembled into two strands **(d)** that wind around each other (like a twine).

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What is the ECM?

Simply put, the ECM is a **macromolecular mesh** that wraps around and binds cells, like noodles seem to wrap themselves around veggies (see **Fig. 5**). This mesh allows cells to be held together as well as regulate multiple functions individually, and with other cells as part of a tissue.

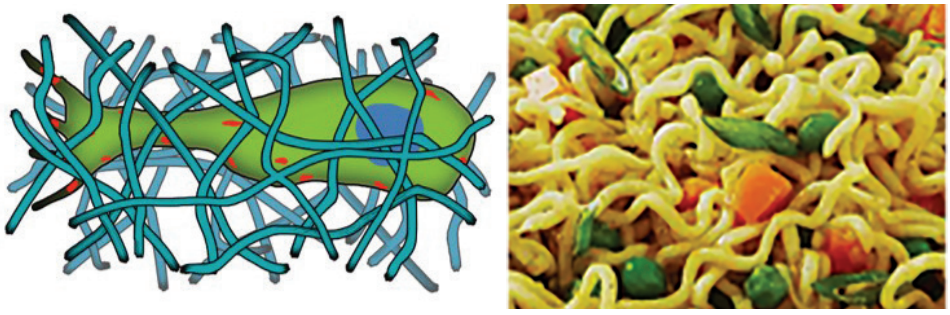

Fig. 5. The matrix is like a bowl of noodles. Mammalian cells (in green) are surrounded and held in the ECM (blue fibers) that they secrete. This is very much like veggies trapped in a bowl of yummy noodles.

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Studies have shown that fibrils of the ECM are physically connected to the cytoskeleton. This association of the inner and outer worlds of cells helps tissues and organs keep the distinct shape and architecture that is vital to their function (see **Fig. 6**).

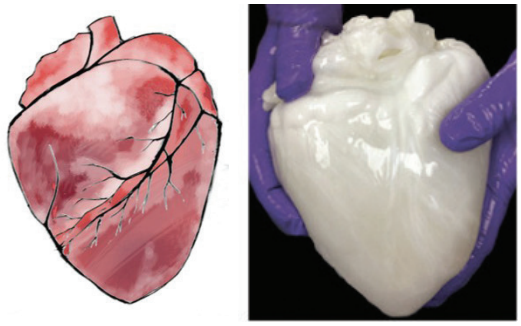

Fig. 6. The white ghost. The white ghost of a heart on the right is a pig heart that is devoid of all cells and now consists of just the matrix. Surprisingly, because of the matrix, the heart without cells can still retain its shape!

Credits: Nagaraj Balasubramanian & Philip Mathew. URL for heart image: http://legacymedsearch.com/implantable-organ-developer-miromatrix-raises-additional-15-7m-in-series-b-funding/heart4/. License: CC-BY-NC.

The composition of the ECM

The ECM is composed of proteins that cells make and secrete.[10] Each protein in the matrix microenvironment binds with other proteins and proteoglycans (where a sugar residue is attached to a core protein) to form multimers and more complex structures. Examples include:

- **Collagen:** Greek for 'glue producing', is the most abundant protein in the basic ECM framework and is ~300 nm in length and 1.6 nm in diameter (see **Fig. 7**)[11],
- **Elastin:** As the name suggests, it is the most 'elastic' matrix protein (see **Fig. 8**)[12,13,]
- **Fibronectin:** It is a high-molecular weight matrix protein that is ~133 nm in length (see **Fig. 9**)[14,] and
- **Fibrinogen:** A matrix glycoprotein (~47 nm) involved in clotting of blood (see **Fig. 10**)[15,16].

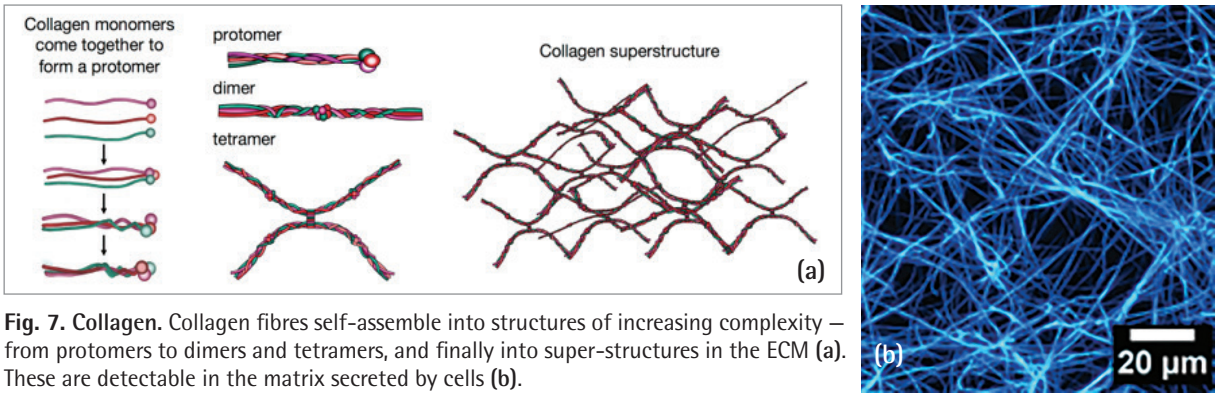

Fig. 7. Collagen. Collagen fibres self-assemble into structures of increasing complexity — from protomers to dimers and tetramers, and finally into super-structures in the ECM **(a)**. These are detectable in the matrix secreted by cells **(b)**.

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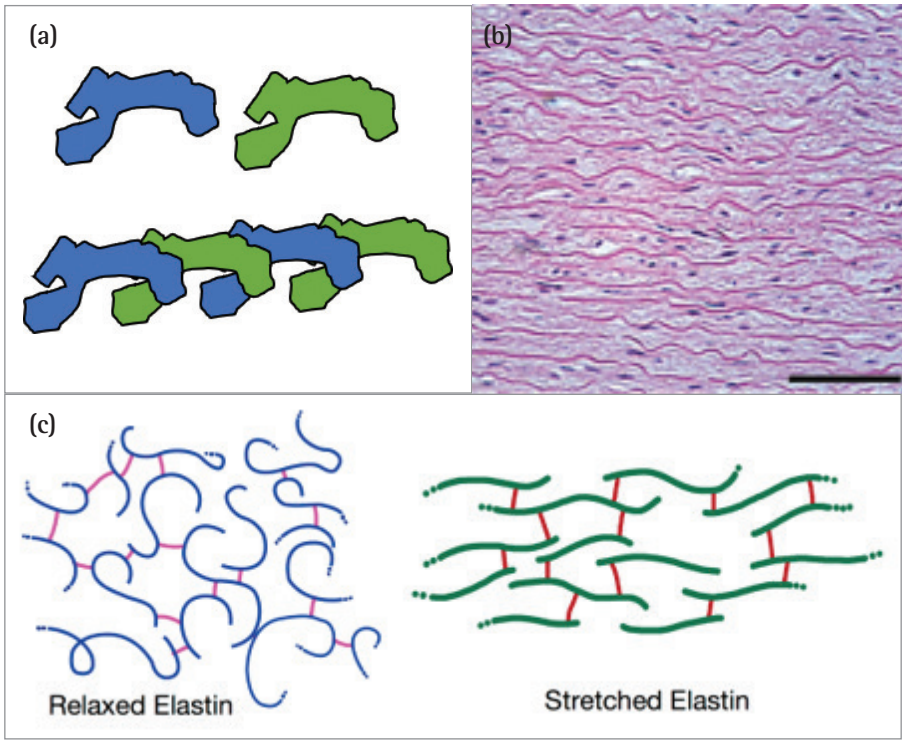

Fig. 8. Elastin. This protein is made up of individual soluble tropoelastin (~20 nm in length) molecules that are assembled into a insoluble complex **(a)**. Present in tissues such as blood vessels **(b)**, it can relax and stretch in a reversible manner **(c)**.

Credits: Nagaraj Balasubramanian & Philip Mathew. URL for heart image: www.kumc.edu/instruction/medicine/anatomy/histoweb/vascular/large/Vasc02.JPG. License: CC-BY-NC.

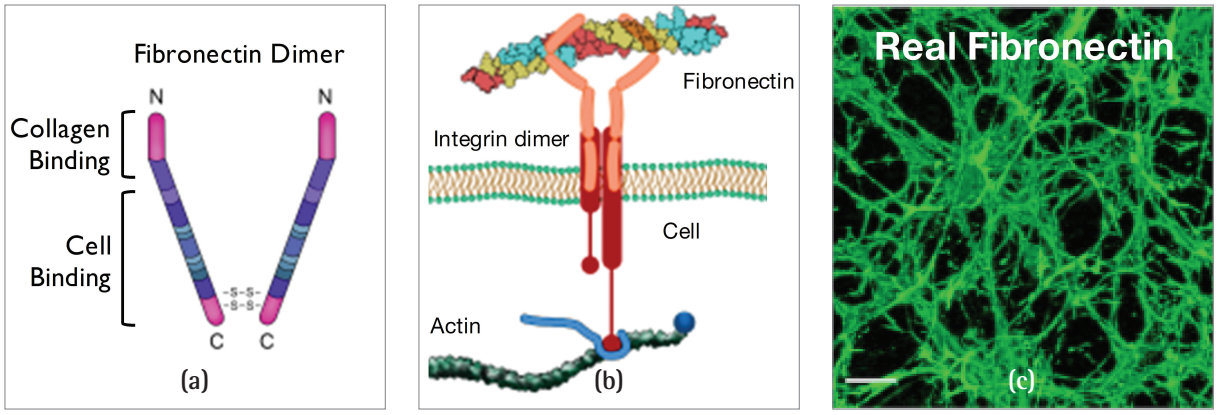

Fig. 9. Fibronectin. Fibronectin monomers are brought together by covalent linkages between thiol groups (R-S-S-R) on amino acids (R) in their C-terminus tails to make dimers and multimers **(a)**. As a result, fibronectin cross-links the matrix by binding collagen at one end and integrin receptors on the cellular membrane at the other **(b)**. Integrin tails inside the cell can bind to other proteins and actin microfilaments, connecting the structural elements shaping cells from within and without. This helps make a better ECM mess...sorry, mesh **(c)**!!!

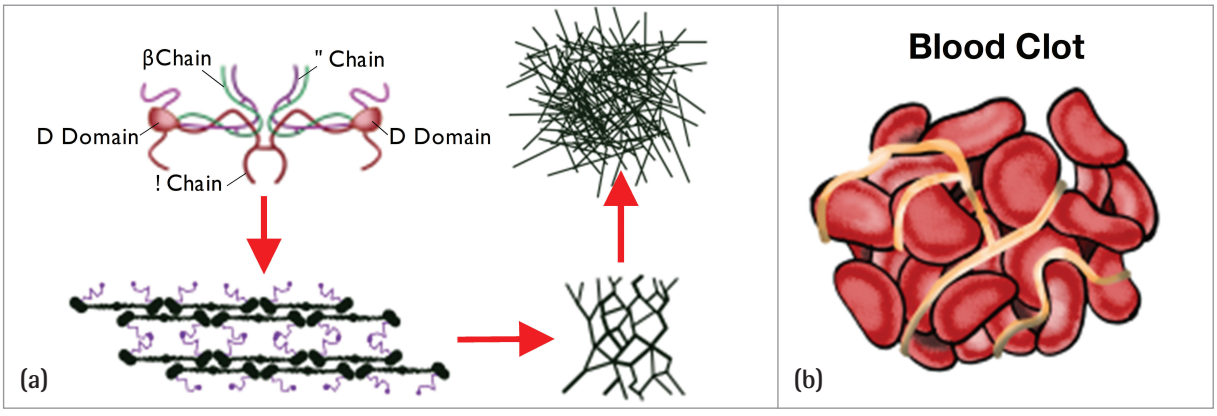

Fig. 10. Fibrinogen. This protein is cleaved by thrombin permitting polymerization of fibrin monomers into an insoluble fibrin network **(a)**. The fibrin network serves as a scaffold for the binding of RBCs, platelets, and plasma proteins to form a clot **(b)**.

The ECM has the capacity to store and sequester growth factors and cytokines (a family of small **proteins or glycoproteins** that act on immune cells) establishing concentration gradients and regulating their availability to cells spatially (where) and temporally (when). The ECM also acts as a reservoir of bioactive fragments released upon the limited breakdown of proteins (proteolysis). These bioactive fragments allow the ECM to regulate physiological processes such as **angiogenesis** (the process of formation of blood vessels).[16,17]

The relative amounts of individual matrix proteins in the ECM (its composition) can vary depending on the cell type and, therefore, across tissues.[18] This affects how the matrix is assembled and crosslinked, and how cells respond when they stick to this matrix. This also means that cells derived from a particular tissue would prefer a matrix that is also from the same tissue.

Regulating cellular functions

The ECM is known to regulate cellular function through both biochemical and biophysical cues.

a. Biochemical cues

The biochemical properties of the ECM allow cells to sense and interact with their extracellular environment. These interactions not only regulate cell function but are also vital for cells to work together as part of a multicellular tissue.

As discussed, these interactions are mediated through receptors on the cell surface called integrins.[19] Integrins poke through the cell membrane to bind the matrix outside as well as many different proteins inside the cell (including the cytoskeleton). In this way, they are able to connect the matrix to inner cell components. This triggers the activation of many vital downstream **signalling pathways in cells**. Integrins can, therefore, detect what happens outside in the matrix microenvironment and convey this information to the inside of the cell, controlling its many functions.[20]

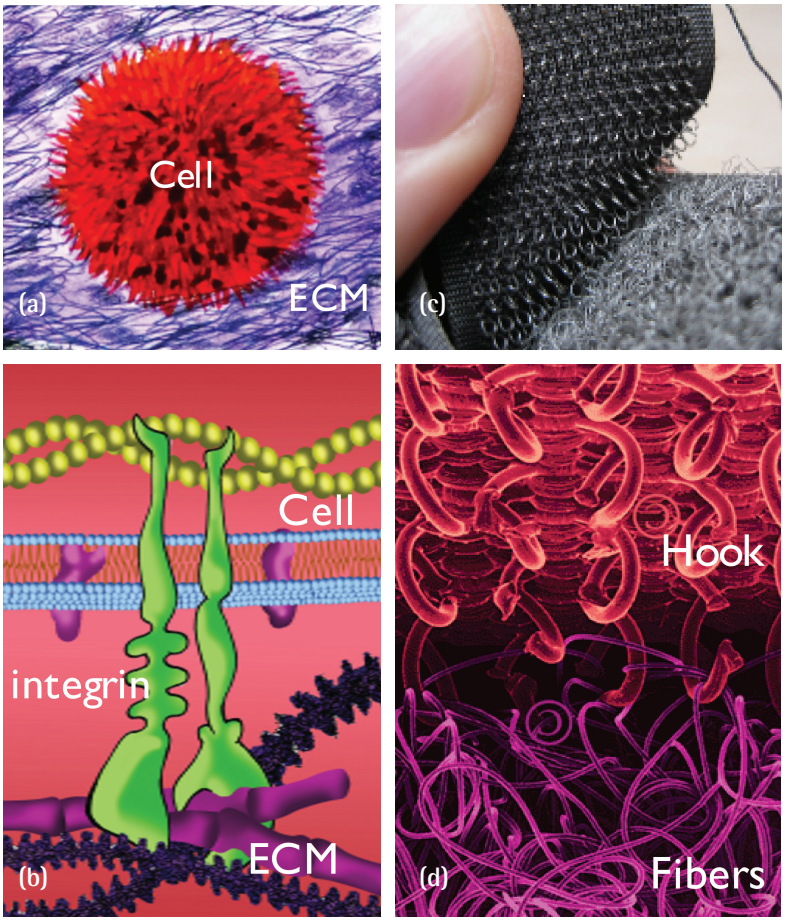

Fig. 11. Matrix binding integrins. Integrins are hook-like receptors on the cell surface **(a)** that anchor cells to the fibres of the matrix **(b)**. Like with the VELCRO on your shoes, these hooks are reusable and can stick—detach—stick again **(c, d)**.

Integrins are made up of two pieces (an alpha and beta subunit) that work together (see **Fig. 11**) to bind the matrix. This results in a conformational change in the integrin molecule that allows for the binding of signalling molecules and the cytoskeleton to its cytoplasmic tail.[20] The ECM is also able to regulate the **clustering of integrins** on the cell membrane, controlling their activation.[20,21] Cells have many flavours of integrins that bind different ECM proteins with varying affinities. This means that cell signalling and functionality can differ based on the flavour of integrins a cell has, and the matrix it is bound to.[21]

b. Biophysical cues

Cells regulate the organisation, porosity (size of pores in the matrix), and stiffness of the ECM. For e.g., the composition of the ECM (or the specific proteins that cells secrete) regulates its organisation and crosslinking in a way that determines its porosity and stiffness.[4] Similarly, the matrix is constantly being remodelled by a special class of enzymes, called **metalloproteinases** (MMPs), secreted by cells. MMPs (proteases with a catalytic mechanism involving a metal) change matrix organisation and stiffness.[18]

This, in turn, controls what forces the cell membrane and receptors on the membrane experience, and their response to the matrix. For e.g., cells change in stiffness on being organised into tissues. This change in their shape and function is partly mediated by how cells respond to the ECM through their cytoskeletal network (see **Fig. 12**).

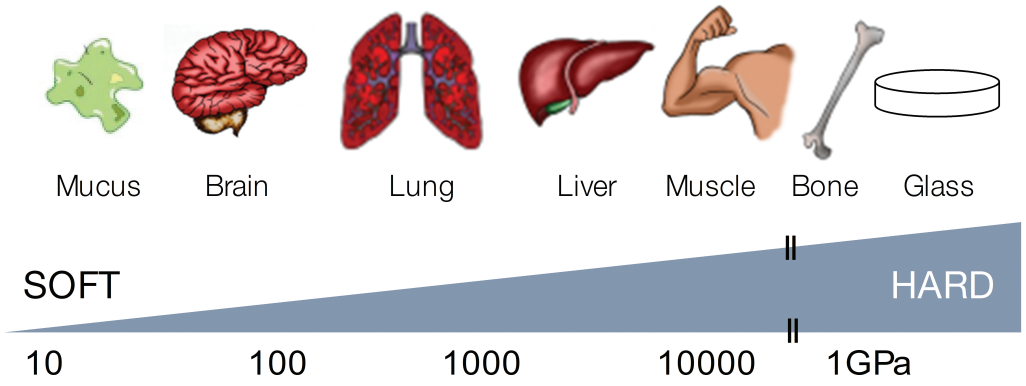

Fig. 12. Changing stiffness and cells. Our brain is much softer than our bones, which is much softer than glass. The ECM in the brain and bone tissue are assembled differently and contribute to their varying stiffness and, hence, cell behaviour. Stiffness is measured in pascals, with changes in stiffness varying from 10 pascals [Pa] (**left end**) to 1 GigaPascals (1000000000 pascals) [GPa] (**right end**).

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The ECM in disease

Changes in matrix composition, organisation and remodelling can alter cell function during aging and disease conditions. For e.g., a change in composition of the matrix can alter the stiffness of blood vessels. This impacts the way endothelial cells lining the inner sides of blood vessels respond to changing blood flow rates and patterns (see **Fig. 13**).[22,23] Together, these changes damage endothelial cells, causing them to detach from the inner layer. This, in turn, causes smooth muscle cells from below the damaged lining to multiply and move up. It also triggers the endothelium to secrete chemical factors that recruit **monocytes** (a kind of white blood cell) to the damaged lesions. The monocytes enter the lesion (site of damage) and differentiate (change their look and function) to become macrophages. The macrophages eat things along the way, including **Low-density Lipoprotein (LDL)-cholesterol** (more popularly known as bad cholesterol, this is the kind that is found in high amounts in junk food), to swell into foam cells.[24]

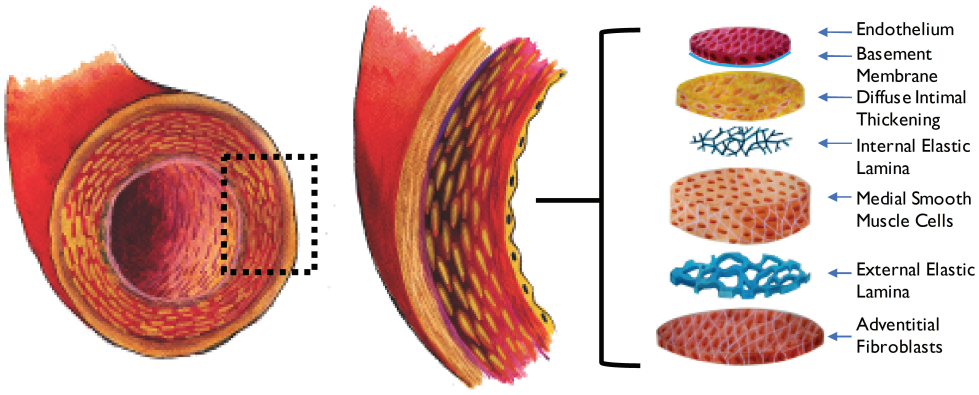

Fig. 13. Cells and the matrix in blood vessels. Blood vessels are a little like a sandwich with layers of different cells held together by the matrix. These cellular layers include the endothelium (innermost), medial smooth muscle cells and adventitial fibroblasts (outermost). Like a layer of tangy chutney that adds much needed flavour to a sandwich, the matrix (in the form of the basement membrane, internal elastic lamina, and external elastic lamina) holds the cellular layers together. This helps make blood vessels strong but flexible, allowing them to contract and relax (using elastin).

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Foam cells are usually very tiny, and do not cause any disease when present in small numbers. On accumulation in large numbers, however, foam cells form plaques that eventually cause **atherosclerosis** (see **Fig. 14a**). Much like a blocked tunnel disrupts the movement of traffic, plaques can block the flow of blood through vessels. They rupture eventually, but damage the blood vessel (and, therefore, the tissues it is associated with) in the process. If the blood vessel happens to be in the heart, it can lead to a heart attack (see **Fig. 14b**).[24]

Their ability to bind to the ECM also influences the way the cells respond to growth factors and, hence, affects the way cells grow. Most normal cells need to be adherent to respond optimally to growth factors — a property that ensures that their growth is regulated. Cancer cells, true to their rebellious nature, overcome this regulation and become **anchorage independent**. This change supports their ability to form tumours and undergo metastasis. Thus, cancer causing **oncogenes**, like the oncogenic Ras protein, are seen to drive anchorage independence.[25] More recently, it has also become apparent that changing tissue stiffness can precede normal physiological processes like ageing and disease development. Mechanical cues can, therefore, drive the progression of diseases like cancer and hypertension.[26]

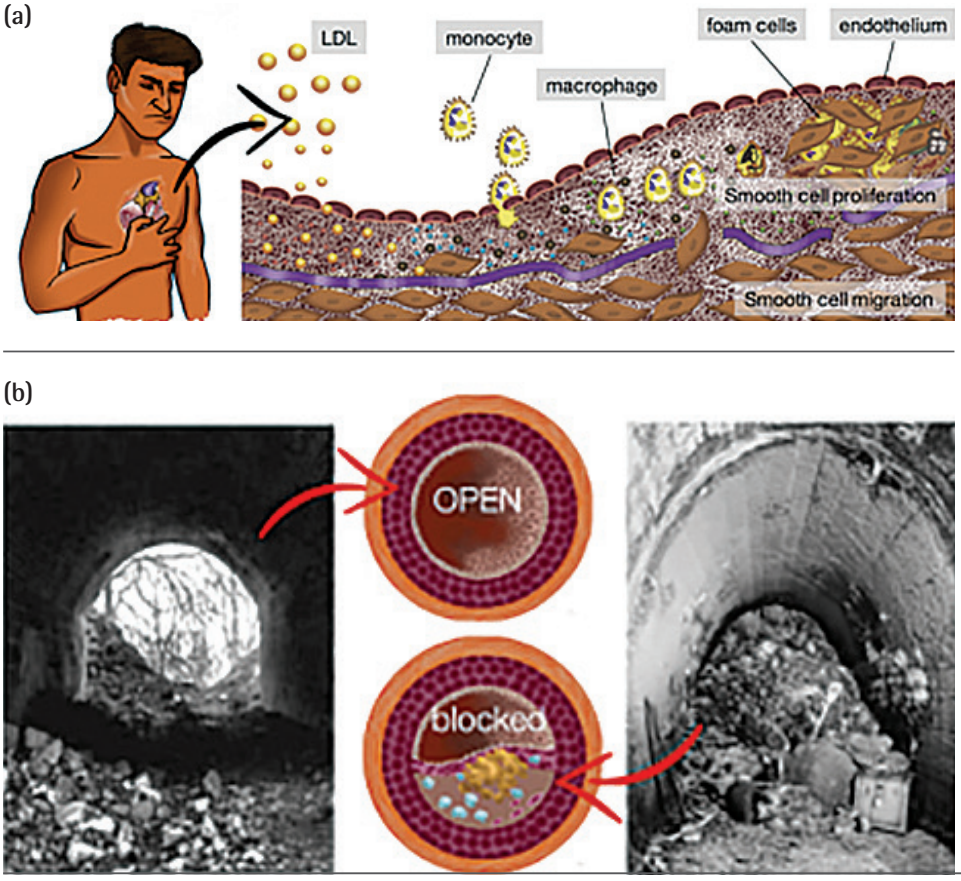


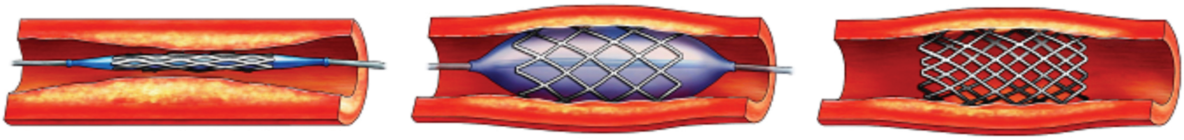
Fig. 14. Blocking of blood vessels. Damaged endothelial cells in the lining of blood vessels cause monocytes to enter the wall of these vessels and become macrophages. Then, they take up low density lipoprotein (LDL) — cholesterol and become foam cells **(a)**. These, along with rapidly dividing and migrating smooth muscle cells, form an atherosclerotic plaque that can block the blood vessel **(b)**.

Current and future trends

Since the binding of matrix proteins can affect cellular function, many studies focus on how the matrix can be used to fight disease.

One application of ECM is in detecting and treating damage to blood vessels. The composition of the ECM (or its specific type) underlying endothelial cells in blood vessels can help determine the responsiveness of these cells to blood flow patterns and the activation of downstream signalling.[27] The presence of certain matrix proteins, called **athero-protective matrix proteins**, have been found to protect endothelial cells in a way that others, called **athero-genic matrix proteins**, do not.[28] This discovery is being studied to improve the effectiveness of metallic stents in atherosclerosis (see **Fig. 15**). For e.g., stents coated with polydopamine (pDA), fibronectin (FN), and ECM enhance cell adhesion.[29] An FN-pDA coating can also help immobilize other ECM molecules, such as collagen and fibrinogen on the surface.[30] Similarly, a stent coating with athero-protective matrix proteins is better at keeping a blocked blood

vessel open longer. Athero-protective proteins can also be combined with growth factors and/or drugs to promote their effectiveness.[31]



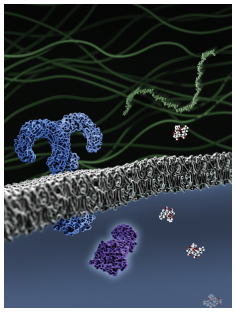
(a) (b) (c)

Fig. 15. Opening a blocked blood vessel. A stent is a metal grill inserted into a blocked blood vessel using a balloon **(a)**. Once the balloon is opened **(b)**, the metal grill locks to stay open and, in doing so, also keeps the blood vessel open **(c)**.

Another application of the ECM is in dental implants. Collagen membranes are used to wrap dental implants to allow better binding of cells to the implant, and help support its integration into the bone. This allows for the implant to hold and function better.[32]

Some emerging clinical strategies (mechano-therapies) focus on regulating the mechanical properties of cells and tissues. These are based on studies showing disease progression as a result of ECM mediated changes in the mechanical properties of a tissue, as well as the unique sensitivity of individual cell types to mechanical stimuli. Thus, attempts to restore favourable matrix stiffness and/or disrupt cellular responses to changing ECM stiffness could hold the key to how we target diseases such as cancer.[26]

Key takeaways



- The extracellular matrix (ECM) is an important live scaffold that wraps around cells and bind them together in tissue.
- This matrix is composed of many proteins, including collagen, elastin, fibronectin and fibrinogen, that cells make and secrete.
- The matrix provides biochemical and biophysical cues that helps multiple cell types work together.
- Integrins on the cell membrane help connect the ECM outside the cell with the cytoskeleton inside the cell, regulating cell shape and function.
- The stiffness of the ECM can vary with its composition, porosity, and extent of crosslinking in ways that control the health and behaviour of cells.
- The ECM is a vital regulator of changes in cell behaviour in disease and can, hence, be targeted to restore normal cell function.

Note: Image used in the background of the article title — An artist's conception of the extracellular matrix, lipid bilayer and cellular components. Credits: NIH Medical Arts, NIH Image Gallery. URL: https://www.flickr.com/photos/nihgov/24191645473/in/photostream/. License: CC-BY-NC.

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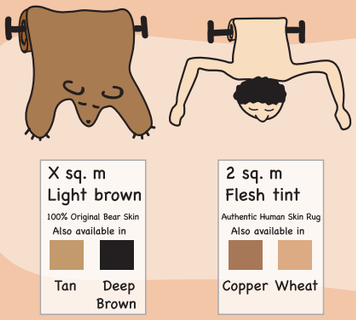
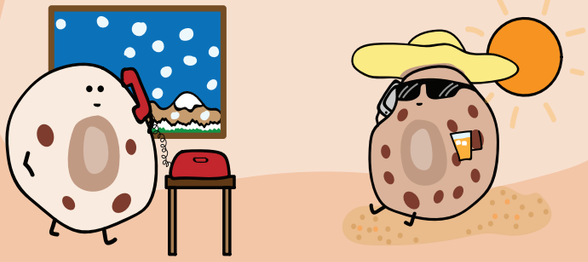
9 things you didn't know about Human Skin



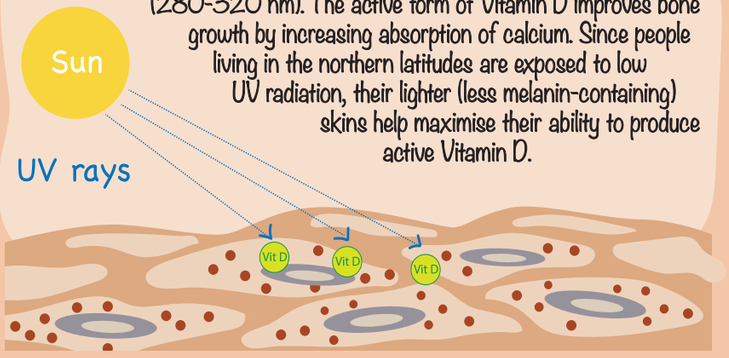
1. An average person's skin covers an area of ~ 2 m^2, and accounts for ~15% of your body weight.

2. It's not as uniformly thin as we think! For e.g. the skin on your eyelids is as thin as 0.2 to 0.5 mm, but that on the palms of your hands & soles of your feet are as thick as 1.4 mm (to account for the wear and tear of gripping & walking).

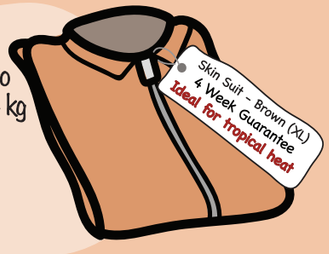
3. It gets its colour from the pigment melanin, produced by cells called melanocytes in the skin's outermost layer. People (~ 1 in 20,000) with a hereditary condition called albinism are at higher risk of skin cancer because they carry mutations that prevent melanin production. When pigment-producing cells die or stop functioning only in certain skin areas, it results in white patches on the body – called Vitiligo.



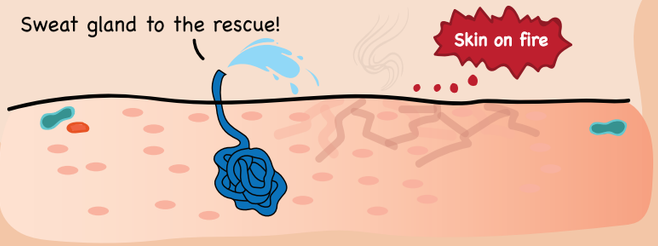
4. It's the site of a reaction that converts the pre-active form of Vitamin D to its active form on exposure to UV-B radiations (280-320 nm). The active form of Vitamin D improves bone growth by increasing absorption of calcium. Since people living in the northern latitudes are exposed to low UV radiation, their lighter (less melanin-containing) skins help maximise their ability to produce active Vitamin D.



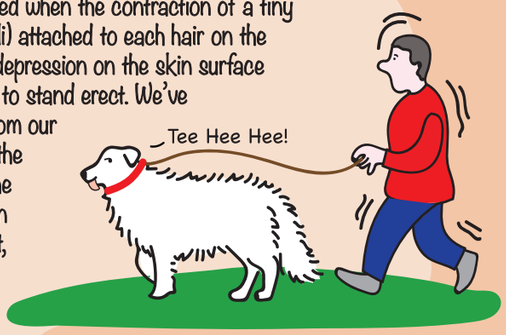
5. It has magical regenerative potential! An adult person sheds about 30,000 to 40,000 dead cells/minute – around 4 kg every year! Except during injury/ inflammation, the outermost layer of our skin is replaced by an entirely new one every 4 weeks.

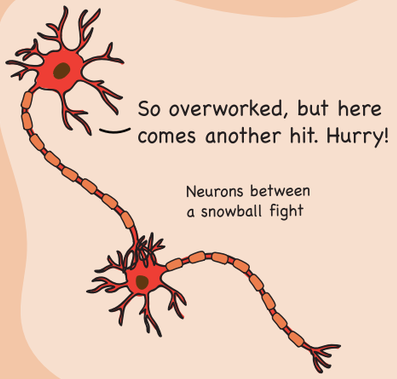


6. It acts as a thermostat, regulating body temperature through body fluids like blood and sweat. For e.g., when you feel hot, evaporating sweat (from sweat glands on the skin) helps cool your body. The blood vessels in your skin dilate, increasing blood flow. The warmer blood loses heat to the colder air at the skin surface by conduction. In contrast, when you feel cold, the blood vessels in your skin constrict, reducing flow of blood to its surface layers and, therefore, limit loss of body heat.



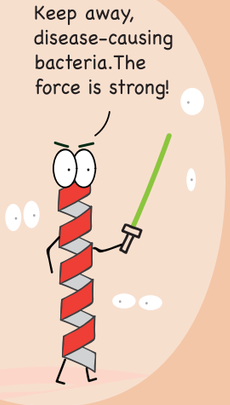
7. It may break out in goosebumps on sudden exposure to cold air. A goosebump is caused when the contraction of a tiny muscle (called arrector pili) attached to each hair on the skin produces a shallow depression on the skin surface and causes our skin hair to stand erect. We've inherited this tendency from our animal ancestors, where the rising of hair increases the amount of insulating air in contact with the skin. But, since we do not have a body coat, goosebumps may not help us in any way.





8. It has an extensive network of neurons connected to receptors for heat, cold, touch and pain that we rely heavily on to detect changes in our immediate environment. What if we lost the ability to feel pain? People born with the very rare condition Hereditary Sensory & Autonomic Neuropathy IV can't sense pain, heat or cold. Such people are more prone to serious self-injury and the risk of early death.

9. Is home to more than a 1000 species of bacteria, fungi and viruses – collectively called skin microbiota. For e.g. our skin harbours almost 50 million bacteria per square inch with as many as 500 million on oily surfaces like that of the face! Our skin produces specific anti-microbial peptides that kill most disease-causing bacteria, while letting beneficial ones grow! Some scientists argue that these good bacteria may have helped our ancestors avoid infections at a time when they weren't taking a bath regularly.



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