

The body has an extensive perineural information system composed of microtubes of protein. What in former decades was known as the connective tissue seems to be an omnidirectional communication system between all the tissues of the human organism, even at the level of the cell. In fact, over the living matrix, each cell knows what another cell is doing. The living matrix is not the nervous system, it is even faster in communication than that. The energetic pathways of the living matrix are even more ancient than the nervous system. Over the transmitting pathway of the collagen the living matrix is a continuous medium for every impulse that is originating in the body or any impulse that at any location is transmitted to that body.

The rough structure of the living matrix is the extra-cellular matrix (ECM) as a histological fact. The ECM is of an extremely high importance in biological medicine. Not only does most interactions between regulation systems take place in the extra-cellular matrix, also the presence or storage of homotoxins at that stage might induce all kind of dysregulations and pathologies, even intra cellular. Therefore a short study of the histology and physiology of the ECM is needed first to understand the importance and depth of impact of the living matrix on the human's health and disease.

## To do

1. Histology of the extra-cellular matrix (ECM)
2. Physiology of the extra-cellular matrix
3. The intra-cellular matrix
4. The nuclear matrix



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From the moment where the French physiologist Claude Bernard postulated his 'internal environment' in the 19<sup>th</sup> century a new world in histology and physiology was opened. Today we deal with the histological fact of the extracellular matrix and even in modern complementary medicine there is a tendency to speak about the living matrix, another dimension in physiological understanding of the human body.

The living matrix is composed out of three levels of matrix that fade into each other; the extra-cellular matrix, the intra cellular matrix and the nuclear matrix. Not only there are interactions over vibrating impulses, electric signals and mediator exchanges at each matrix level. The 3 levels interact between and influence each other over their anatomical physical borders. This means that any deregulation that takes place out of the cell (in the extra-cellular matrix) might have an intra cellular or even intra nuclear consequence and vice versa. Even composed out of 3 different levels, the living matrix is one coherent interactive system.

Beside this interesting characteristics of interactive communication between the different levels of the living matrix, the histology and physiology of the extracellular matrix is of a great importance for those who want to understand the terrain of action of antihomotoxic medication. This is the objective of this lecture, to understand the matrix and to be able to intervene in it with regulation therapy

## Why is it important to study the matrix?

- Hydrophilic environment of the cell
- Electric charged structure
- Capacity to regenerate
- Complex information system
- Depot of homotoxins



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There are five reasons why we should study the matrix in antihomotoxic medicine:

1. By the presence of a high concentration of proteoglycans in the matrix, the whole matrix becomes hydrophilic. As we will see further in detail this hydrophilic environment of the cell makes transport of substances easier but makes water soluble toxins easier to remain and stored in the matrix.
2. The electrical charge of the proteoglycans is negative. That enables positive loaded homotoxins to adhere on the ECM structure and remain there. The electric charge plays also a crucial role in electron streams in the matrix.
3. By the presence of fibroblasts in the matrix his structure can be repaired after damage and this within minutes. The firbroblast plays an essential role in the protection of the living cell by restoring continuously the 3-dimensionsl web structure around it.
4. Over the matrix most interactive communications between the different auto regulating systems takes place. This includes complex feedback loops over mediators, PH-control, electric potential control, etc...
5. Although a holding away of homotoxins from the cell is a positive characteristic of the matrix, it can cause problems on long term if the same homotoxins are not drained away from the matrix and detoxified. In reality we see that a lot of pathologies start by a deposition of homotoxins in the ECM and their negative effects on the functioning of the cell.



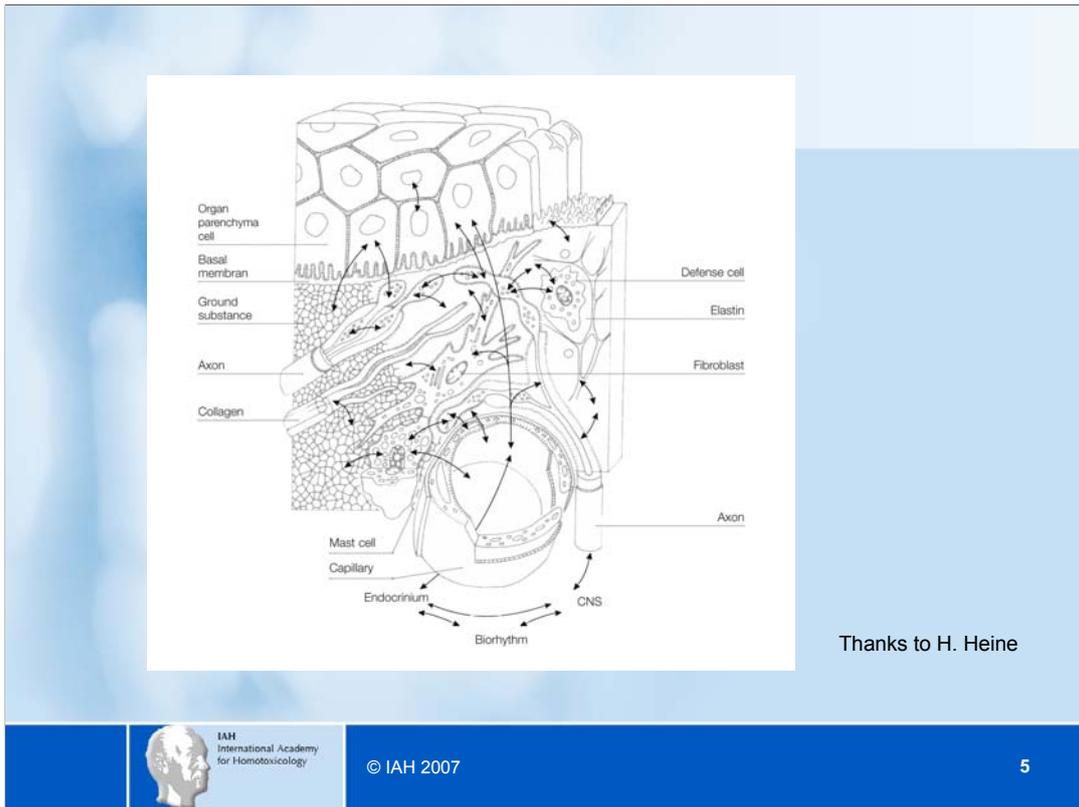
# 1. Histology of the ECM

*Virchow*

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Let us take a closer look at the histology of the extra-cellular matrix first. What are the components it is built of?



Beside the amoeba and other single cell organisms that have a direct contact with the external environment of the organism, all other multi cellular organisms have a cell protective area between the external environment and their cells, wherever this cell is in the organism and whatever her task is. This cell protective area is called the extra-cellular space. No substance can get directly from the external environment to the cell.

Either the living cell is part of an organ structure and plugged in on a basal membrane or the cell is functioning apart from other cells in a structure, it will always be surrounded by matrix. This matrix is a 3-dimensional fine structured biophysical filter that controls the transmission of cell nutrition and waste products, mediators, and any other substance in the environment of the cell. No substance can go directly from the blood stream to the cell and vice versa. Even the release of neurotransmitters by a nerve cell has to reach the cell over the ECM.

Most interactions between different systems in the body acts over the ECM. The reason why the picture above shows all interacting arrows between the different systems.



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## The fibroblast is essential

- Synthesis of the PG structure and GAGs by the golgi apparatus
- Reacts to damage of the ECM and restores it
- The quality of the biophysical filter of PGs and GAGs in the ECM depends on the accuracy of the fibroblast
- The life quality of the organ cell depends on the accuracy of the fibroblast. This means that an effective fibroblast will repair the damage on the ECM structure and protects in this way the cell from direct contact with toxic burdens out of the blood stream



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Fibroblasts are essential for the extra-cellular matrix. The fine meshed 3-dimensional web between the organ cell on one side and capillaries and lymph vessels on the other side are composed of proteoglycans and glycosaminoglycans. Both substances are secreted by the fibroblast's golgi apparatus. If this basic structure is damaged by a wound or infection the fibroblasts will try to restore it.

As the main physical function of the ECM is to filter all substances that are transmitted from capillaries to cell and vice versa the quality of the structure is a guarantee for the health of the organ cell. A massive dysfunction of the fibroblasts with inaccurate matrix as a consequence will result in a higher risk for cell intoxication, and by this for the development of chronic degenerative pathologies.

Accurate and healthy fibroblasts can generate glycosaminoglycans within minutes so that a quick restoring after damage is possible and cell protection is regained.

## Local cells of the ground system

- They are responsible for the non-specific defense mechanisms
- They show a plural potential to change in different functional forms



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Beside the supporting cells mentioned in preceding slides other cells are present and are part of the ground system.

Especially the macrophages and mast cells get our attention. Locally they will assure the non-specific defense against intruders of different origin, and if needed, will trigger the whole defense system to start up an inflammation process to cleanse the matrix. In this way they are the main and 'first wave cleaners' of the ECM.

## Fibroblast and psyche

- Psychological stimuli can influence the fibroblast's response
- Together with the endocrine system, they can create a matrix which will adapt to the neuroendocrine status
- Psycho-neuro-endocrine regulation



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Psycho-Neuro-Endocrine-Immunology (PNEI) studies the interactions between emotions, neurological stimuli and transmitters, endocrine secretions and the defense system. Many studies have shown the immunosuppressive influence of prolonged stress and depression. Fibroblasts e.g., will be less effective in wound healing under psychological stress. As emotions play a main part in the influence (and lesser the thoughts) some authors talk about Emotio-Neuro-Endocrine-Immunology instead of Psycho-Neuro-Endocrine-Immunology.

Psychological stress has also been shown to increase susceptibility to viral infection. Subjects exposed to stress showed increases in infection rates from 74% to 90%, and clinical colds rose from 27% to 47%. Earlier studies have shown that medical students have an increased risk of mononucleosis during examination periods (McEwen & Stellar, 1993).

## Extra-cellular matrix

- Physical characteristics of the tissue
- Structural framework, in which the cells are embedded
- Cell adhesion more with the ECM than with other cells



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The tissue of the extra-cellular matrix has some specific characteristics. It is a structural framework in which the cells are embedded. In fact there is more adhesion between the cells and the structure of the ECM than with other cells in the neighbourhood. Between a coarse structure of collagen and elastin fibers there is a fine structure of the ground substance composed out of proteoglycans and glycosaminoglycans. Especially the last two create a biophysical filter and are responsible for the hydrophilic characteristics of the matrix as they easily can bound and keep water.

## Extra-cellular matrix

- Structural proteins
- Fibrillar proteins
- Proteoglycans



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The matrix is composed, from coarse to fine structure, out of structural proteins, fibrillar proteins and proteoglycans.

## Structural proteins

- Sturdiness of the connective tissue
- Collagen
- Elastin



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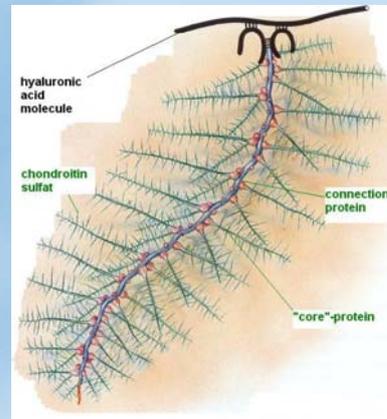
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Structural proteins offer the sturdiness of the connective tissue. They make the structure well bind and flexible at the same time. The main characteristic of collagen is sturdiness there as the main characteristic of elastin is flexibility. Collagen fibers are also thicker than elastin. Collagen and elastin form the basic, more rude structure of the ECM.

At least 16 types of collagen exists. Damage to the collagen structure due to trauma or other cause might trigger restoring parameters and induce inflammation.

## Proteoglycans

- Carrier protein with transverse intersections of glycosaminoglycans fitted on a hyaluronic acid molecule
- Because of the glycosaminoglycans it is very hydrophilic



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A proteoglycan is a tree-like shaped structure of a hyaluronic acid molecule on which a carrier protein carries transverse core proteins. The smallest building stones of a proteoglycan (PG) are mucopolysaccharides, long repeating polymers of disaccharides called glycosaminoglycans (GAG's). One sugar of the disaccharide is an uronic acid, the other one is an amminosugar. At least one of the both sugars carries one or two sulphate bridges to connect to further structure.

The GAG's in the PG is hydrophilic. As the fine structuring of the ECM is mainly build out of PGs and GAGs the matrix is easily keeping water within his structure. One of the best known GAG's is chondroitin sulphate. It is built up out of a chain of glucosamin sulphates.

Proteoglycans are not only found in the ECM but are also attached to the plasma membrane of cells. In this way they have an attachment function too.

In cartilage the main proteoglycan is called aggrecan. The concentration of chondroitin sulphate and keratan sulphate (both GAGs) in agrrecan is in normal cartilage condition quite high. Keratan sulphate is found more at the bases of the aggrecan, near to where it is fixed on the hyaluronic molecule. Chondroitin sulphate is found at the middle and top of the aggrecan structure.

Syndecan is a typical example of a proteoglycan attached to the cell surface. The GAGs in syndecan are heparan sulphate chains. Sundecan binds extracellularly to collagen and fibronectin and intracellularly to cytoskeleton.

## Glycosaminoglycans

- Synonym: mucopolysaccharides
- Unbranched chains of polysaccharides, built up over 70 to 200 repeated disaccharides



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As mentioned before, glycosaminoglycans are the basic building stones of the ECM. They are the main component in proteoglycans. Former called mucopolysaccharides they are unbranched repeated chains of disaccharides. They can be very long (up till 200 repeated saccharides) The main hydrophylic characteristic of the ECM is due to a high overall presence of GAGs in his structure.

## Glycosaminoglycans

- Hydrated gel of big polysaccharides
- Shrinking of the proteoglycans structure by strong negative charge, hydrophilic characteristics and spatial structure
- Diffusion of the substances through the extra-cellular matrix



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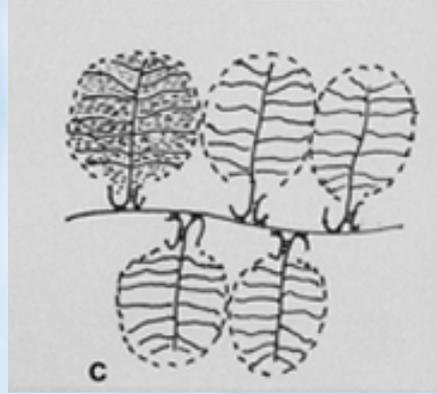
The fine structure of GAGs at the branched ends of the PGs create a narrow 3 dimensional web that functions as a biophysical filter. It looks like a hydrated gel in which all kind of substances are transported from the capillaries to the cell and vice versa. As the distances between two core proteins on a carrier protein in the PG's structure is only about 15 till 20 nm, big entities get easy stacked in the ECM.

According to F. Perger the electric potential in the ECM is about 240 microvolt. This will be higher in the acid phase of an inflammation and lower in the alkaline stage.

A strong negative charge at the level of the ECM will create a shrinking or of 'wring out' movement of it. So, changing electric charges will influence the hydrophilic capacities of the matrix.

Diffusion of the substances through the extra-cellular matrix is only possible due its hydrophilic capacities.

## Network structure



H. Heine



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The image shows the network structure of different proteoglycans connected to the same hyaluronic acid molecule. Repeated in 3 dimensions a fine meshed filter is created that functions at molecular level.

## Biosynthesis of the glycosaminoglycans (GAG)

- The synthesis of the PG/GAG occurs in only 1 to 2 minutes
  - Lozzo 1985, Heine 1997
- Their average lifespan is between 2 and 120 days

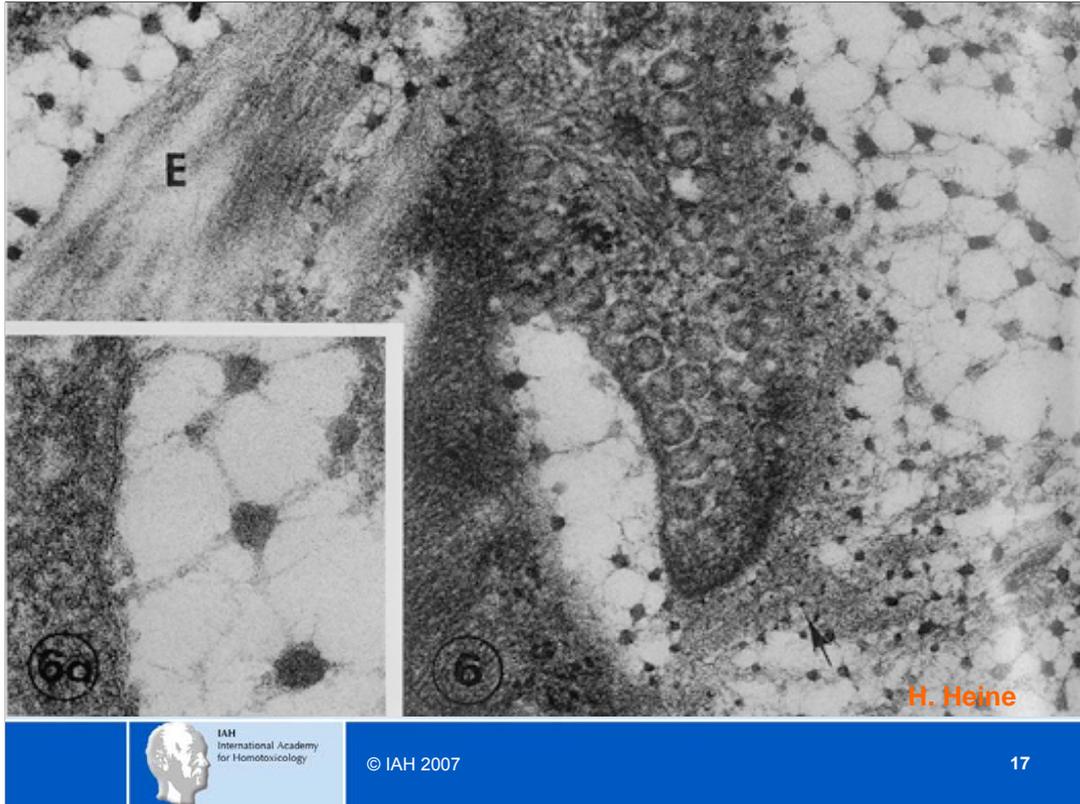


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The synthesis of glycosaminoglycans and proteoglycans are amazingly fast. Fibroblasts are able to create these structures within minutes. Although they are made randomly and a 'filling in' of a hole or gap is never like it was before, the main characteristics of fine meshed and hydrophilic are always kept. As due to an inflammation the matrix can be extremely damaged it is very important to be able to restore the structure and his filtering capacities in a very short delay of time.

In normal conditions proteoglycans and glycosaminoglycans are replaced after maximum 4 months. Their average lifespan is between 2 and 120 days. This is one of the reasons why in heavy intoxication we should not drain and detoxify for weeks, but for months.



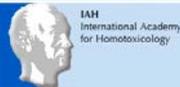
This is an helicopter view on a histological preparation of the ECM. In the middle of the picture we see the organ cells on their basal lamina, surrounded at the right side by the network of proteoglycans and glycosaminoglycans. Under 'E' we see the rough structure of collagen fibers and again, even more left of that, the web structure of PGs and GAGs again. In the small insert we see a magnification of the fine meshed spider web structure of the PGs and GAGs.

Any substance that comes from any side from a capillary to a cell will have to go over a kind of transmission area where it is filtered by the biophysical filter the ECM is.

At any organ related location in the human body this structure will be found.

## Basal membrane

- Specialized surface
- Functions:
  - Cell adhesion
  - Cell growth-regulation
  - Diffusion filter



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The basal membrane is a specialised surface of the extra-cellular matrix. One type of ECM is exemplified by the thin, sheet-like basal laminae (BL) or basement membrane, upon which layers of epithelial cells rest. A BL also surrounds muscle cells, adipose cells and peripheral nerves. ECM, however, is most abundant in connective tissue beneath epithelial cell layers consisting predominantly of an ECM in which fibroblasts are sparsely distributed. Other types of connective tissue, such as bone, tendon, and cartilage, similarly consist of ECM, which mainly accounts for its structure and function.

The basement membrane is a layer on which epithelium sits. This layer is approximately 40-50 nm thick and composed of the lumina lucida and the lumina densa. The lumina lucida is adjacent to the epithelial cells and composed of laminin (a proteoglycan) and collagen (Type IV). The lumina densa is composed of collagen (Type VII).

The basal membrane has 3 main functions:

1. Cell adhesion. Organ cells are attached to the basal membrane what keeps them at their place (together with the bindings to the ECM)
2. Cell growth regulation
3. Diffusion filter. not all substances can get through the basal membrane, so its structure makes it a selective filter.

## The intercellular (interstitial) fluid:

- An indispensable medium that makes it possible to maintain homeostasis between the intra- and extra-cellular zones



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Interstitial fluid is compound of a water carrier containing mainly fatty acids, amino acids, sugars, coenzymes, messenger substances like hormones, neurotransmitters and other substances like salts, minerals, waste products from cells, etc...

Interstitial fluid can be compared to the water in the aquarium of the gold fish. The life quality of the cell depends of the quality of the liquid it bathes in like the life quality of the gold fish depends on the water of his aquarium he is living in. Not only should there be enough nutrition components to survive but also a cleanse of the waste products he himself produced.

The interstitial liquid provides the cell with nutrition and building blocks, take waste products away and enable the cells to communicate with each other (transport of electric impulses, cytokines, etc...)

## The organ cells

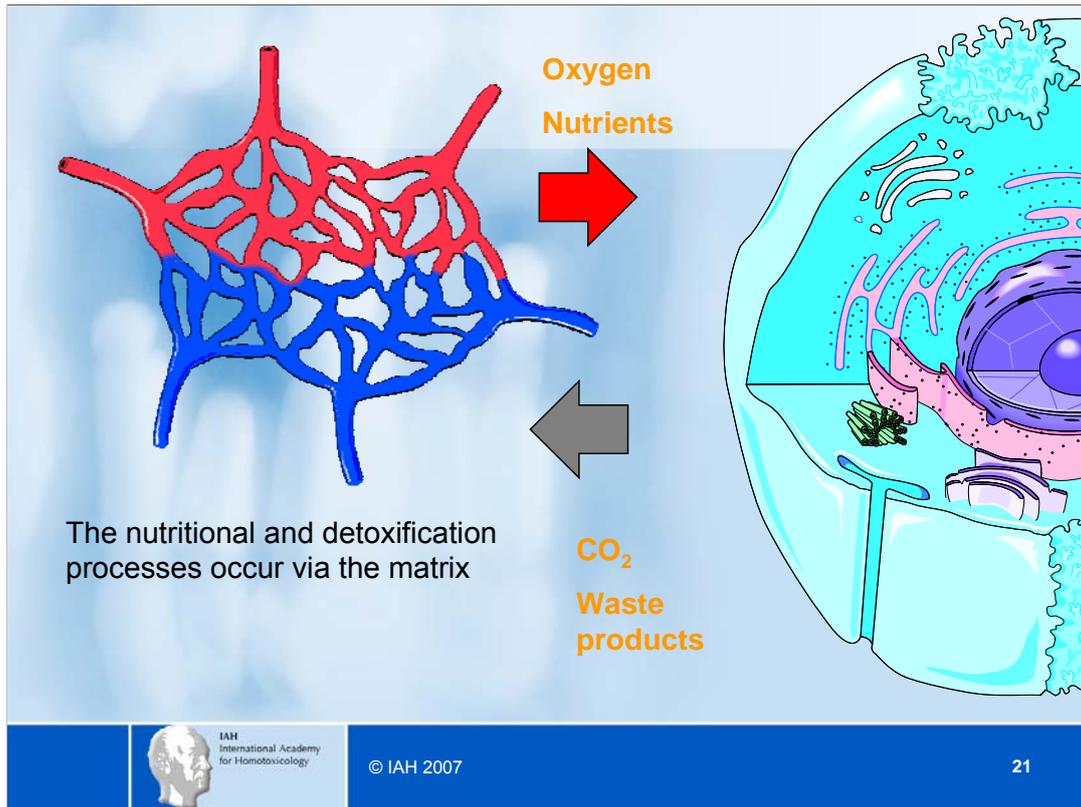
- Living interactive units
- Self maintaining
- Dependent on their environment (ECM)



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Cells are self-contained and self-maintaining if they are living in a clean extracellular matrix. The cells must take in nutrients to survive and function and are fully depending of what they obtain from the extracellular matrix as no cell is directly nourished by a capillary. Cells will convert nutrition into energy for proper use. The specificity of the cells (each cell has his own instructions imbedded) makes it fulfil certain tasks in the body, in favour of the whole organism. Most cells will reproduce if necessary



In bidirectional way nutrition is brought to the cell over the ECM and waste products of the cell are transported over this same structure to the venous system and the lymphatic system. Massive storage of homotoxins at the level of the ECM might disturb the fluent transmission of nutrients and waste product creating a 'suffocating' stage for the cell.

## Conclusion: Histology of the ECM

- The ECM is built up like a 3-dimensional network
- Apart from the proteoglycans and glucosaminoglycans, the collagen, elastin and other basic fibres, it contains capillaries, lymphatic and nerve ends, defense cells and basal membranes
- It is present all over the organism and is the main pathway for vicariation



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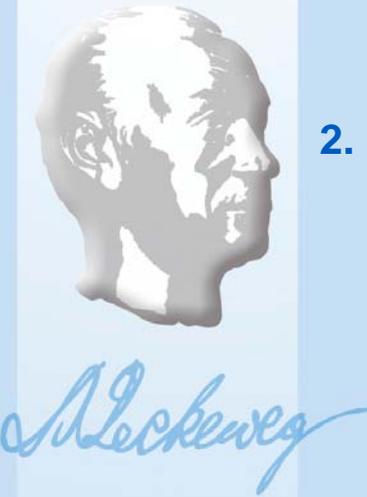
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### Conclusion:

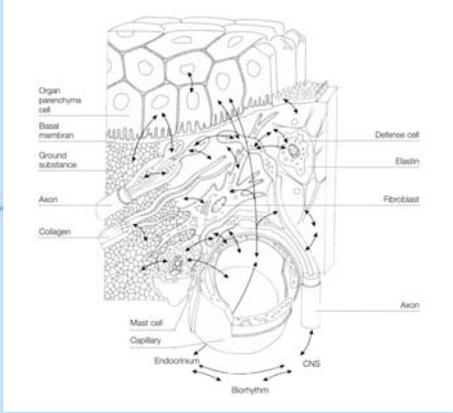
The extracellular matrix is a three dimensional web-like structure, surrounding in any dimension the organ cells. His structure is made in such a way it can fulfil his physiological task of biophysical filter.

The main components of the ECm are collagen, elastin, proteoglycans and glycosaminoglycans. The ECM is the place where arterial capillaries ends and venous capillaries begins. Also the lymphatic system collects his content out of the ECM and is by this a parallel system transporting system of the venous one. Nerves ends and begins in the ECM, triggering with nerve signals or collecting information. All over between this different compounds and structures defense cells like macrophages and mast cells are present to take care, cleanse and defend the organism.

As homotoxins can travel over the ECM to other locations, the matrix becomes the main pathway for disease and health evolutions.



## 2. Physiology of the ECM





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To understand the importance of the ECM in any biotherapeutical approach of the patient we will have to study, beside the histology of the ECM, also his physiology.

The discovery of the ECM as a histological fact has a long history. That's why it is interesting to get a closer view on some scientists creating the bases for what is known now as the main compound of the terrain of the patient.

## Historical view

- Carl Rokitansky
- Claude Bernard
- Rudolf Virchow
- Alfred Pischinger
- Hartmut Heine
- James Oschman



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Six scientists are at the bases of the importance of the understanding of the living matrix in biological medicine: the Bohemian Rokitansky, the French Bernard, the German Virchow, the Austrian Pischinger, the German Heine and the American Oschman. All six of them have brought an essential aspect to the understanding and discovery of the ECM and the modern concept of the living matrix.

## Carl Rokitansky

1804 - 1878

- No medical practice: 30.000 autopsies. Naked eye pathology
- Father of the objective experimental pathology
- Claims that cellular elements and disease develop from body fluids



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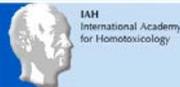
Carl Rokitansky was a Czech scientist. Although he had a medical degree he had no medical practice. Nevertheless he was very involved in medicine in his time as already as a young university professor he saw the importance for medical science of pathological anatomy or anatomopathology. With Rokitansky medicine evolved from an old fashion philosophical nature oriented medicine to a more modern science oriented medicine.

Prof. Rokitansky did more than 30.000 autopsies in his career. His scientific medical trends were set by 'naked eye' pathology. He is the real father of the objective experimental pathology. He claimed that cellular elements and diseases develop from body fluids (humoral).

## Carl Rokitansky

1804 - 1878

- Humoral: the blood is the cause of disease and organic changes
- Crases and stases
- His most important histological investigations were published in 1854 in an article titled "On the growth of connective tissues"  
– "Über das Auswachsen der Binde-Gewebssubstanzen"



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The cause of a disease must be searched in the composition of the blood which is present all over the human body. Blood changes are the main cause for diseases and organic changes.

He divided pathologies into crases (deficit) and stases (deposition, accumulation)

A lot of medical anatomical or pathological terms carry the name Rokitansky:

- Rokitansky's diverticulum
- Rokitansky's triad (lung stenosis)
- Rokitansky-Cushing ulcer
- Rokitansky-Aschoff sinuses (gallbladder)
- Rokitansky-Maude-Abbott syndrome
- ...

Especially an in 1854 published article on the growth of connective tissue is of extremely importance for the basics of what later will become the ECM in modern histological leading books.

## Claude Bernard

1813 - 1878



- Father of experimental physiology in France
- Developed the term “Le milieu intérieur” (the interior terrain of the organism or “the internal environment”)
- The cell is influenced by its direct environment



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The French physiologist Claude Bernard was the father of the ‘interior terrain’. A term that refers to the direct environment of the cell, bathing into the interstitial liquid by which it is fed and to which it gives its toxic waste products. The healthy state of the extracellular environment is essential for health and unpurity of this terrain will cause disease.

Claude Bernard, who in 1855 became a full professor, aimed to establish scientific methodology. He wasn't impressed by any statement and relied only what could be proved by experiment. His first medical discovery was the pancreas gland of which he proved the main importance in digestion. Although he is most known for the discovery of the glycogenic function of the liver he also discovered the vasomotorical system.

In biological medical context he is very well known for the term ‘milieu intérieur’, French for internal environment or terrain. What he meant by this is that the world around us changes constantly but in a good functioning body the homeostasis makes that everything stays about the same and no intoxication lasts. Only in dysfunction of the homeostasis, in dysbalance, diseases appear.

As Dr. H. H. Reckeweg one century later, Bernard was very interested in the physiological effects of poison on the human organism. He experimented with curare and carbon monoxide gas. As experiments where the bases of his scientific method he loved vivisections.

The importance of Claude Bernard for medical science was the scientific price he got from the French Academy of Sciences and the public funeral he got when he died (until than no citizen had had a public funeral in France)

## Rudolf Virchow

1821 - 1902



- Cellular pathology
- The cell is the smallest living unit of the organism
- Diseases are the consequence of cell disturbances
- Diseases are directly related to the cell



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Rudolf Virchow studied medicine in Berlin. In 1847 he became professor, 4 years after he graduated as a medical doctor.

He is very well known in medicine for his law or rule: 'every cell generates from another cell' (omnis cellula e cellula, 1855).

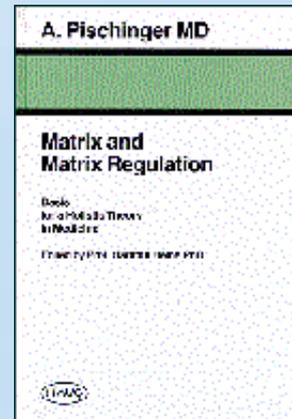
Prof. Virchow founded the medical discipline of the cellular pathology. Beside an interest into the cell as basic unit of the human organism he had also a huge interest in anthropology. He founded the Society for Anthropology, Ethnology and Prehistory.

As to Virchow not all the cells of the human body could create disease but every disease was the direct consequence of cell disturbances. As to Virchow diseases were directly related to the cell.

## Alfred Pischinger

1899-1983

- The Ground Regulation System called GRS
- The ground substance
- Whole body is functioning over this regulatory system
- First published in German only in 1975 (after more than 20 years of proper research)



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Prof. Alfred Pischinger was Head of the Anatomical Institute of the University of Vienna. He was the father of the ground substance in the ECM and described it as an amorphous gel-like substance filling the whole extracellular environment. The whole structure around the cell was in a later stage called the ground regulating system (GRS). He described the anatomical structure of this exchanging system.

Pischinger, for sure, is a disowned genius in regular medicine. Although a lot of his research is accepted in regular medicine, his name is rarely mentioned in scientific bibliographies. In complementary medicinal education he is basic knowledge.

His book 'Matrix and Matrix Regulation' is a standard work in ECM literature.

## Ground System or ECM

- Alfred Pischinger
- System of homeostasis, Basic-Bio-Regulation-System, vegetative system
- The whole concept of the extra-vascular, extra-cellular space with the extra-cellular matrix, the supporting cells, free terminal nerve endings, capillary and immunocytes



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The term 'ground system' was first used by Prof. A. Pischinger. It is a system of homeostasis .

Homeostasis should be defined as the capacity of an organism to regulate his proper internal environment. The subtle regulations or adjustments on the balance of homeostasis is done over multiple interactions between different regulation systems. The concept of the Basic Bio Regulation System (BBRS, a more to function than structure referring term for ECM or ground system) finds in this homeostasis its origin.

The components of the ECM are described in former slides in this lecture.

## Ground system or ECM: some characteristics

- 20 % of the body mass
- Electric potential set point: 240 $\mu$ V
- Auto regenerated by the fibroblasts
- Action field of most regulatory processes in the body
- Battle field of the non-specific defense system
- Direct environment of the cell



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Different authors estimate that the ECM takes 20% of our total body mass. In that way it becomes our biggest organ. As to the life quality of the cell it even is the main protective organ.

The electrical potential of the ECM in rest is 240  $\mu$ V, changeable in function of different parameters like acidity, stress, inflammation, medication, ...

If the matrix is damaged it will be mainly regenerated by the fibroblast.

The ECM is the main action field of regulatory processes in the body. Close to the cell both RELY ON each other.

We can say that life quality is highly depending of the purity of the extra-cellular matrix.

## Ground system or ECM: functions

### Function:

- Transmitter function: material, energy and information must go through the ground system
- Basic life functions: oxygen, electrolytes, pH,...
- Non-specific defense system



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The ground system is a transmission area and the main task of this system is transmission of all kind of information over messenger substances (cytokines, hormones, neurotransmitters, ...) and electric potential and impulses.

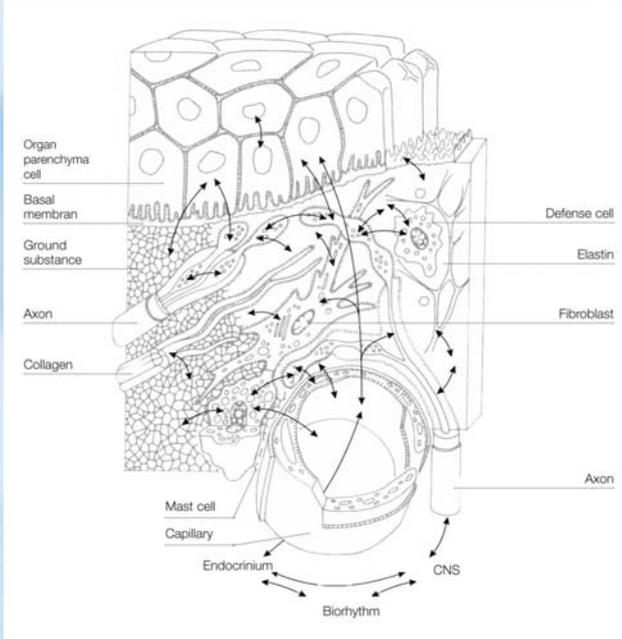
Regulation takes place at the level of the ground system to optimize basic life functions. pH-value is regulated, extravasations and absorption of electrolytes regulate the electrolyte status in the interstitial liquid, oxygen is transmitted to the cell and CO<sub>2</sub> is removed, nutrients are brought to the cell and waste products are eliminated,...

During all these transmission activities the non-specific defense system will 'control' the passage of substances and will, if the number of homotoxins is triggering a higher defense reaction, light an inflammation reaction. The presence of the non-specific defense system at the level of the ECM is essential for life. Common macrophages, neutrophils and other phagocytes will eliminate most unwanted substances but might trigger a general mobilisation of defense if a cell toxic element is found in an exceeding number. Beside phagocytes also mast cells are present in the ground system. Release of histamine and phospholipids are essential for the inflammation cascade. Also cytotoxic cells (cT-cells) and natural killer cells (NK-cells) are present to eliminate deviating or intracellular intoxicated or damaged cells.



Ground  
system  
or  
ECM

H. Heine





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The arrows on this picture show the huge number of interactions that take place at the level of the ECM. Not all the interactions take place between organ cells and environmental systems. Also cell environmental systems will interact one another.

We discussed already the transmission pathway of nutrients from capillaries to the cell and of waste products from cell to blood stream or lymphatic system. Information from nerve to cell and vice versa is another pathway.

Diffusion of messengers out of the blood stream can trigger nerves, defense cells, fibroblasts and is in turn be influenced by the endocrine system over the release of hormones. Biorhythm will influence the central nervous system that will influence in turn the biorhythm itself, the endocrine system and the whole nerve system. Fibroblasts generate proteoglycan matrix and repair damaged collagen.

Last but not least: cells will interact one another so that all the cells of an organ work as a 'team' to fulfil the organ's function or even more extended: all the cells of the organism interact over the ECM and work together and appear as one living unit.

## Synonyms of the ECM

- The terrain: Claude Bernard
- The mesenchyme: old regular terminology
- Connective tissue: old regular terminology (histological) without any physiological value
- The Ground Regulating System (GRS): Pischinger
- The Basic Bio Regulating System (BBRS): Lamers, Van Wijk and Linnemans
- The Extra-Cellular Matrix (ECM): current terminology
- The Living Matrix: new terminology in complementary medicine thanks to the work of James Oschman



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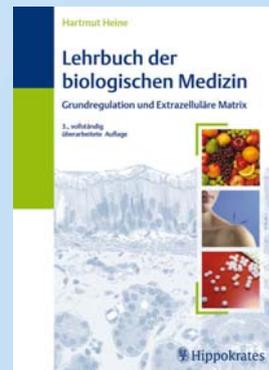
In literature a lot of synonyms are used to point at the same system. In fact, 'extra-cellular matrix' (ECM) is the only correct scientific term. The others mentioned on the slide above are synonyms that have been used by certain authors. Although BBRS is the most correct term to name and define the function of the ECM it is purely used and certainly not internationally accepted.

ECM is the current terminology and should be overall used.

## Hartmut Heine

born 1941

- Histologist
- Histological preparation of an acupuncture point (1987)
- Further research on ECM, especially on proteoglycans and glucosaminoglycans
- Basic research on autoregulatory processes in ECM
- Immunological Bystander Reaction as a possible working mechanism behind antihomotoxic medications (IBR)



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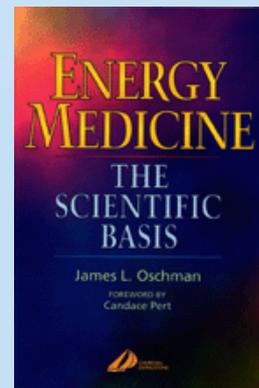
The German histologist, Prof. H. Heine did a lot of scientific research in biological medicine. He was the first to describe an acupuncture point in histological way after some microscopic observations of histological preparations. He brought complementary medicine a broad knowledge on the microscopic structure of the ECM that he described in detail in different publications.

Thanks to the work of Heine we better understand the regulating processes in the ECM.

In the inflammation process he proved in full blood cultures that micro dosages of organic material (plants, suis organ extracts) can trigger an immunological bystander reaction. Over motif formation on regulating Th-3 cells, pro inflammatory Th-1 and Th-2 cells are inhibited by the release of TGF- $\beta$ .

## James L. Oschman

- Phd, biophysics and biology
- Research at different universities
- In depth research on the peculiarities of the matrix, more precisely the energetic aspects
- Modern research on living matrix and his scientific base for complementary holistic medicine



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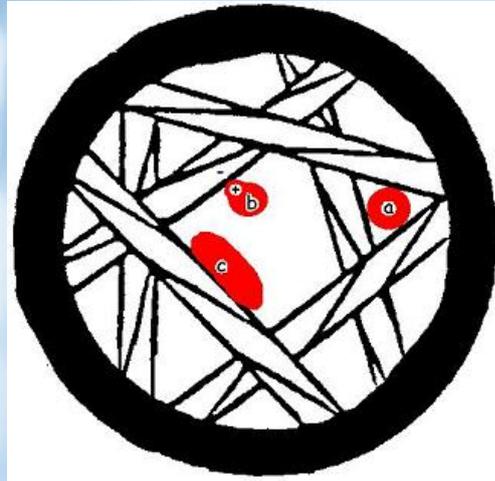
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Oschman has both the academic credentials and the background in alternative therapies to carry out his explorations. He has degrees in Biophysics and Biology from the University of Pittsburgh. He has worked in major research labs around the world. These include Cambridge University in England, Case-Western Reserve University in Cleveland, Ohio, the University of Copenhagen, Northwestern University in Evanston, Illinois, where he was on the faculty, and the Marine Biological Laboratory in Woods Hole, where he was a staff scientist. His many scientific papers have been published in the world's leading journals.

## James L. Oschman

- A. Mechanical trapping
- B. Ionic binding
- C. Hydro-related binding



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According to Oschman, there are 3 ways toxic materials (ions, molecules, clusters of molecules) can become trapped in the matrix. By matrix, I am referring to the extracellular, cytoplasmic, and nuclear matrices that form a continuously interconnected fabric extending throughout the body. It is the operation of this system that is compromised by toxic accumulation. The functioning of virtually all of the physiological systems will be enhanced by toxic removal.

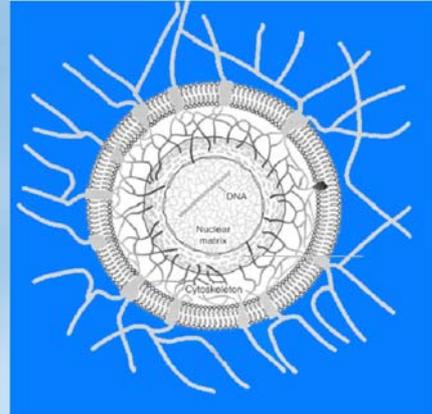
In the illustration, (a) refers to mechanical trapping; (b) refers to ionic binding to charges on the matrix surfaces; and (c) refers to hydrophobic & hydrophilic binding (e.g. uncharged molecules adhering to the matrix).

Oschman uses a positive charge toxin in B, such as a cation. This is because the matrix (the hyaluronan gel) is predominantly negatively charged. The hyaluronan has a number of remarkable and important properties:

- Regulates cell division and movement
- Huge domain
- Molecular weight 3-4 million
- Randomly coiled
- Stiff due to H bonds
- A large hydrated sphere with a radius of 200 nm
- Abundant fixed strongly negative charges

## James L. Oschman

- Extra-cellular matrix
- Intra-cellular matrix (cytoskeleton and other structures)
- Nuclear matrix



J. Oschman



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According to Oschman the living matrix is present at three levels, fading into each other. There is the environment of the cell, called the extra-cellular matrix, full of collagen, elastin, proteoglycans and glycosaminoglycans. There is the intra cellular matrix, representing the cytoskeleton. And finally in the centre of the cell there is the nuclear matrix.

Although most toxins will be present and stored in the extracellular matrix, their influence is often intra cellular and nuclear. For this reason we can't see the extra-cellular matrix as an isolated autonome interactive and informative structure but have to stay focused on the interactions between the different 'levels' of matrix in the living matrix.

## James L. Oschman: connective tissue conduction

- Proteins function as crystal semi-conductors
- Movement creates piezoelectricity
- At any moment every cell is bind to any other cell and communicates with each other



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Oschman: „ Because of piezoelectricity, every movement of the body, every pressure and every tension anywhere, generates a variety of oscillating signals or microcurrents. If the parts of the organism are cooperative and coordinated in their functioning and every cell knows what every cell is doing, t is due to the continuity and signaling properties of the connective tissue.“

Acupuncture, Osteopathy, Reiki, massage all have their healing effect over the living matrix. Also antihomotoxica use the signaling functions of the living matrix to create health in the deregulated or intoxicated organism.



The cytoskeleton is unique to eukaryotic cells. It is a dynamic three-dimensional structure that fills the cytoplasm. This structure acts as both muscle and skeleton, for movement and stability. The long fibers of the cytoskeleton are polymers of subunits. The primary types of fibers comprising the cytoskeleton are microfilaments, microtubules, and intermediate filaments.

Also here the fine 3 dimensional structure functions as a conducting communication system. The slightest extra-cellular change in electric potential might be a trigger to contract the cytoskeleton. extra-cellular intoxication can be communicated to the deepest cell structures and the other way around, cell dysfunction can be communicated to the direct cell environment and even any other cell in the organism.



The nuclear matrix is the network of fibers found throughout the inside of a cell nucleus. Although the exact function of the nuclear matrix is still disputed there are highly valuable hypotheses that it is involved in cell function regulation.

The nuclear matrix is in 3 dimensions directly connected to the intra cellular matrix and can therefore react on external impulses of a different kind (chemical, electrical,...).

## Conclusion (1)

- The ECM is the transmitter area and main area of action of mediators in the human body
- It is part of the living matrix and not to be seen as a separate communication system
- It is the terrain where the organism deals with homotoxins in inflammatory or storage pathways
- The ECM guarantees the quality of life of the cell and is therefore crucial for the organ function



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To take away from this lecture:

1. The ECM is the transmission area for many substances that travel from bloodstream to cell and vice versa. It is also the main terrain of interaction between the different regulation systems.
2. The ECM is also the main area where homotoxins will be stored (deposition phases) or will be eliminated by inflammatory processes (inflammation phases).
3. As direct micro-environment of the cell, the ECM guarantees under normal conditions the life quality of the cell. The ECM is therefore crucial for cell surviving and is a main terrain of action for biological medical therapies. In the ECM present or stored homotoxins will disturb in minor or major degree the cell function and should therefore be avoided at any time to keep the organism in full health.

## Conclusion (2)

- Dysfunction of the ECM will finally result in dysfunction of the cell
- Health and the patient's quality of life is directly relied to the purity and efficient regulating processes in the living matrix. Chronic diseases are the consequence of the persisting inability of the organism to deal in a proper way with the toxins in the ECM.



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To remind from this lecture:

4. Any regulation dysfunction at the level of the ECM will finally disturb or influence the cell function in a negative way. Regulation therapies intervene at the level of auto regulating systems and try to restore the harmonious condition of good homeostasis and interactive communications between the systems and the cells, and this omnidirectional.

5. Drain therapies will target the purity of the ECM as the presence of homotoxins in a long term will induce chronic degenerative pathologies where cell dysfunction and cell death are the main characteristics.

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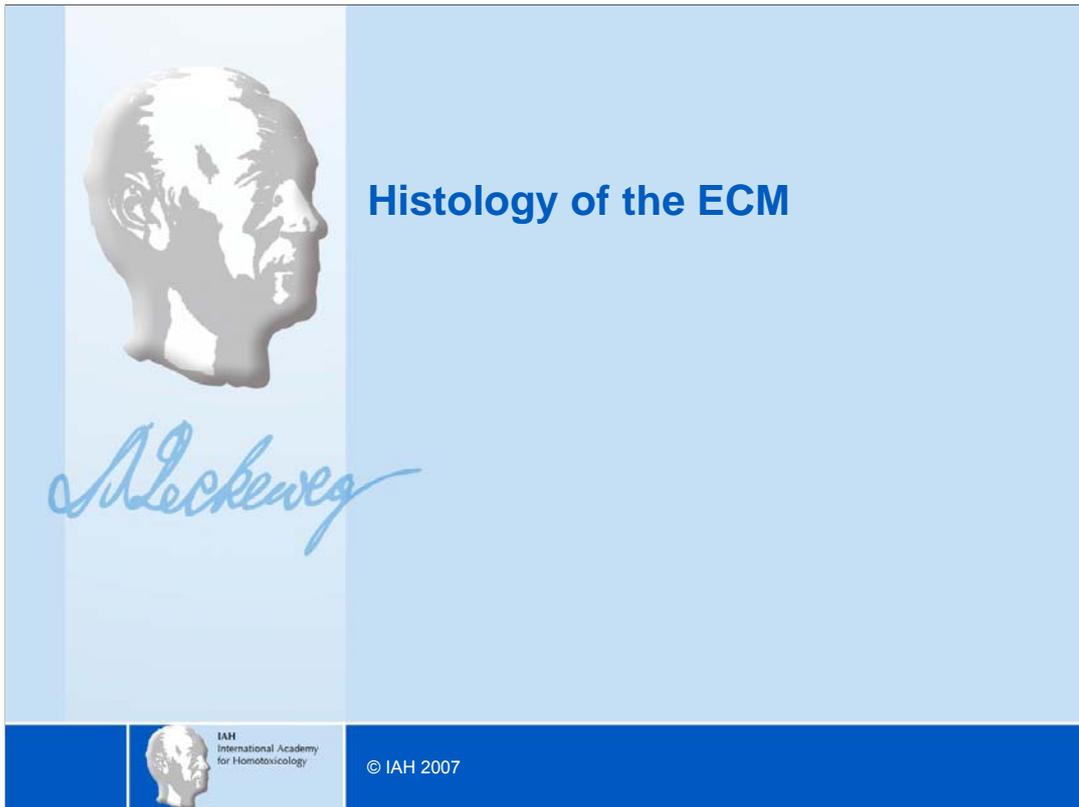
*Neckweg*

## Backup on histology of the matrix



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Let us take an even closer look at the histological compounds of the extra-cellular matrix. What are the more detailed components it is built of?

## Tissue

- Connective tissue: misunderstood organ
- Organ cells



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Two main types of structures are dependent on each other. The connective tissue on the one hand, which is found in the interstitial space, and the organ cells on the other hand.

As for many years the connective tissue was explained as a pure support and binding structure between other tissues we can say it has been for decades a fully misunderstood 'organ'. We will see further on that modern histology and physiology of the connective tissue shows a large differentiation of tasks done by this tissue. Beside the pure binding function it has storage capacities for homotoxins, forms a transmission area for a lot of mediators and other substances and is a fine meshed three dimensional biophysical filter. That is why in some European literature the term Basic Bio Regulation System (BBRS) is used (Lamers, Linnemans & Van Wijk) instead of connective tissue or even ECM.

### **BBRS**

Basic, because it is present as an extra cellular environment for any organ cell in the body.

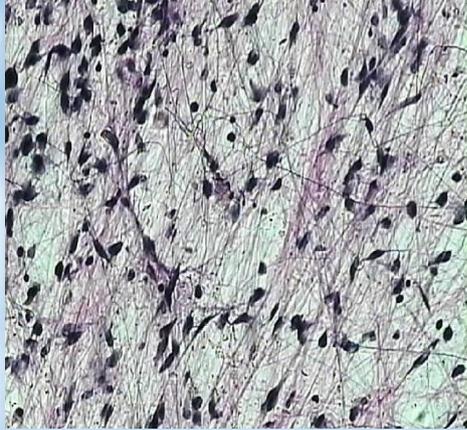
Bio, because it is essential for life and is in normal conditions regenerated if damaged.

Regulation, because most interactions between autoregulative systems takes place at that level.

System, because it corresponds to rules and therefore in many ways is predictable.

## Connective tissue

- Specific cells
- Extra-cellular matrix



Within the connective tissue we find specific cells and the fine structure of the extra-cellular matrix.

## Specific cells

- Embryological development out of the mesenchym
- Secretion of the extra-cellular matrix



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Out of the mesodermal embryological layer, more precisely the mesenchym, the different specific (supporting) cells are developed. Although they are slightly different in function and location where they can be find in the body, their main task of these cells remains the same: secretion of the extra-cellular matrix.

The main supporting cells are the fibroblasts and fibrocytes, chondroblasts and chondrocytes, osteoblasts and osteocytes, the myofibroblasts and the adipocytes.

## Supporting cells

- Fibroblasts and fibrocytes in fibrocollagenous supporting tissue
- Chondroblasts and chondrocytes are creating cartilage, which is strongly associated with bone structure
- Osteoblasts and osteocytes



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Fibroblasts manufacture the structural fibers and groundsubstance of the extracellular matrix. The ground substance is mainly composed out of proteoglycans (PGs) and glycosaminoglycans (GAGs). Fibrocytes are smaller (and younger) and are inactive, which means they do not make structural fibers and groundsubstance.

Fibroblasts create collagen, glycosaminoglycans, elastic fibers, and proteoglycans found in the ECM. In growing individuals fibroblasts are dividing and synthesizing ground substance. If the tissue is damaged fibrocytes are stimulated and will induce the mitosis of fibroblasts which over secretion of essential fibers and groundsubstance will try to restore the healthy situation.

Chondroblasts create cartilage. Chondrocytes are the only cells found in the cartilage. They maintain the matrix structure of the cartilage.

Osteoblasts secrete osteoid, a protein mixture which once mineralized becomes bone. Osteocytes are osteoblasts that are 'trapped' into the bone structure.

## Supporting cells

- Myofibroblasts have characteristics of fibroblasts and unstriated muscle cells
- Adipocytes are storing fat and play a role in temperature regulation



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Myofibroblasts are in fact fibroblasts that have differentiated towards a smooth muscle phenotype. Myofibroblasts play a role in wound healing *of organs*. By contraction they pull the wound edges one to another which speeds up the wound healing. In normal conditions they disappear after wound healing due to apoptosis.

Adipocytes or fat cells store energy in the form of fat. They are also classified under the supporting cells although they are not directly responsible for secretion of ECM-components.

## Fibrillar proteins

- Flexibility of the connective tissue
  - Fibrillin
  - Fibronectin
  - Laminin



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The small fibrillar proteins like fibrillin, fibronectin and laminin are important building stones of the ECM structure and are mainly responsible for its flexibility.

## Fibrillin

- Component of microfibrilles
- Important component of elastic fibres
- 3 types



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Fibrillin is an essential component of elastic fibers in the ECM. Fibrillin is a glycoprotein.

Three types of fibrillin have been described.

- Fibrillin-1 is the main component in the microfibrils that forms elastin.
- Fibrillin-2 is thought to play a role in early elastogenesis
- Fibrillin-3 is more recently discovered and is mainly found in the brain.

Marfan syndrome is a connective tissue disorder that is related to fibrillin dysfunction, more precisely Fibrillin-1. The disease is linked to the FBN1 gene on chromosome 15. FBN1 codes for Fibrillin-1.

## Fibronectin

- Adhesion between cells and ECM
- Binding places for collagen, heparin and adhesion molecules



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Fibronectin binds to receptors proteins at the cell membrane and will connect or bind the cell to its extra-cellular environment. Fibronectin is a binding adhesive component between the cell and the ECM structures. It is also a glycoprotein but of a much higher weight than fibrillin. In combination with integrin receptors it binds to almost any component of the cell's environment.

Fibronectin is also found in its soluble form in blood plasma. It is secreted by hepatocytes in the liver.

Fibronectin is extremely important in wound healing and is in this even used as therapeutic agent.

## Laminin

- Structural element of the basal membrane
- Vitamin C stimulates the formation of laminin



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The basic structural compound of the basal membrane is laminin.

Laminin is also a glycoprotein found in the basal membranes of humans and most animal species. It binds to most cell membranes and is also responsible for attachment of cells to their direct environment like basal membrane and other cells. Laminin will inhibit the movement of cells and is a critical factor in the maintenance of tissue phenotype.

Some forms of muscular dystrophy are associated to a dysfunctional structure of Laminin-2. Laminin-2 is found in the brain and muscles.