Microbiom (english version)

> *„I had no idea everything was so integrated and beautiful … each organelle could be shown in a dynamic dance of parts that continuously embrace. I had no idea everything was so integrated and beautiful … each organelle could be shown in a dynamic dance of parts that continuously embrace.“ Dolgin 2019*

Content

Overview

We are made up of viruses and bacteria

Certain bacteria and viruses are just as typical of humans as cells. Other microorganisms can be useful as guests or roommates. Parasites use our habitat without making themselves known or causing damage. The boundaries between these possibilities and forms of communication in ecosystems are fluid and changing.

All life in the body and in its environment communicates. Animals and plants resemble state structures in which individual living beings work together. Their shape is formed from the confluence of different functions flowing together to form a whole. They adapt flexibly to their environment, exchange ideas and generate new ones from within themselves. If internal and external interactions oscillate smoothly and peacefully, minor disturbances can be overcome without permanent damage.

Illness is a communication disorder.

Whether people survive colonization with a pathogen or whether they die depends not only on the type of external threat. More important is the quality of the interaction between the body's own viruses, bacteria, cells and cell components. And the ability of a healthy organism to react calmly and calmly to external stresses.

Many individual functions are involved in the flow balances and interactions: The immune system, the gut, gut bacteria and viruses, cells, mitochondria and many more. The environment can have a beneficial effect (providing security, fulfilling basic needs) or a detrimental one (through stress or toxins).

Cells are also ecosystems

A human cell resembles a medieval town. In the centre, protected by a wall, rests the city core with the town hall and a library of knowledge. In front of it grazes a herd of goats: the so-called mitochondria. In times of peace, the city gates are open. Inside and outside interact with each other. The city is bounded by a wall: the cell membrane. The city uses it to communicate intensively with the neighbouring lands and the entire state.

Without a „herd of goats", a human cell would not be viable. The mitochondria provide the energy required to burn oxygen. They have their own genes for this purpose. They are controlled, determined and influenced by the cell nucleus. Conversely, they have an effect on the cell nucleus. Mitochondria change, merge with each other, divide. If they age or produce too much waste, they are eliminated, like sick farm animals.

External challenges can be met with resilience if the interactions inside the cell are peaceful. Overloading the mitochondria as a result of drug over-therapy, old age, overloading with toxins, high-stress levels, lack of exercise (and much more) can lead to disorders.

Relatively small challenges can then trigger immune overreactions. For example, when the mitochondria send out distress signals. The entire immune system can then be activated explosively, resulting in serious illnesses. Or chronic fatigue, autoimmune inflammation, neurodegenerative diseases or

many other disorders that cause lasting damage.

Microbiome and immune system

All body systems (including the microbiome, the brain and the immune system etc.) form a functional unit.

In the course of evolution, the complex interaction of microorganisms and cells typical of humans has led to the development of a mature immune system that nourishes and protects the organism.

Without bacteria in the gut, important messenger substances would be missing. The metabolism of certain cells of the immune system would not be regulated.

If an immune response is triggered by an infection, so-called Asterix cells play an important role. They are part of the innate immune system and carry receptors that recognize patterns of invading pathogens. The cells initially react by releasing messenger substances that attract further immune cells. At the same time, they absorb the mini-organisms, break them down and then present individual fragments as antigens on their cell surface. This activates the controlling „T cells“ of the learning immune system, which trigger a targeted response. If the control functions are activated by Asterix cells that present protein components from their own body as something „foreign“, autoimmune diseases develop. (Schaupp,2020)

The importance of the first days of life

In the first days and weeks of life, the balance between intestinal, immune and nerve cells and the microbiome is still very unstable. Brain development and immune function only slowly mature together. The interaction of the child’s cells with the bacteria typical of humans, which the mother transfers to the child, influences the entire (neurological, immunological, motor) development of a child.

Pregnant women, mothers and newborns must therefore be comprehensively protected in this important phase of life.

Poor hygiene is a major cause of child mortality. But too much hygiene is also dangerous. Babies who grow up in extreme isolation are more likely to

develop chronic inflammation of the intestines and lungs. In contrast, „garden dirt“ seems to protect children from autoimmune diseases, as long as it contains only „garden bacteria“ and no environmental toxins. An environment rich in microorganisms is important for the healthy development of young children. This is because the experiences that the immune system has in early childhood help to differentiate between harmless and dangerous germs: for life.

Interventions are only ethically justifiable in the period of programming in the womb and in the period of early childhood adaptation if life-threatening dangers are averted and the intervention itself does not pose any significant risks. All unnecessary medical interventions should be avoided.

Humans are „hybrids“

The human genetic material in the cell nucleus consists of just over 22,000 genes. This means that we have 8,000 more genes than an earthworm. However, we also have 9,000 fewer genes than the water flea Daphnia. What makes humans special is therefore not limited to their cell nucleus genetics. The way in which different carriers of information oscillate and interact in an overall system must have a considerable significance that has hardly been researched to date. It is now also known that human-specific genetic information is also transmitted during and immediately after birth (microbiome).

The Nobel Prize winner in medicine, Svante Pääbo, succeeded in proving that several percents of the cell nucleus genes of Europeans are descended from early humans. Gene transfer from other archaic humans is also suspected in Africans and Asians (Bodensis, Denisova, Naledi).

Large numbers of mitochondria are stored in a „dormant state“ in the maternal egg cell. The mitochondria of the fathers commit collective suicide after uniting with the egg cell.

Genes of human mitochondria that do not originate from the genus Homo sapiens have not yet been detected. (SpdW 12/2022)

Human Superorganism

Part 1: Human Ecosystem

Jaeger H: Ökosystem Mensch: Pädiatrische Praxis, Januar 2023, 99(2)193-204

Summary

Humans are superorganisms. They consist not only of cells, but also (among other things) of bacteria and viruses. These individual organisms are interwoven with each other and with the intestines, brain, nerves, metabolism, immune system and musculoskeletal system in various feedback loops. They work harmoniously in a complex system and thus enable this organism to adapt flexibly to external stresses. In the first months and weeks of life, the balance between immature intestinal epithelium, immune cells and nerve cells and the intestinal microbiome is still unstable. Postnatal microbial maturation runs parallel to brain development and the development of immune function. This early interaction between bacteria, immune function and the nervous system thus also influences the child’s cognitive, immunological and motor development. To prevent psychiatric, neurological and auto-immunological diseases, it is necessary to provide comprehensive protection for pregnant women, mothers, foetuses and newborns during this essential phase of life. Medical interventions that are not absolutely necessary should be avoided wherever possible.

The evolution of the human ecosystem

Humans consist not only of cells, but also of bacteria and viruses, among other things. These are interwoven with each other and with the gut, brain, nervous, metabolic and immune systems and musculoskeletal system in multiple feedback loops. The early interaction between bacteria, immune function and the nervous system thus also influences the child’s cognitive, immunological and motor development.

War and peace

170 years ago, Rudolf Virchow surmised that diseases were the result of intracellular disorders. Shortly afterwards, Antoine Béchamp described mini-organisms on the surfaces of diseased plants. (Nouclerq 1982)

He considered these „microzymes“ to be natural components of living

organisms which, in the event of an internal imbalance, were released to the outside and continued to multiply there. A decade later, Louis Pasteur also adopted Béchamp’s theory. However, Pasteur, Ferdinand Cohn and Robert Koch considered the bacilli or „small rods“ (Greek ‚bakterion‘) to be enemies of healthy life forms. (Hume 1942)

Their militant view still characterises infectiology today, especially as ever more effective weapons have been developed. Paul Ehrlich first discovered chemical substances that killed bacteria but caused relatively little damage to cells. He called them „magic bullets“. He used his first drug „Salvarsan“ (Latin salvare = to save, sanus = healthy), an organic arsenic compound, to treat syphilis. However, it proved to have many side effects. (Mildenberger 2014)

The final breakthrough in antimicrobial therapy came in 1928 when Alexander Fleming observed the growth-inhibiting effect of fungi of the genus Penicillium on staphylococcus cultures. His penicillin marked the beginning of the triumphant advance of antibiotics, which is now coming to a halt 100 years later in the face of increasing antibiotic resistance worldwide.

This is because antibiotics select resistant infectious pathogens, for which the therapies open up new evolutionary niches. (Mendelson 2017)

The modern, ecological view of the germs that live around and in humans was opened up by the biologist John Whipps. (Whipps 1988)

who coined the term microbiome in 1988 for „a microbial community that occupies a reasonably well-defined area and has certain physico-chemical properties“. The Nobel Prize winner Joshua Lederberg understood this to mean the coexistence of commensal, symbiotic and pathogenic microorganisms that share our habitat. (Lederberg 2001, Gerabek 2005)

He described the intra- and extracorporeal co-inhabitants as infinitely diverse and variable, interacting with each other and with others on a broad spectrum ranging from indispensable usefulness to great danger. Some germs are parasitic or pathological, while others are commensal, beneficial or even indispensable. A little later, it was discovered that the presence of certain pathogenic germs does not necessarily have harm the host organism. This is because they train the immune defence and thus indirectly inhibit the proliferation of other infectious pathogens (Parker 2016).

For example, the microbiome selects certain variants of potentially pathological bacteria (such as staphylococci or streptococci), which then calibrate epithelial cells about tolerance and immunity, increasingly displace pathological variants and even play a healing-promoting role in the repair processes of tissue defects (Stacey 2019).

Today it is certain that all living cells develop in a symbiotic co-evolution with the surrounding microorganisms. The environment, microbiome, cells and organ functions must therefore be understood in terms of their interrelationships, feedback, interactions and dynamics (Stegen 2018).

The essential characteristic of the health of such ecosystems is their diversity. In humans, however, an increasing depletion of the microbiome is being observed, which can lead to various disorders (XXX).

Human superorganism

The first sequencing studies with the human microbiome around 2005 only included data from a few people. In 2008, the „Human Microbiome Project“ of the American „National Institute of Health“ began to catalogue microbiomes obtained from five different body sites of a few hundred people. Today (after tens of thousands of further studies), biology describes living organisms as „holobionts“ or „superorganisms“ (Dieter 2016).

They consist of colonies of very different sub- or partial organisms that together form large superordinate organisms.

In addition to cells, humans consist predominantly of typical bacteria and viruses. 93% of the total DNA of the microbiome of the internal and external body surfaces comes from bacteria (mostly Firmicutes and Bacterioides), 0.2% from protozoa, 0.1% from fungi, 0.8% from archaebacteria and about 5.8% from viruses. Some even estimate the viral proportion of the total DNA of the microbiome to be over 20% (Skhoporov 2019, Douglas2018, Dhanragu 2022).

Virome

The sum of all human-typical cell-bound (eukaryotic) and bacteria-bound (prokaryotic) viruses is known as the virome. The classification into favourable, trivial and dangerous viruses within the microbiome is at the

beginning of its research. Endogenous retroviruses constitute about 8 % of the human genome (Wylie 2012).

They have been integrated into the information strands of our chromosomes after millions of years of infection and fulfil important functions within the cells, including in connection with the interferon metabolism of the immune system (Chuong 2016).

Another essential component is viruses that destroy bacteria (bacteriophages). They play an important role in the regulation and control of bacterial populations, particularly in the distal colon (Skoporov 2019).

They thus fulfil control tasks, for example by reducing bacterial invasions when embedded in mucus on cell surfaces (Olgievie 2015).

The microbiome of the body’s surfaces

The number of cells corresponds approximately to the number of bacteria in the body. In and around the human body, however, there are about ten times as many bacteria as body cells (Sender 2016).

This mature microbiome has a body weight of more than one kilo. It contains about one hundred times more genes than human cell nuclei. The microbiome of the body’s surfaces is part of a complex process in which the gut, the endocrine system, the nervous system, the musculoskeletal system and the immune system interact with each other. It is shaped in the first phase of life and through environmental adaptation, and is more typical of each individual person than their fingerprint. People can even be recognised indoors by the cloud of bacteria swirling around them in the air (Meadow 2018).

The bacterial microbiome resembles a functional unit and not a disjointed collection of germs. Its totality, diversity, dynamics and multiplicity are associated with health, and its degradation with disease (50).

The complex fluid balance of the microbiome system is characterised on the one hand by the memory of phylogenetic development and on the other by the experience (and epigenetics) during pregnancy, at birth and in the first period of life. Colonisation with bacteria typical of humans protects against pathogenic germs, produces biochemical building blocks and promotes the development of the immune system between tolerance, reassurance and

training. The community as a whole selects the type of microbes that are most favourable for the functional context. The bacteria compete and thus control each other. The greater the diversity, the better (Blaser 2014).

Gut, immune system and brain

The main functions of the intestine are to absorb food and to mediate a balance between tolerance and immunity, between the self and the antigens of the non-self. From the perspective of the gut, the musculoskeletal system has to ensure a rhythm of activity and rest and a regular supply of water and food. The central nervous system (including neuro-endocrinological, neuro-immunological and autonomic functions), the intestinal nerve plexus and the microorganisms living on the inner and outer surfaces of the body form multi-directional feedback loops. This regulatory interplay works via vascular permeability, immune modulation and the production of cytokines and neurotransmitters, among other things. One of the most important nerves in this context is the vagus nerve, whose motor parts originate from two different regions of the brain: the dorsal motor nucleus and the ventral nucleus ambiguus. Its sensory fibres ascend into the nucleus tractus solitarius. The microbiome is involved in the importance of many messenger peptides, which have an anti-inflammatory effect, influence the production of ACTH and, via tryptophan, form the prerequisites for serotonin availability in the brain. Furthermore, certain bacteria produce neurotransmitters, such as GABA, which has an inhibitory effect in the brain (Dian 2015).

The gut is a sensory organ with around 200-600,000,000 neurones. The neuronal connection to the brain via motor and sensory fibres of the vagus nerve has a calming effect on brain function, behaviour, immune function and metabolism (16). The vagal function appears to have a protective and repair function for the epithelium in test subjects and to lead to an increased connection between the epithelial cells. The intestinal epithelium appears to function better during restful exercise, whereas stress responses impede cellular attachment (e.g. leaky gut syndrome) and thus promote chronic inflammation (Mogiloski 2019, van Houton 2015).

The basis for the maintenance of homeostasis is formed by complex interacting neuro-immune cell units (NICO), in which afferent and efferent nerve fibres (sympathetic nervous system, vagus nerve) form a complex interaction with macrophages, connective tissue cells and bacteria.

Bacteria and cells can apparently communicate with each other, including via a separate transport mechanism (norephedrine, dopamine, histamine, tyramine, tryptophan and others) (Lyte 2018).

Disruptions in this dialogue between genome, microbiome and virome (dysbiosis) are important causes of disease (Veiga-Ferandez 2018, Lum 2020).

There is increasing evidence that dysbiosis in the gut, mouth and vagina can lead to immune dysregulation as a trigger for many chronic conditions. Disruption of microbial colonisation (e.g. after antibiotic therapies), central immune modulation in the brainstem (e.g. during stress) or immune cell dysfunction (e.g. during autoimmune reactions) can reinforce each other and thus gradually develop into severe dysregulation (Scarpellini 2015, Veira 2014).

The gut, immune system and microbiome influence the brain and behaviour (and vice versa) (13, 58-60). In order for an organism to adapt flexibly to requirements, these complex system functions must interact harmoniously (Carabotti 2015, Belkaid 2014).

In leaky gut syndrome, epithelial cell connections are disrupted. The constant low-threshold activation of the immune system manifests itself here through increased cytokine levels, which, in addition to inflammation, can also lead to depressive mood (Kelly 2015, Silverman 2019, Clemente 2018).

The fact that depressive patients are often found to have a disturbed and impoverished intestinal flora also speaks in favour of such connections (Lum 2020, Pennisi 2019).

In metabolic diseases (diabetes, among others) and immune disorders (asthma, neurodermatitis, among others), these relationships are increasingly well studied (Belkaid 2014); the same applies to obesity (Thaiss 2018). However, they also appear to be important in the development of many other diseases (O’Mahony 2017): for example in rheumatoid arthritis (Rogers 2015) or disorders of the maturation of brainstem function (Dinan 2015, Foster 2017) or in the development of multiple sclerosis (Holfeld 2015, Haghikia 2015).

Early childhood differentiation of immune function and brain

The development of the child in utero is influenced by epigenetic imprints regarding its metabolic, immunological and neuronal differentiation. The child’s brain development is in a particularly critical phase in the last trimester. Brain folding initiates a qualitative change in the brain. The last months of intrauterine development, the postpartum period and presumably the first three years after birth are significant for the development of the interaction between neuronal cells and bacteria: They shape the entire rest of human life (Faa 2017, Hrubý 2013, Aagard 2019)

The placenta is not sterile. It harbours a rudimentary microbiome with numerous bacteria and viruses that is typical for pregnant women (Aagard 2019).

Foetuses swallow large quantities of amniotic fluid, so that at birth the foetus’s intestine is already equipped with a rudimentary microbiome. In addition, during pregnancy, the variability of the microbiome in the vagina is reduced to the cultures that are important for the colonisation of the child’s intestine (Staude 2018, Willyard 2018).

For this reason, the type of nutrition during pregnancy presumably has a lasting influence on the development of the child’s microbiome (Aagard 2019).

The time before birth and the first two weeks of life are crucial for the success of the physiological conversion processes: for the adaptation of respiration and circulatory function and for the formation of essential synapses, for myelinisation and the maturation of the diversity of the microbiome and the associated development of immune function (Rea 2016, Jonas 2016).

Breast milk bacteria have a lasting influence on the structure and development of the infant microbiome (Holhlfeld 2018).

They have a distinct carbohydrate metabolism, amino acid metabolism, energy metabolism, for example the lactic acid bacteria (bifido bacteria), which are essential for the healthy development of the newborn (O’Connell 2019).

Breastfeeding also protects against obesity. And the transfer of the maternal microbiome during breastfeeding stimulates the maturation of the child’s immune system by presenting bacterial components to the T-cells in the thymus gland (Hsu 2018).

The development of the microbiome during pregnancy is influenced by the mother’s behaviour, including stress, smoking, pet ownership and drug consumption. Negative events during this sensitive early phase pose a particular risk to somatic and psychomotor development (Stauda 2018).

Disruptions in the programming of early childhood nerve and immune development can cause lifelong, possibly irreversible damage, such as autoimmune maldevelopment (diabetes, SLE, multiple sclerosis, Alzheimer’s disease), obesity, neuropsychiatric disorders such as depression or autism spectrum disorders. The well-studied influencing factors include stress, diet, smoking, alcohol, drugs, medication, high blood pressure, metabolic disorders, liver disorders, placental insufficiency, premature birth, immune stimulation, primary caesarean sections, antibiotics, bottle feeding and exposure to environmental toxins (Foster 2017, Faa 2016, Fanni 2018, Molina-Torre 2019, Stower 2019).

Prevention of premature birth and postnatal sepsis

The reasons for premature birth include psychosocial stress, hormonal fluctuations and uterine contraction tendency, cervical diseases, vascular disorders or a breakdown of the materno-fetal unit. Inflammatory symptoms are often the trigger. They are caused by the proliferation of pathogenic germs, the disappearance of the natural microbiome or an increased agitation of the immune system. For a long time, it was assumed that infection with a certain bacterium triggers premature birth. It has now become clear that it is more likely to be a complex process of dysbiosis of the vaginal and possibly also placental microbiome, both of which change during pregnancy (Chun 2018).

The newborn is at risk from numerous endogenous and environmental factors in the postnatal period. Bonding serves the general calming of the child and thus also directly the intestinal function and favours the development of a functioning microbiome. And, of course, it serves hygiene to protect against nosocomial infections, against which there is still no defence.

Significant risk factors are stress, lack of bonding and also lack of breastfeeding, as the diversity of the bacterial flora (including Bacteroides and Firmicutes) in breast milk protects against potentially pathological species (Stauda 2018).

In the case of early onset neonatal spesis (EONS), ß-hemolytic streptococci (group B streptococci – GBS) or enterococci were predominantly found, but also staphylococci, enteroviruses or fungi. The mortality risk is particularly high with enterococcal colonisation (Simonsen 2014).

Very different serogroups of these microorganisms occur as commensal components of the microbiome in numerous pregnant women. Disorders of the local microbiome enable their pathological proliferation and increase the risk of subsequent immune dysfunction (Kim 2019).

Such dysbioses are exacerbated by prophylactic antibiotics, as they reduce the richness and diversity of the microbiome, regardless of the drug class (Meyer 2016).

The goal of reducing colonisation in the event of pathogen detection (e.g. GBS) is therefore countered by risks: the selection and multiplication of other serogroups of the same pathogen or undetected EONS pathogens such as enterococci (Simonsen 2014).

Therefore, even in the case of colonisation with a pathological serogroup of ß-hemolytic streptococci, the administration of antibiotics is controversial and there is an increasing search for alternatives to prevent GBS infections (Vornhagen 2017, Edwards 2019).

The AWMF guideline (AWMF 2016) on the prevention of ß-hemolytic streptococcal infections in newborns, which is valid in Germany, does not consider the findings on the transmission of the maternal microbiome. The next revision of the guideline was planned for March 2021. Given the exponential growth of available knowledge on and stabilisation of the disease during pregnancy and in the newborn, it is strongly recommended that the guideline is now revised based on efficiency. The continued existence of an outdated guideline does not justify not providing affected women with comprehensive information about the consequences for the infant before administering an antibiotic.

Conclusion

The human superorganism is an ecological system that has evolved from a modulation of environment, nutrition, immune function and resistance to pathogens. Bacteria have colonised the earth for 3.8 billion years, eukaryotic organisms emerged around 2.2 billion years ago, and the first interaction of colonising microorganisms with a host organism developed perhaps 500 million years ago as a precursor to the immune system. The mini-organisms represent a kind of organic interface between inside and outside. Foetuses carry maternal mitochondria, and their environment is not sterile either.

Even after birth, the maternal microbiome is passed on through breastfeeding and skin contact and continues to be fed through breast milk. For example, through end products of human metabolism (urea, oxalates and others), which are useless for human cells but essential for bacterial growth. A direct benefit of the microbiome for the newborn is the rapid onset of vitamin K production, which was barely able to cross the placental barrier before birth. Constant breastfeeding trains the child’s immune system, and the innate (aggressive, non-specific) immune system is gradually overlaid by the more intelligent immune system acquired through learning.

If this process is disrupted (by stress, lack of bonding, primary caesarean sections, lack of breastfeeding, antibiotic therapies), somatic and psychiatric illnesses can develop in the child. The advantages and disadvantages of the practice of transferring the mother’s microbiome to the newborn during a caesarean delivery (by vaginal swab immediately before the procedure) are still controversial. To better understand the factors influencing the stabilisation of microbiome transfer, children need to be followed prospectively in their development and regarding their risk of disease and mortality (Dominguez-Bello 2019).

Research into the connections between the microbiome is opening up a new pharmaceutical market for the production of probiotics and food supplements, for example oligosaccharides and fructo-oligosaccharides, which are intended to promote the growth of bifido bacteria. Research is also being carried out into the production of phages. The demand for these products is increasing due to growing marketing. However, whether they work better than „nothing“ or a yoghurt from the organic market is still

controversial (93). In addition to researching new technical possibilities for manipulating the microbiome, it also seems sensible to me to think about how harmonious communication between these different hosts could be promoted: through more natural births, protecting the mother-child bond, breastfeeding, reducing stress and many other things. For in the infinitely complex interrelationships described above, it is not only the individual influencing factors that are important, but above all the relationships between them (Foster 2017, Diehlman 2022, Praeven 2015, Li 2022).

The new understanding of the human ecosystem requires a different attitude towards the ecosystem that makes up the human being: “Antibiotic resistance is a language problem … With the crisis before us, it is time to use the power of words to change the course of events“ (Mendelson 2017)

Part 2: Ecosystem cell (mitochondria)

Jaeger H. Ökosystem Zelle: Pädiatrische Praxis, Mai 2023, 99(4):634-641

Summary

Disorders and ageing processes are directly dependent on the health of the mitochondria. Targeted mitochondrial therapies for all disorders cannot be expected in the foreseeable future due to the complex interactions in the cells. What has proven to be highly effective, however, is prevention through behaviour: Reduction of stress, a balanced, calm lifestyle, ensuring adequate sleep, no drugs (especially nicotine), a healthy diet, calming communication, mindfulness and plenty of relaxed exercise. Mitochondria are responsible for numerous essential cellular functions such as metabolism, regulation of calcium, formation of reactive oxygen species and initiation of apoptosis. Mitochondrial dysfunction is associated with many pathologies, including inflammatory bowel disease, autoimmune diseases, neurodegenerative disorders and neuropsychiatric conditions, negated metabolic diseases and even cancer. All behavioural changes that lead to an improvement in mitochondrial functions improve the health of the entire organism. Mitochondrial dysfunction is associated with many pathologies. Due to the complex interactions in the cells, targeted therapies for such disorders are not expected in the foreseeable future. What has proven to be highly effective, however, is prevention through behaviour.

„I had no idea everything was so integrated and beautiful … each organelle could be shown in a dynamic dance of parts that continuously embrace.“ (Dolgin 2019)

Introduction

Mitochondria are key organisms. They are subject to constant morphological changes: they fuse (fusion), divide (fission) and degrade (mitophagy). Mitochondria are responsible for numerous essential cellular functions such as metabolism, the regulation of calcium, the formation of reactive oxygen species and the initiation of apoptosis. Disorders of the human microbiome and its interactions with the immune, endocrine and nervous systems are correlated with various diseases (Valdes-Aguayo 2021).

It is therefore not surprising that mitochondrial dysfunction also underlies many pathologies, including cancer (Chin 2020) and Covid 19 (XXX).

Heredity is more than nuclear genetics

When the egg is fertilised by a sperm, genetic information packaged in chromosomes fuses. The slightly more than 20,000 genes in the chromosomes encode the production of proteins. However, the number of human proteins far exceeds the number of cell nucleus genes. The structure of the majority of human-typical proteins is (at least) influenced or (sometimes) determined by genes outside the human body.

The entirety of human-typical genetic information that is not encoded in the cell genome is called the microbiome and virome (for human-typical bacteria and viruses). They are transmitted during birth and breastfeeding and interact with the body’s cells in an interplay between defence and tolerance (Breiting 2011).

Cellular power plants

The cells contain (to a certain extent independent) former bacteria that infected seedless cell precursors one to two billion years ago through the exclusion of air (Seligman 2019, Kramer 2018).

These mitochondria are only inherited from the mother. After fusion with

the egg cell, mitochondria of the sperm (exhausted at the end of their journey) are actively eliminated. Membrane proteins of the paternal mitochondria migrate into their inner structures immediately after fertilisation and trigger degeneration processes there. This activates the egg cell’s clearance mechanisms, and the paternal hara-kiri mitochondria are immediately disposed of. (Zhou 2016)

The programmed suicide of the paternal mitochondria ensures the survival of the new cells. This is because they would suffer damage if similar but slightly different genes were activated. It would then be much more difficult for them to distinguish between friend (belonging to the cell) and foe (intruder) inside the cell. Embryos in which the clearance processes of the male mitochondria are delayed die.

The maternal mitochondria in the egg cell are in a kind of slumber at the time of fusion. Some of them are passed on in their untouched state to cells that later give rise to egg cells in girls. Some maternally inherited mitochondria therefore live forever, as long as they can be passed on from generation to generation.

Mitochondria are 100% Homo-sapiens typical

The cell nucleus genes of humans in Eurasia contain two or more per cent of the genetic information of other early human types (Ding 2014).

Women of African Homo sapiens immigrants to Europe apparently had sex (more or less voluntarily) with (male) Neanderthals. They bore children who, if they survived birth and early infancy, were better able to adapt to the harsh northern climate than their original cousins who had migrated from Africa.

What is really typical of Homo sapiens is therefore not the genome in the cell nucleus, but the circular DNA of the mitochondria. This was only inherited (in a pure line) from Homo sapiens women.

Function of the mitochondria

If you were to compare a cell to a medieval town, the cell nucleus would be the town hall and library. The mitochondria, on the other hand, would resemble a herd of goats grazing peacefully outside the city wall.

These domestic animals do not need to be tethered or fenced in because they are not viable without the genes of the cell nucleus. Mitochondria are determined by the cell nucleus and in turn influence it. However, they also have a certain degree of independence due to their own genes.

Their main function is to provide the cell with energy. They possess a protein that synthesises a high-energy molecule using oxygen: adenosine triphosphate synthetase. Mitochondrial functions are particularly important in places with high-energy consumption, such as at the contact points between cells (synapses), in the intestine (phagocytosis), in rapidly growing tissues and above all in the brain (Rossi 2019).

Mitochondria can deform and fuse (for example, to produce more energy). Or they split into smaller units in preparation for their degradation or to be better transported along nerve axons, for example. This mitochondrial transformation dynamic (between fusion and fission, among other things) is an essential aspect of internal cellular information transfer. Another signalling system is based on changes to its outer membrane, which connects it to other cell organelles: It reacts to signals and, conversely, sends out information (Giaconello 2020).

The interplay between fusion and fission in particular allows flexible adaptation to stress and ensures information transfer between the cells. Disruptions to this functional regulation are very dangerous for the nervous system, muscles and lungs (Chan 2020).

Mitochondria play an essential role not only in life but also in cell death. The permeability of the outer membrane of mitochondria leads to pro-inflammatory signalling during stress and can initiate the (often physiologically necessary) death of cells. Mitochondria play the role of a hub that is needed to switch the immune response on and off (Bock 2020).

The concentration of free radicals, which are produced as waste from mitochondrial metabolism, also represents a signalling system. Free radicals are aggressive and reactive molecules that are produced during chemical processes in which oxygen is also involved (oxidation). They are dangerous not only for the cytoplasmic but also for the mitochondria themselves (Adrian 2013).

Normally, mitochondria look like cucumbers. If the concentration of free radicals is too high (during stress), mitochondria change from this shape

to a donut-like form and eventually clump together.

If the immune system is activated, the concentration of free radicals increases. Conversely, an increase in free radicals leads to a stimulation of the immune response. The concentration of free radicals (within a physiological framework of stress and rest) therefore conveys information (within a physiological range). Consequently, it is not a good idea to eliminate free radicals through medication (e.g. through antioxidants in food supplements).

The function of the mitochondria in the brain is particularly important, as it consumes only 2% of the body’s weight, but 20% of the body’s energy. In the gut, mitochondria are involved in the complex dietary processing of polysaccharides into ’short fatty acids‘ (SCFA), which can be utilised as energy sources in the liver and muscle cells. SCFA improve endurance performance because they maintain glycaemia, mitochondria and the gut microbiome, thus contribute to the success of physical exercise.

Conversely, mitochondria are stimulated by regular, relaxed exercise. SCFA also appear to influence neutrophil leukocyte function and migration, reduce intestinal mucosal permeability, inhibit inflammatory cytokines and control the redox environment in the cell, i.e. they help to delay fatigue during endurance exercise (Mach 2017).

Cytoskeleton and mitochondria

Mitochondria are distributed three-dimensionally in the cytoplasmic space. The cell has a cell scaffold that defines its shape and (depending on its function) enables it to adapt its shape and, if necessary, to move. Mitochondria are connected to these structures of the cell and deform with them under the influence of gravity.

They supply the energy required for movement. A disruption of this functional unit could be involved in the development of cancer, among other things. This is because the cytoskeleton of cancer cells exhibits many malfunctions, which have a particularly detrimental effect on cell division (Duesberg 2005).

Energy channels and mitochondria

The mitochondria are involved in the homeostasis of calcium metabolism. They ensure that the voltage level of the calcium channels in the cell membrane is maintained. Activation of the calcium channels requires close interaction between the mitochondria and the endoplasmic reticulum. Their depolarisation is crucial for the transmission of information (Yamakage 2002, Vallese 2020).

Disturbances in the function of the calcium channels are therefore highly dangerous, especially in the brain.

The different types of calcium channels polarise abruptly, i.e. not as a result of a relatively slow chemical process, but as a quantum physical phenomenon. These ion channels are not switched on or off mechanically, but oscillate according to frequency patterns that are modulated by many influencing factors (Coen 2020).

Just as clocks tick, bridges and skyscrapers vibrate, neuronal networks oscillate. Neuronal oscillations, whose energy comes from mitochondria, are an essential part of the construction of the brain (20). Human genetic studies and more recent ones in animal models suggest that precise control of ion flux (calcium, sodium and potassium) contributes to developmental processes in utero such as neuronal proliferation, migration and differentiation. In particular, energy-consuming processes such as brain folding can be negatively influenced by malfunctioning calcium channels (Smith 2020).

This is followed by an immediate provision of energy, with an avalanche-like spread of the excitation impulses via movement programmes, ultimately resulting in a visible movement that determines the animal’s own consciousness and is seen by external observers (Llinas 2009, Antonakou 2019).

Why does the cell allow these useful animals a certain degree of autonomy?

Mitochondria are closely interwoven with the other cell organelles. They receive control impulses from the cell nucleus and interact particularly

intensively with the endoplasmic reticulum of the cell (Zhou 2020).

However, they were allowed to retain 37 of their original genes. Why were they not completely incorporated, disassembled and digested in the course of evolution and their genetic information completely incorporated into the cell genome?

The reason for their relative self-similarity could be that it is easier for the cell to coordinate numerous decentralised energy devices and thus influence them flexibly as required. A centralised (cell-controlled) cell power plant can be switched on and off in a regulated and controlled manner. However, this is not sufficient for situational adjustments. A centralised control system could cause major damage in the event of a malfunction. If, on the other hand, only one of many decentralised mini-generators were to malfunction, this malfunction could be quickly eliminated (Zhou 2016).

Communication in the cell

Cells form a complex system that has been optimised over billions of years. They consist of many different types of components, each with numerous copies that all work together. They interact and form a high-order functional unit (25). For example, there is direct, intensive communication between the gene activation of the cell nucleus and the circular mitochondrial DNA (Soledad 2019, Ziviani 2016, Dolgin 2019).

The growth and prosperity of mitochondria are closely monitored in the cells. As in a herd of farm animals, dysfunctional, damaged and older specimens are weeded out. The regulatory interplay between mitochondrial tolerance and their orderly degradation is one of the fundamental and most important functions of cellular health (Gkikas 2018, Abrigo 2019).

For example, the mitochondrial hall metabolism in immune cells is altered by signals from the intestinal microbiota, among other things, and can thus initiate and favour inflammatory processes (Chen 2020).

In a healthy immune system, there is a homeostasis of mitochondrial degradation and proliferation as part of the organism’s adaptation to different requirements (Xu 2020).

Excessive degradation (mitophagy) causes various autoimmune disorders or the death of (sometimes essential) cells, such as in Parkinson’s, Alzheimer’s or neurodegenerative diseases (Lezi 2012).

Mitochondria are also involved in the function of the so-called anti-inflammatory reflex: on their outer membrane, mitochondria possess alpha-7 nicotinic-like receptors (nAChR), which play a central role in dampening the immune response (Mogilevski 2019).

These receptors might also be part of a defence system to protect the organelles from mitophagy. Their blockade by nicotine or downregulation of vagus nerve function in the context of stress could lead to increased mitophagy, damage developmental processes in the unborn and newborn and favour cell ageing processes (Dihlmann 2022).

Disturbances of the intracellular ecosystem

Mitochondrial diseases and defects play a special role in ageing processes, the development of cancer, neurodegenerative processes and various other diseases. Toxic side effects of many drugs such as painkillers, antiepileptics, antibiotics, tuberculostatics, but also radiation, heat, environmental toxins and many others can damage mitochondria and cause cellular hypoxia (Ramachandran 2018).

Mitochondrial defects lead to an increased level of free oxygen radicals, H2O2, intracytoplasmic calcium levels and the release of pro-inflammatory cytokines. The resulting immunological excitability favours disorders such as arteriosclerosis, type 2 diabetes, inflammatory bowel syndrome, metabolic syndrome, neurodegenerative diseases and many others.

Brain cells can be particularly easily damaged by the increase in free radicals and the subsequent mitochondrial dysfunction. When the brain’s mitochondria can no longer provide enough energy, neurons break down, which can lead to dementia and many other brain dysfunctions. Drug approaches to improve mitochondrial function have so far been unconvincing. In contrast, many studies have shown that restful exercise, adequate sleep, low stress, sun exposure, good food and meditation have a favourable effect on mitochondrial function and health (Lezi 2012).

The mitochondrial immune response triggered by stress is involved in the

initial antimicrobial defence via the products of free radicals. Excessive activation of this innate immune system leads to auto-inflammatory diseases by damaging the mitochondria. In the cell, an immune tolerance towards the mitochondria must be found, with simultaneous regulation and degradation in the event of disturbances. The long-term health development of the entire organism depends on this interplay of tolerance and aggression. Numerous proteins are involved in the control of immune tolerance, which ensure that healthy mitochondria are clearly differentiated from bacterial invaders, while dysfunctional mitochondria must be cleared away in good time (Grünewald 2019).

Mitochondrial DNA is ten to twenty times more sensitive to unfavourable mutations than the genome in the cell nucleus. The resulting mitochondria, which are recognised as functional and efficient, are cleaved, cut up and disposed of. Excessive or premature mitophagy appears to be one of the main causes of premature ageing, shortened lifespan and neurodegenerative processes (Rougvaux 2018).

The quality of communication between the cell nucleus and the mitochondria appears to be one of the main causes of lifespan and ageing processes in the cell (Miwa 2022).

If the mitochondria are doing well, the body is healthy

The dynamics of mitochondria in all processes of fission and fusion, multiplication and degradation are the basis of human health. They are more than just the cell’s energy suppliers. Via their outer membrane and their connection with other organelles (especially the endoplasmic reticulum), their metabolism is central to the signalling within the cell. It is also indispensable for communication with the surrounding neighbours (Chan 2020, Amesley 2019).

And also for the balance of the game between intracellular tolerance of mitochondria and their disposal protects against disease and premature ageing.

The control of mitochondrial function and its dynamics are not only associated with neurodegenerative diseases, but also with chronic obstructive pulmonary disease (COPD) and pulmonary fibrosis, among others

(Amesley 2019).

It is therefore not surprising that the disruption of mitochondrial metabolism appears to play a significant role in infections such as SARS-CoV-2, especially in connection with drug side effects in the context of overtreatment (polypragamsia). The RNA of SARS-CoV-2 appears to enter the mitochondria and manipulate their function. The situation is similar with mRNA vaccination. As a result, fragmentation can occur in pre-existing mitochondria, which can trigger pro-inflammatory reactions and ultimately lead to a (sometimes fatal) cytokine storm (Singh 2020, Sharma 2022).

> *The unknown unknowns in these complex interrelationships are unlimited. What seems certain, however, is that exercise, rest, sleep, sunlight, low stress and diet have been shown to have a favourable effect on mitochondrial health and longevity (Kramer 2018).*

Chronic exhaustion

More and more people are feeling burnt out. The number of serious physical and mental illnesses is increasing:

Chronic exhaustion, depression, immune disorders, intestinal diseases, long Covid, long vaccination, …, caused by permanent stress, toxins, immune-activating pharmaceutical products, infections, old age, particulate matter, and many more. (see Lit below)

Disruptive effects intensify. They overstimulate the immune system and put it on alert. A relatively minor event is often enough to cause the immune regulation to collapse.

Mitochondrial function is disturbed in all states of exhaustion. As a result, malfunctions develop that lead to cell diseases such as immune overreaction, cancer, nerve cell dysfunction and many more (see Lit below)

If many mitochondria are stressed at the same time, their alarm signals can trigger a general activation of the immune system. Such a ‚cytokine storm‘ causes similarly long-lasting damage as the detonation of a hand grenade in an ammunition depot.

Mitochondrial metabolism is one of the foundations of human health.

If the mitochondria are doing well, a person is healthy. Physical exercise, meditation, sleep, breathing freely, sunlight, low stress and diet have a positive effect on mitochondrial health and lifespan.

Too much medication and environmental toxins are harmful. All attempts to „mechanistically“ fiddle with these highly complex interactions inside the cell are risky.

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Anti inflammatory reflex

- Vagus function (recommended translation: deepl.com)