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Review

Mitochondria, pattern recognition receptors and autophagy under physiological and pathological conditions, including viral infections

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Research on the health of mammals invariably shows how dynamic immunology is and how the role of many elements and immune processes of the macroorganism, developed in the process of evolution in protecting against threats, including infections, is changing. Among these elements conditioning the homeostasis of the macroorganism are mitochondria, PRR receptors (pattern recognition receptors) and the phenomenon of autophagy. In the context of physiological and pathological states in the body, mitochondria perform various functions. The primary function of these organelles is to produce energy in the cell, but on the other hand, they are heavily involved in various cellular processes, including ROS production and calcium homeostasis. They are largely involved in the activation of immune mechanisms during infectious and non-infectious conditions through mtDNA and the mitochondrial MAVS protein. Mitochondrial involvement has been also determined in PRR-related mechanisms as mtDNA has the ability to directly stimulate TLRs. On the other hand, mitochondria are also associated with apoptotic cell death and autophagy.

Key words: mitochondria, pattern recognition receptors, autophagy

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Abbreviations: APC, antigen presenting cells; ATP, adenosine triphosphate; Bak, BCL2-antagonist/ killer 1; Bax, BCL2 Associated X, Apoptosis Regulator; BCl-2, B-cell CLL/lymphoma 2; CARD, caspase requirement domain; Cardif, CARD-containing adapter protein; DAMP, damage/danger-associated molecular patterns; ER, endoplasmic reticulum; FAS, Fas-associated Heath domain; IFN, interferon; IL, interleukin; IPS-I, interferon-β promoter stimulator 1; IRF-3, Interferon regulatory factor 3; IRF3, interferon regulatory factor 3; LGP-2, Probable ATP-dependent RNA helicase DHX58; LPS, lipopolysaccharide; MAC, mitochondria apoptosis-induced channel; MAPK, mitogen-activated protein kinases; MAVS, mitochondrial antiviral-signaling protein; MDA5, melanoma-differentiation-associated gene 5; mtDNA, mitochondrial DNA; nDNA, nuclear genome; NET, neutrophil extracellular trap; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; NLR, Nod-like receptors; NLRP3, NOD-like receptor family pyrin domain containing 3; PAMP, pathogen associated molecular patterns; PINK1, PTEN-induced putative kinase 1; PKB, protein kinase B; PRR, pattern recognition receptors; PTP, permeability transition pore; RIG-I, retinoic-acid-inducible protein 1; RLR, Rig-like receptors; ROS, reactive oxygen species; STING, stimulator of interferon genes; TFAM, mitochondrial transcription factor A; TLR, Toll-like receptors; TRAF3, TNF receptor-associated factor 3; TRIAL, TNF-related apoptosis-inducing ligand; VISA, virus-induced signaling adapter

MITOCHONDRIA AND PHYSIOLOGICAL AND PATHOLOGICAL STATES, INCLUDING VIRAL INFECTIONS

Mitochondria are cellular structures not only responsible for the production of energy necessary for cell metabolism by accumulation of ATP through oxidative phosphorylation, but also the place where genetic material is deposited – methylated mtDNA and unmethylated DNA called the CpG islands (Choi *et al.*, 2020; Liu *et al.*, 2016; West & Shadel, 2017). These organelles are also involved in anabolic and catabolic pathways, including regulation of cell signaling, apoptosis, ROS production, and calcium homeostasis (Chelombitko *et al.*, 2020; Choi *et al.*, 2020; Karmakar *et al.*, 2019; Klein *et al.*, 2020). The role of mitochondria is also related to the immune system, including infectious diseases (Choi *et al.*, 2020; Ren *et al.*, 2020). It has been shown that during infection anabolism is changed into catabolism in immune cells, i.e. in T lymphocytes, including Treg, macrophages M1 and M2 (Chelombitko *et al.*, 2020), neutrophils and mast cells (Chelombitko *et al.*, 2020; Klein *et al.*, 2020), thanks to which mitochondria are involved in molecular mechanisms coordinating energy processes (Chelombitko *et al.*, 2020). Mitochondria in the T effector cells, M1 macrophages and mast cells become fragmented, and in the Treg cells and M2 macrophages they become elongated. This phenomenon determines the regulatory function of mitochondrial morphology, because it is associated with their energy transformation – glycolysis occurs in the T effector lymphocytes and M1 macrophages, and oxidative phosphorylation and β-fatty acid oxidation in the Treg lymphocytes and M2 macrophages (Chelombitko *et al.*, 2020).

Through mtDNA and mitochondrial MAVS, mitochondria generate a dynamic "network" capable of expression and signaling leading to activation of immunological factors, including pro-inflammatory cytokines, e.g. type I IFN, which currently includes not only IFN-α and β, but also δ, ε, κ, θ, ω, λ, τ, ζ and ν – important elements of natural immunity, but also in the process of apoptosis and efferocytosis (Bandurska *et al.*, 2014; Chelombitko *et al.*, 2020; Choi *et al.*, 2020; Cloonan and Choi, 2013; Crouse *et al.*, 2015; Pérez-Hernández *et al.*, 2020; Reczek & Chandel, 2015; Ren *et al.*, 2020). It has also been shown that under physiological and pathological conditions, including viral infections, the constant cleavage and fusion of a number of kinetic proteins in the cell is dependent on the dynamic balance of the mitochondrial network. (Karmakar *et al.*, 2019; Ren *et al.*,

2020). In the case of infections that interact both, directly and indirectly with the mitochondria *via* mtDNA and MAVS proteins, they lead to a change in the mitochondrial environment, which may cause disturbances (Chelombitko *et al.*, 2020; Ren *et al.*, 2020). These organelles, by blocking programmed death receptor 1 – PD-1 or cytotoxic T cell antigen 4 – CTLA-4 signaling, play a role of immune checkpoint inhibitors which prevents depletion of T lymphocytes (Klein *et al.*, 2020). It has been shown (Kang *et al.*, 2007; West *et al.*, 2015) that mtDNA determines activation of many immune mechanisms that influence health, as the transcription factor TFAM binds to mtDNA, stabilizes its structure and influences the number of its copies. In addition, mtDNA is responsible for activation of the innate immunity mechanisms related to the signaling pathways of PRR receptors, as mtDNA molecules, due to the presence in the mitochondria of the CpG islands – elements characteristic for bacterial DNA, are recognized as DAMP (Bandurska *et al.*, 2014; Meyer *et al.*, 2018; Poniewierska-Baran *et al.*, 2018). It has been reported that mtDNA also has the ability to directly stimulate intracellular TLR receptors (Liu *et al.*, 2016; Meyer *et al.*, 2018), which are a marker for cytosolic DNA and endogenous genetic material (Acuña-Castroviejo *et al.*, 2017; Choi *et al.*, 2020). In the absence of direct release of mtDNA through the mitochondrial pores into the cytoplasm, this process may occur via mitochondrial – derived vesicles – MDVs (West & Shadel, 2017).

The role of mtDNA is also important during inflammatory and infectious processes, as it plays a fundamental role in the formation and activation of a functional receptor, which is the NLRP3 inflammasome (Klein *et al.*, 2020; Liu *et al.*, 2016). It has been shown (Rivera-Vargas *et al.*, 2017) that the basic form of NLRP3 is located near the ER, but it migrates to the nucleus after stimulation, which puts NLRP3 in contact not only with the mitochondria and ER, but also with the nucleus. Its special features are the ability to recognize a wide spectrum of PAMP and DAMP patterns (Klein *et al.*, 2020; Liu *et al.*, 2016) and the fact that it is an element in the mtDNA migration to the cytosol and is involved in the signaling of IL-1β and IL-18 by macrophages (Karmakar *et al.*, 2019; Rivera Vargas *et al.*, 2017). NLRP3 inflammasome is also involved in the process of mtDNA release with participation of ATP and the release of mitochondrial reactive oxygen species – mROS. Moreover, oxidized mtDNA shows the ability to directly bind NLRP3 inflammasome, which enhances its activation (Cloonan & Choi, 2012; Liu *et al.*, 2016). Activation of the NLRP3 inflammasome by mtDNA also occurs due to the presence of bacterial LPS and ATP (Klein *et al.*, 2020; Nakahira *et al.*, 2011).

The role of mitochondria through mtDNA is noticeable in the activation of a pathway associated with the interferon gene stimulating protein STING, which is a key element in the induction of an immune response in viral infections (Ohta & Nishiyama, 201; Ren *et al.*, 2020; Scott, 2009). STING, belonging to the family of ER-related signaling molecules (Hu *et al.*, 2018; Ohta & Nishyama, 2011), is necessary for the production of type I IFN in fibroblasts, macrophages and dendritic cells in response to cytoplasmic dsDNA, as well as viral DNA, RNA and DNA of intracellular bacteria (Choi *et al.*, 2020; Hu *et al.*, 2018; Ohta & Nishyama, 2011; Ren *et al.*, 2020). The incorrect activation of the STING pathway may lead to increased inflammation caused by type I IFN, as well as apoptosis, and even necroptosis and pyroptosis (Luo *et al.*, 2017). The responses of mitochondrial metabolites also influences the killer functions of macrophages and thus enhances innate immunity (Ren *et al.*, 2020; Sancho *et al.*, 2017). TFAM induced by infection with a herpesvirus causes the loss of stability of the mtDNA molecule, which in turn leads to the release of mtDNA fragments into the cytoplasm (West *et al.*, 2015). These particles trigger a series of messengers in the cytoplasm of the cell, which leads to activation of the STING gene pathway that stimulates kinase 1, which in turn initiates a cascade leading to activation of IRF-3, and which then induces synthesis and activates type I IFN (West *et al.*, 2015) – an element of the innate antiviral immunity (Meyer *et al.*, 2018; Piotrowska *et al.*, 2016; Ren *et al.*, 2020; West *et al.*, 2015).

Antibacterial properties of mtDNA were also recorded (West *et al.*, 2015), resulting from cooperation with eosinophils and Th17 lymphocytes (Acuña-Castroviejo *et al.*, 2017; Chelombitko *et al.*, 2020). In the case of mtDNA of eosinophils, after their stimulation by LPS of Gram-negative bacteria, mechanisms similar to the NET network occur (Acuña-Castroviejo *et al.*, 2017). On the other hand, in the case of mtDNA of Th17 lymphocytes, its effect is manifested by the ability of mtDNA to bind to IL-26 (Acuña-Castroviejo *et al.*, 2017), which leads to stimulation of IFN-secretion by dendritic cells (Acuña-Castroviejo *et al.*, 2017). MtDNA may also bind to natural immune peptides, e.g. cathelicidines – LL37, which leads to stimulation of monocytes and macrophages towards the synthesis of the pro-inflammatory cytokine TNF-α (Acuña-Castroviejo *et al.*, 2017). Summary of the role of mtDNA in a macroorganism is presented in Fig. 1.

The stimulation with PAMP molecules of the MAVS protein (also referred to as VISA, Cardif or IPS-I) (Popkov *et al.*, 2016), which is located on the outer surface of the mitochondrial membrane (Meyer *et al.*, 2018; West and Shadel, 2011, similarly to mtDNA, leads to the activation of many elements of immunity (Huang *et al.*, 2015; Poyton *et al.*, 2009; Ren *et al.*, 2020), especially components of the innate antiviral response (Meyer *et al.*, 2018; Ren *et al.*, 2020; West and Shadel, 2011). It has been reported that the abnormally functioning MAVS protein is associated not only with the occurrence of hepatitis A, B and C virus infections, cytomegalovirus, reproductive and respiratory syndrome virus and vaccinia virus, but also with increasing inflammation in the course of non-infectious diseases in the fatty liver dis-

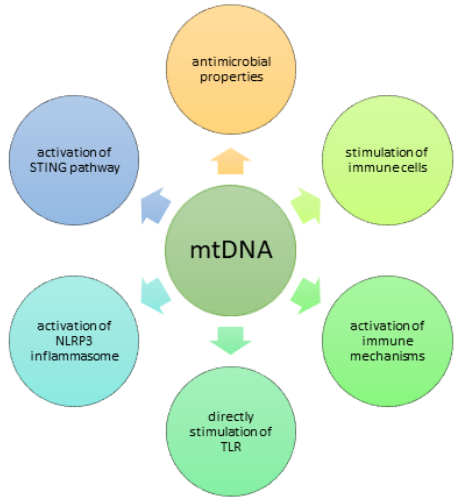

Figure 1. The role of mtDNA under physiological and pathological conditions.

ease and systemic lupus erythematosus (Cloonan & Choi, 2012; Ren *et al*., 2020). It has been shown that the Cardif protein, also present in the cytosolic receptors RIG-I and MDA5, is involved in detection of genetic material of viruses not only at the stage of their infection, but also at the stage of their replication (Monlun *et al*., 2016; Scott, 2009). This applies in particular to the RNA viruses characterized by high variability (Millis *et al*., 2017). It should be added that RIG-I receptors recognize not only the 5 'phosphorylated ssRNA viruses with positive and negative polarity (Liu *et al*., 2016), but also dsDNA viruses (Monlun *et al*., 2016), including paramyxoviruses, the influenza virus and Japanese encephalitis virus, where such an infection induces the synthesis of INFs (Hu *et al*., 2018). On the other hand, MDA5 receptors and the mitochondrial MAVS proteins interacting with them are key receptors in immunity against picornaviruses (Hu *et al*., 2018), although they also bind the viral genetic material of dsRNA (Liu *et al*., 2016). It was recorded that the length of the viral genetic material chain determines participation of an appropriate receptor. RIG-1 tags bind relatively short fragments of dsRNA (21-27 nucleotides in length), and the MDA5 tag inclines towards the recognition of fragments longer than 2 kbp (Monlun *et al*., 2016). Binding of RIG-I and MDA5 receptors with the mitochondrial protein MAVS also triggers a reaction cascade that activates the transcription factors IRF3 and NF-ϰB, which leads to the synthesis of IFN-β (Khan *et al*., 2016; Vazquez & Horner, 2015). Activity of the MAVS protein is regulated by various mechanisms arising during the antiviral response, in which the mRNA level of this protein is maintained at an appropriate level due to the negative ROS feedback (Ren *et al*., 2020; Xu *et al*., 2012). It has been reported that during viral infections, formation of large MAVS aggregates occurs through the produced "prion-like" fibrils, which have a strong stimulating effect on the cytosolic IRF3, showing the ability to transform endogenous MAVS into functional aggregates (Hou *et al*., 2011). Studies have shown (Hu *et al*., 2018) that the DNA of adenoviruses and herpesviruses, i.e. the Epstein-Barr virus and herpes simplex virus 1, induce INF-β expression through RIG-1 stimulation (Hu *et al*., 2018). It was reported (Hu *et al*., 2018) that the DNA-dependent RNA polymerase III (Pol-III) of adenoviruses and HSV-1, responsible for the synthesis of 5'-triphosphate RNA from cytoplasmic poly (dA-dT) DNA, is an intense mediator in the signaling reaction associated with the RIG-1 receptor which is in part the role of these receptors in detecting and neutralizing RNA and DNA viruses (Hu *et al*., 2018). It was also reported that activation of RIG-1 and MDA5 leads to initiation of reactions leading to activation of NF-ϰB transcription factors and production of pro-inflammatory cytokines, as well as activation of IRF and induction of type I IFN synthesis (Monlun *et al*., 2016). Moreover, the process of oligomerization of the CARD domain of the RIG-1 receptor enables CARD to bind to the mitochondrial MAVS protein, which activates the tumor necrosis factor receptor type 1-associated death domain – TRADD protein (Monlun *et al*., 2016). This condition results inactivation of two alternative signaling pathways, i.e. the TRAF3 protein-dependent pathway, which ends with the synthesis of type I IFN, and the other FAS protein-dependent pathway, leading to activation of inhibitor of ϰB which undergoes phosphorylation and destruction in the proteasome, and leads to the release of NF-ϰB, which strongly activates the synthesis of pro-inflammatory cytokines after translocation to the nucleus (Monlun *et al*., 2016). Summary of the role of the MAVS protein in a macroorganism is presented in Fig. 2.

Involvement of mitochondria is important in the early phase of viral infection due to interactions of inflammatory mediators reacting with receptors that recognize the PRR patterns, which leads to activation of signaling pathways, e.g. transcription factor NF-ϰB, MAPK and PKB (Ren *et al*., 2020). Under these conditions expression and activity of coactivators and transcription factors, such as Peroxisome proliferator-activated receptor gamma coactivator1-α), Nuclear respiratory factor 1 and Nuclear factor (erythroid-derived2-like 2) (Cherry & Piantadosi, 2015; Ren *et al*., 2020), are increased which results in activation of the defense process of apoptosis (Ren *et al*., 2020). During a viral infection, if the signal comes from outside the cell, the ligand binds to the membrane receptor and, as a result, activates caspases in the external and internal apoptotic pathway and cell death (Deptula *et al*., 2006; Niedźwiedzka-Rystwej & Deptula, 2009; Ren *et al*., 2020). Moreover, in the case of the intrinsic apoptotic pathway, mitochondria are direct receivers of the pro-apoptotic signals from inside the cell (Ren *et al*., 2020). In the case of the extrinsic apoptotic pathway, it is triggered by ligand binding to death receptors, which include CD95/FasL, the tumor necrosis factor receptor TNF-α, and receptor 1 and 2 related to TNF-dependent receptor from apoptosis – TRIAL (Hu *et al*., 2018), while in the internal apoptotic pathway these reactions occur through mitochondrial PTP mega canals, located in the area where both mitochondrial membranes meet, and therefore mitochondria are key elements in these responses (Jóźwiak & Marczak, 2006; Ren *et al*., 2020).

The defensive role of mitochondria in the macroorganism is also realized through the process of apoptosis, which occurs as a result of various types of stimuli, including oxidative stress, DNA damage, electrolyte transport disturbances, increase in calcium ion concentration and increase in ROS concentration in the cytoplasm of the cell (Chelombitko *et al*., 2020; Cloonan & Choi, 2013; Jóźwiak & Marczak, 2006). Activation of apoptosis also occurs because of a change in the membrane potential and disruption of the continuity of the mitochondrial membrane which is observed during viral infections (Chelombitko *et al*., 2020; Cloonan & Choi, 2013; Ren *et al*., 2020). It has been shown that after opening the PTP mitochondrial mega canals, one of the elements permitted through the membrane is cytochrome *c*, which after getting into the cytosol is combined with apoptotic

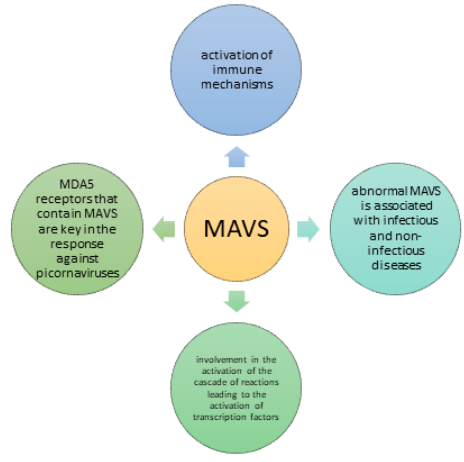

Figure 2. The role of the MAVS protein under physiological and pathological conditions.

protease activating factor 2 and procaspase 9, the effect of which is the so-called apoptosome whose role is to mobilize caspase 9, initiating the cascade of changes leading to cell death (Jóźwiak & Marczak, 2006). Moreover, when caspase 8 is activated in both, the internal and external apoptotic pathways, the permeability of the mitochondrial membrane and the release of cytochrome c is increased, which occurs by opening not only PTP but also MAC channels that arise at early stages of programmed cell death (Cloonan & Choi, 2013; Liu *et al*., 2014; Peixoto *et al*., 2011). It has been proven (Łabędzka *et al*., 2006) that MAC channels are regulated by proteins of the Bcl-2 family which are the group of the most known proteins regulating the apoptotic pathway, among which there are both, the proteins that inhibit this process and pro-apoptotic ones, i.e. the Bax and Bak proteins. Activation of these proteins leads to the release of cytochrome c and the apoptosis inducing factor (Scott, 2009).

It has been shown that during a viral infection, synthesis of factors affecting apoptosis occurs due to "unfolding" of specific strategic mechanisms by viruses aimed at avoiding the immune response and releasing progeny particles during infection (Chmielewska *et al*., 2017; Cloonan & Choi, 2013; Łabędzka *et al*., 2006; Ren *et al*., 2020). This is the case for the Epstein-Barr virus, African swine fever, cytomegalovirus, hepatitis B and C virus, as well as PRRSV and rotavirus, as they have, inter alia, the ability to synthesize caspase inhibitors that inhibit apoptosis, including ability to recruit Bax proteins to mitochondria (Galluzil *et al*., 2008; Ren *et al*., 2020). However, in the case of the herpes simplex virus and the human papillomavirus, both inhibitory and stimulating effects on apoptosis occur (Halford *et al*., 2001; Miszczak, 2013). In the case of a rabies virus infection, it was shown that the M protein of this virus, acting on mitochondria, induces mitochondrial programmed cell death at the late stages of infection through caspase-dependent and independent pathways (Xu *et al*., 2012), which was also observed for rotavirus infections (Ren *et al*., 2020). Hence, it can be concluded that the role of mitochondria in the process of apoptosis in viral infections, through mitochondrial cleavage and then their fusion, leads to enhancement of the immune status of the macroorganism and the virus removal, although this process may also affect the replication of viruses (Cloonan & Choi, 2013; Ren *et al*., 2020). It has been reported that if apoptosis occurs at the viral replication stage, the process is fruitless, and if it is related to the virus entry into the cell, it is effective (Ren *et al*., 2020). It has been also described that syncytial viruses, including the Newcastle disease virus, cause cell death by formation of syncytium - multinucleated cells, and in the case of the Coxsackie B virus infection, extracellular microbubbles are released (Ren *et al*., 2020), and the Epstein-Barr virus causes migration of cells leading to tumor formation as a result of disturbances in the dynamics of mitochondria (Ren *et al*., 2020).

The role of mitochondria is also related to the expression of nuclear genes, and then differentiation of stem cells, and thus by affecting the immune system mitochondria participate in the inflammatory response and diseases of the infectious and non-infectious background (Chelombitko *et al*., 2020; Poyton *et al*., 2009; Ren *et al*., 2020; Tokarz and Blasiak, 2014). Their role was recorded, inter alia, in non-infectious diseases, e.g. non-alcoholic fatty liver, as a result of increased mitochondrial fatty acid oxidation (Murphy & Hartley, 2018). Moreover, it is possible to use mitochondrial therapies in the treatment of viral (Choi *et al*., 2020) and parasitic infections caused by *Trypanosoma (T.) cruzi*, *T. brucei* and *Plasmodium falciparum* protozoa, as well as in non-infectious diseases, such as retinal dysfunction and heart failure (Murphy & Hartley, 2018).

Mitochondria are associated with such processes as aging, as described, among others, in the Mitochondrial Free Radical Theory of Aging (Reczek & Chandel, 2015; Sanz & Stefanatos, 2008; Tokarz & Blasiak, 2014), which assumes that the accumulation of ROS produced by these organelles causes damage to nucleic acids and proteins (Bernhardt *et al*., 2014; Chang *et al*., 2015; Chelombitko *et al*., 2020) and leads to mutational changes in mtDNA (Chelombitko *et al*., 2020; Ren *et al*., 2020). It is assumed that mutations in the mitochondrial genome and oxidative damage in cellular components significantly affect the impairment of a macroorganism's functions, including defense, and this also initiates the aging process (Molnar & Covacs, 2018). It has been shown that enzymatic proteins play an important role in regulation of the antioxidant system of the macroorganism, including mitochondria which catalyze transformation of ROS into less toxic compounds (Choi *et al*., 2020; Karmakar *et al*., 2019; Klein *et al*., 2020; Ren *et al*., 2020). These substances (Choi *et al*., 2020) also determine the viability of the macroorganism, because it has been shown that inactivation of one of the five mitochondrial superoxide dismutase in *Caenorhabditis elegans* results in prolonged viability of this nematode (Chang *et al*., 2015). In these studies (Chang *et al*., 2015), it was also observed that only certain mutations within the enzyme-forming subunits in the mitochondrial electron transport pathway reduced the viability of *Caenorhabditis elegans* (Chang *et al*., 2015). Also, mutants of this animal with various levels of viability are silenced for relevant genes in the mitochondrial pathway, which causes disturbances in nutrition and defecation, as well as slower growth and reduced mass of this nematode (Chang *et al*., 2015). Summing up, the role of mitochondria in this matter is not obvious, being a kind of a double-edge sword. Research conducted on *Drosophilia melanogaster* and rodents from the Muridae family also confirm impact of disturbances in the mitochondrial electron transport pathway on the lifespan of these animals (Tokarz & Blasiak, 2014). In the case of mice with a mutation in the mitochondrial gamma polymerase gene, a decrease in their viability was recorded (Tokarz & Blasiak, 2014). Moreover, studies conducted (Pérez-Hernández *et al*., 2020) on mitochondria during initial stage of innate immunity with participation of fumarate, a mitochondrial metabolite, had shown that its use caused an immediate effect of mitochondrial activation both in the human monocytes and in the organism of *C. elegans*, which was accompanied by their fusion, polarization and the approach of intra-mitochondrial folds, as well as the influx of calcium into the cytoplasm. Moreover, in the case of *C. elegans*, mitochondrial fusion in these animals was accompanied by an increase in resistance to an *Escherichia coli* infection (Pérez-Hernández *et al*., 2020).

The accumulation of mutations within mtDNA, disrupts the functioning of the mitochondria, which may contribute to the initiation of processes resulting from their cleavage and fusion, which results in inflammation, metabolic syndromes and heart diseases, neurodegenerative diseases and neoplasms (Gregorczyk, 2017; Klein *et al*., 2020; Ren *et al*., 2020; Shefa *et al*., 2019). It has been shown that insufficient intensification of the process of removing damaged mitochondria in the mitophagy process (Meyer *et al*., 2018) results in accumulation of ROS

in the cell, which leads to formation of defects in the mitochondrial and nuclear genetic material, which then leads to formation of neoplastic changes (Meyer *et al*., 2018; Ren *et al*., 2020; Shefa *et al*., 2019). In the case of insufficient intensification of mitochondrial "utilization", which is necessary at the initial stages of carcinogenesis, this process remains also an indispensable element in the further stages of oncogenesis (Shefa *et al*., 2019). It has been described that the process of carcinogenesis may be supported by ROS as these compounds affect the mitochondria and the cell nucleus, and thus affect various processes in the cell, including DNA damage, inactivation of suppressive proteins, or even activation of proto-oncogenes and cell proliferation (Tokarz & Blasiak, 2014; Czarnecka *et al*., 2011; Klein *et al*., 2020).

It has been observed that the resulting mtDNA damage has a significant impact on the events leading to an increase in ROS production, which in turn increases the oxidative stress and leads to the activation of signaling pathways towards increased proliferation and formation of the neoplastic process (Craven *et al*., 2017). These mtDNA changes can occur as a result of various events, including mutations in mtDNA coding sequences, or changes in the number of mtDNA copies (Craven *et al*., 2017). These predilection mutational changes in mtDNA are observed within the D-loop (D-loop or Displacement loop), which is conditioned by the presence of a triple-stranded structure (Craven *et al*., 2017). It should be emphasized that the loop-D sequences play an essential role in the process of mtDNA replication and transcription, and also play a role in its stabilization (Tokarz & Blasiak, 2014). "Errors" in the mtDNA structure may also arise as a result of instability of mtDNA microsatellite sequences and as polymorphic changes in the D loop, mainly in the poly-C sequence at positions 303-309 (Tokarz & Blasiak, 2014), while changes in microsatellite sequences are found primarily in the form of insertions and deletions (Craven *et al*., 2017), which were recorded in cancer of the stomach, breast, esophagus, glioblastoma multiforme, ovarian cancer, prostate cancer – Prostate Intraepithelial Neoplasia, lung and head and neck cancers (Craven *et al*., 2017). The Leber's hereditary optic neuropathy is also one of the diseases associated with point mutations in mtDNA (Tońska *et al*., 2018).

It has been reported that changes damaging mtDNA in the mitochondrial apoptosis pathway lead to increased survival of cells entering the carcinogenic pathway, as well as increased resistance to anticancer drugs (Tokarz & Blasiak, 2014). Studies by Huang and others (Huang *et al*., 2015) indicate that by reducing expression and oligomerization of pro-apoptotic Bak proteins located in the mitochondria, it is possible to induce apoptosis in neoplastic cells by treating them with NPM – N-(l-pyrenyl) maleimide, which shows a cytotoxic effect on neoplastic cells (Huang *et al*., 2015). It should be added that many oncogenic viruses encode homologues of anti-apoptotic Bcl-2 proteins, which disrupt the functioning of the mitochondria. As a result, neoplastic processes induced by oncogenic viruses are initiated (Cavallari *et al*., 2018). It has been proven that the Bcl-2 protein regulates not only the energy balance of the cell by influencing the electron transport chain and mitochondrial inner membrane complexes, but also the mitochondrial Ca^{2+} ion economy and ROS production (Cavallari *et al*., 2018). It is assumed that the discovery of the possibility of artificial induction of the apoptotic pathway, e.g. *via* mitochondria, including their oxidative phosphorylation which is an important component for cancer cell survival or ROS production, is a promising target for the development of new, effective and non-invasive anti-cancer therapies (Murphy & Hartley, 2018). Disturbances in the mitochondria can also cause neurodegenerative diseases, such as Alzheimer's, Parkinson's, Huntington's, and Amyotrophic lateral sclerosis (ALS) (Bernardini *et al*., 2016; Murphy & Hartley, 2018; Ren *et al*., 2020). It has been shown that changes in mtDNA registered in the cells of the brain, heart and skeletal muscles in humans (Tokarz & Blasiak, 2014) may be the cause of muscle weakness, neurological diseases or lactic acidosis (Chang *et al*., 2015; Durhuus *et al*., 2014). It has been reported that as many as 72-85% of various pathological conditions may be the cause of mitochondrial abnormalities, including mutations in the nDNA, as most mitochondrial proteins are encoded by nDNA (Pronicka *et al*., 2008; Tońska *et al*., 2018).

It is worth adding that the phenomenon of heteroplasmy – the presence of more than one type of mtDNA, is characterized by the presence of genetic material with the correct sequence and that with defective, burdened with mutational changes (Tońska *et al*., 2018), which usually cause disease symptoms with 60–80% of defective mtDNA molecules. These genetic conditions negatively affect the energy processes taking place in the cell in the mitochondria, which have been identified in relation to diseases resulting from deficits in the respiratory chain (Piętka *et al*., 2008). It has been reported that the underlying cause of disease in children with the Leigh's syndrome is deficiency of the surfeit locus protein 1 which participates in the assembly of complex IV of the respiratory chain running in the mitochondria (Piętka *et al*., 2008). In the course of this disease, apparently healthy children begin to experience many disease symptoms less than a year after birth due to progressive encephalopathy, which leads to death before reaching 4 years of age (Piętka *et al*., 2008). Moreover, there are assumptions that disturbances in the delivery of ATP which is produced in the mitochondria to the brain cells may contribute to an increased susceptibility to migraine attacks (Fila *et al*., 2018). One of the common pathologies closely related to mitochondrial dysfunction in humans is the Lefora's disease which manifests itself in progressive myoclinic epilepsy, ataxia, psychosis and dementia, which may also occur as a result of pathological activation of the p53 protein (Durhuus *et al*., 2014). Impairment of mitochondrial function in humans is also associated with formation of insulin resistance, as reduced biogenesis of mitochondrial proteins and inhibition of oxidative protein activity leads to accumulation of fatty acids, including diacylglycerols and ceramides that can inhibit insulin signaling (Montgomery & Turner, 2015; Murphy & Hartley, 2018).

Also, inhibition of certain processes in the electron transport pathway was found in a study of mutations within individual subunits involved in cellular respiration (Chang *et al*., 2015). This process occurs as a result of mitophagy, which is the process by which mitochondria are degraded in the autophagolysosomes. This process is initially characterized by the fact that mitochondria are fragmented by the dynamin related protein 1 (Hamacher-Brady & Brady, 2016).The resulting new "organelles" are divided into polarized "structures" that can undergo fusion and those whose membranes are depolarized and eventually degraded during mitophagy (Bednarczyk *et al*., 2016). This process is regulated by the PINK1 kinase and ubiquitin ligase paracetase, hence in the "healthy" mitochondria the level of PINK1 is kept low, which prevents organelles from entering the path of mitophagy. It should be added that at the initial stage of

mitophagy, PINK1 recruits on the surface of mitochondria the Parkin protein found in the cytosol, which leads to activation of the E3 Parkin ligase and involvement of a number of additional proteins in the mitophagy process which play an important role in the initiation of this phenomenon (Lenart, 2017). It is worth noting that mitophagy is a process that affects cells in the period of adaptation to their functions, e.g. it concerns the removal of mitochondria in mature erythrocytes, which is an element necessary for the transport of hemoglobin by these cells (Piotrowska & Bartnik, 2014). An example of mitophagy is also the process of removing paternal mitochondria from a fertilized egg, which further explains the inheritance of mtDNA in the maternal line (Piotrowska & Bartnik, 2014). Disturbances in mitochondrial dynamics in the field of electron transport result, among others, in fission of mitochondria, mitophagy and apoptosis of cells, including the nerve cells, that are recorded in viral infections (Ren *et al*., 2020). These processes suppresses the immune response and weakens the immune status of the organism (Ren *et al*., 2020).

PRR RECEPTORS AND AUTOPHAGY VERSUS PHYSIOLOGICAL AND PATHOLOGICAL STATES, INCLUDING VIRAL INFECTIONS

Among elements that affect macroorganism's hoomeostasis, including the immune system, and thus are important under physiological and pathological states, are pattern recognition receptors (PRR), whose task is to recognize molecular patterns of pathogens – PAMP, but also patterns associated with the danger – DAMP (Deptuła *et al*., 2006). PRR markers are divided into: – secreted receptors (opsonins, collectins, phicolins and pentaxins), – receptors initiating phagocytosis – the so-called endocytic (transmembrane proteins mediating the internalization of pathogens, mannose receptor and scavenger receptors) – and signaling receptors (Deptuła *et al*., 2006). The latter markers include transmembrane TLR receptors and typical cytosolic receptors, which include RLR, NLR, and functional receptors – inflammasomes (Niedźwiedzka-Rystwej *et al*., 2016).

TLR receptors are present on the cell membrane, but also inside the cell, where they are responsible, among others, for the detection of components of microorganisms, including viruses (Thompson & Locarnini, 2007). In the case of infectious agents, including viruses that "penetrated" the immune barrier created on the cell membrane, conditioned by TLR, at a later stage intracellular RLR receptors are mainly involved in antiviral defense, including RIG-I, MDA5 and LGP2 (Cloonan & Choi, 2013), NLR e.g. NOD2 and the NLRP3 inflammasome (Chen & Ichinohe, 2015; Jacobs & Domania, 2012; Śliwa-Dominiak & Deptuła, 2011; Śliwa-Dominiak *et al*., 2014). Among intracellular TLRs that detect viral PRR patterns, including patterns in the form of unmethylated DNA, the TLR3, TLR7, TLR8 and TLR9 receptors should be mentioned (Thompson & Locarnini, 2007), as well as RLR tags (RIG-1, MDA5, LGP2) that recognize viral ssRNA, dsRNA and its synthetic analog – poly (I: C) (polyriboinosyl: polyribocytidyl acid) and NLR tags, including NOD and NLRP3, that recognize mainly viral dsRNA (Ren *et al*., 2020; Śliwa-Dominiak & Deptuła, 2011). Intracellular TLR3 receptors have been shown to recognize dsRNA viruses, and TLR 7 and 8 recognize ssRNA viruses, while TLR9 recognize viral ds-DNA, which contains unmethylated DNA together with CpG islands (Xagorari & Chlichlia, 2008).

Intracellular TLRs 3, 7, 8 and 9, after recognizing viral genetic material, trigger the synthesis of type I IFN which is immunostimulatory and in particular induces antiviral immunity (Xagorari & Chlichlia, 2008). It has been also reported that TLR3, recognizing purified dsRNA from reovirus-1 and poly (I: C), causes the synthesis of IFN-β, IL-12, IL-6 and TNF-α (Hewson *et al*., 2005). In turn, by detecting viral ssRNA, TLR7 and TLR8 activate separate signaling pathways that contribute to formation of various phenotypes of immune system cells (de Marken *et al*., 2019). Studies have shown (de Marken *et al*., 2019) that signaling through TLR7 increases expression of the transcription factor fos-1 (FOS1), which decreses production of IL-27 and TNF-alpha, and inhibits the type I IFN response (de Marken *et al*., 2019). In addition, in the case of TLR9, these markers recognize unmethylated CpG islands commonly found in viral and bacterial DNA and activate plasmacytoid dendritic cells (pDCs) and other DC types, as found for infections with Murine cytomegalovirus, Herpes simplex virus 1, Herpes simplex virus 2 and poxviruses. It was also reported that the varicella zoster virus and cytomegalovirus, via the TLR9, trigger production of IFN-α (Lester and Li, 2014). On the other hand, cytosolic RLR receptors, after recognizing viruses, activate NF-κB and IRF-3, which leads to production of IFN type I and proinflammatory cytokines, such as: IL-1 and TNF-α (Cloonan & Choi, 2013; Śliwa-Dominiak *et al*., 2014). It has been shown that production of type I IFN induced by these receptors stimulates differentiation, maturation and migration of APC, proliferation of natural killer cells, as well as increased expression of MHC class I receptors on immune cells, resulting in activation of the immune response and increase in immunity (Cloonan & Choi, 2013; Śliwa-Dominiak & Deptuła, 2011; Śliwa-Dominiak & Deptuła, 2011a).

It has been shown that during viral infections, RLR receptors can be blocked by viruses which reduces expression of the type I IFN genes and lowers immunity, and thus weakens the immune response (Cloonan & Choi, 2013; Śliwa-Dominiak & Deptuła, 2011; Śliwa-Dominiak & Deptuła, 2011a). Such a state may arise during the initial phase of viral infection, during transmission of signals activating expression of mainly type I IFN, that involves many viral proteins, which has been observed, among others, in the case of hepatitis A, B and C viruses, influenza A, vaccinia, Ebola and rabies (Ramos & Gale, 2011).

It has been also reported that other intracellular markers – NLR, affect the immune status by reacting with PAMP and DAMP markers (Chen & Ichinohe, 2015; Poniewierska-Baran *et al*., 2018; Śliwa-Dominiak & Deptuła, 2011; Śliwa-Dominiak & Deptuła, 2011a). It has been reported that stimulation of NLR receptors by viral PAMP markers leads to activation of caspase-1 and synthesis of mature forms of IL-1, which induces inflammatory responses, including activation of anti-apoptotic signaling mediated by IL-2R, and stimulates effector lymphocytes and regulatory, as well as B lymphocytes (Tokarz-Deptuła *et al*., 2011). Moreover, stimulation of viral NLR receptors also leads to the release of IL-18 which promotes activity of the Th2 lymphocytes and enhances synthesis of INF-γ and cytotoxicity of natural killer cells (Tokarz-Deptuła *et al*., 2011). It has been shown that under the influence of viral ssRNA, NLR markers bind to IPS-1 which also strongly activates synthesis of type I IFN (Crouse *et al*., 2015). During a viral infection, NLRs also affect the immune system of the macroorganism by activating the mitochondrial MAVS protein

Table 1. Signal receptors activated in infectious states and their function.

Receptor group	Receptor type	Recognized genetic material	Consequence of stimulation
TLR	TLR3	dsRNA	activation of IFN type I; after recognition of the reovirus dsRNA and poly (I: C), TLR 3 causes the synthesis of IFN-β, IL-12, IL-6, TNF-α
	TLR7 TLR8	ssRNA	activation of IFN type I; TLR 7 and TLR8 activate signaling pathways that lead to different phenotypes of immune cells; TLR7 increases expression of FOS1 which causes a decrease in the production of IL-27, TNF-α and inhibition of the response with IFN type I;
	TLR9	dsDNA CpG islands	activation of IFN type I; activation of pDC and other types of DCs; affects the production of IFN-α;
RLR	RIG-I MDA5 LGP2	ssRNA dsRNA poli(I:C)	activation of NF-κB and IRF-3, leading to the synthesis of type I IFN, IL-1, TNF-α;
NLR	NOD2 NLRP3	dsRNA	PAMP stimulation leads to caspase-1 activation and IL-1 synthesis; NLR stimulates the secretion of IL-18; MAVS and mitophagy activation; NLRP3 converts procaspases into caspases and, through IL-1β and IL-18, initiates inflammation and pyroptosis in infected cells

and activating mitophagy (Chen & Ichinohe, 2015; Mills *et al*., 2017; Ren *et al*., 2020). It has been also described that the activated intracellular marker - the NLRP3 inflammasome, converts procaspases into active caspases through its CARD domain, and through caspase-1 initiates a pro-inflammatory response through IL-1β and IL-18 and death of infected cells by pyroptosis, taking part in health and disease (Niedźwiedzka-Rystwej *et al*., 2016).

The signal receptors involved in infectious states in the macroorganism and the consequences of their activation are summarized in Table 1.

An important process conditioning proper homeostasis and immune status of the organism is the phenomenon of autophagy which is important for the macroorganism especially in the case of nutrient deficiency during infection (Dinkins *et al*., 2015; Tal and Iwasaki, 2011; Tokarz-Deptuła *et al*., 2011), as well as the neoplastic process (Dinkins *et al*., 2015; Niedźwiedzka-Rystwej & Deptuła, 2009, Świderek & Strządała, 2013). This process is indispensable when it is necessary to degrade one's own cellular components, which is recorded under physiological states in the mammary gland of mammals during the "dry" period (Lee *et al*., 2007; Niedźwiedzka-Rystwej & Deptuła, 2009; Tal & Iwasaki, 2011). During infection, this occurs as a result of inhibiting of the secretion of pro-inflammatory IL-1β and limiting the effects of inflammatory reactions, that inhibits the formation of tissue damage, which is part of the maintenance of proper homeostasis of the organism, and thus good immune status (Dinkins *et al*., 2015; Tokarz-Deptuła *et al*., 2011).

The autophagy process is carried out by monocytes, B lymphocytes, dendritic cells and epithelial cells (Niedźwiedzka-Rystwej & Deptuła, 2009). It is associated with TLR receptors (Cadwell *et al*., 2008; Lee *et al*., 2007; Niedźwiedzka-Rystwej & Deptuła, 2009), as they play a key role in antigen presentation and pathogen degradation by presenting internalized viral ligands to pDC cells (Śliwa-Dominiak & Deptuła, 2011; Tal & Iwasaki, 2011). This condition leads to the synthesis of pro-inflammatory cytokines, including type I IFN and chemokines (Tal & Iwasaki, 2011). It has been proven that the ssRNA viruses, e.g. the Sendai virus or vesicular stomatitis, are recognized through intracellular TLR7 during autophagy, thanks to which the viral RNA is enclosed inside the lysosomal vesicle (Tal & Iwasaki, 2011). It has been observed that during autophagy of single- and double-stranded RNA viruses in the lysosomal vesicle, secretion of IFN-α is stimulated (Cadwell *et al*., 2008; Tal & Iwasaki, 2011; Nakai *et al*., 2007). NLRs are also involved in the process of autophagy during viral infections (Jacobs & Domania, 2012).

During mitochondrial autophagy – mitophagy, accumulation of reactive oxygen species – ROS in the cell is an important indicator assessing the state of homeostasis and antiviral immunity (Tal & Iwasaki, 2011). It has been shown that ROS accumulation influences carcinogenesis because these compounds not only initiate mutations within the host cell DNA, but also inactivate mitochondrial functions and inhibit pro-apoptotic processes, leading to the development of neoplastic diseases (Dinkins *et al*., 2015; Niedźwiedzka-Rystwej & Deptuła, 2009; Reczek & Chandel, 2015). Mitochondrial autophagy – mitophagy is also associated with hypoxia resulting from ATP deficiency and pathological activation of the mitochondrial protein BCL2/adenovirus E1B 19 kDa protein–interacting protein 3 (Świderek & Strządała, 2013).

The process of autophagy, enabling access to nutrients stored in the tumor cell structures, causes the development of tumor resistance to anti-angiogenic therapy (Świderek & Strządała, 2013) and, depending on the type and genetic conditions, may protect the macroorganism against neoplasms (Choi, 2012; Kimura *et al*., 2013). This is due to the fact that if the elements of oxidative stress – ROS are removed, autophagy contributes to tumor elimination, while when this stress is prevented, it causes an increase in the activity of oncogenes and tumor growth. The involvement of autophagy has been also recorded in the Parkinson's and Alzheimer's disease, as in these diseases, e.g. due to damage to the mitochondria, autophagy is impaired (Pickerell *et al*., 2015). It has been also described that under conditions of weakened autophagy, the cells become "cluttered" which may lead to such diseases as heart failure (Hidvegi *et al*., 2010), cardiomyopathy (Nakai *et al*., 2007), Leśniewski-Crohn's

Table 2. Summary of the role of mitochondria under physiological and pathological conditions.

Physiological condition	Pathological condition
oxidative phosphorylation (ATP)	mitochondria are involved in apoptosis during infection, and this can affect viral replication/virus removal
location of deposit of mtDNA and CpG islands	increasing mitochondrial fatty acid oxidation can cause the fatty liver disease
Regulation of cell signaling	accumulation of mtDNA mutations may affect metabolic syndromes and carcinogenesis
ROS production	diseases caused by mtDNA heteroplasmy
Calcium homeostasis	diseases caused by mitochondrial dysfunction: Leigh's syndrome, Leber's disease, insulin resistance
participation in the apoptotic pathway	related to the aging process of the organism
activation of type I IFN	abnormally functioning MAVS protein is associated with the occurrence of hepatitis A, B, C, cytomegalovirus infections, Reproductive and Respiratory Syndrome Virus (PRRSV) and Vaccinia virus
activation of NLRP3 inflammasome	abnormal MAVS protein is associated with increased inflammation in the course of non-infectious diseases, including systemic lupus erythematosus
coordinating energy processes in immune cells during infection	low level of mitophagy may result in the accumulation of ROS in the cell and thus carcinogenesis
mtDNA has antibacterial properties	mtDNA damage can cause ROS accumulation in the cell and carcinogenesis
mtDNA can bind to cathelicidins stimulating monocytes and macrophages toward TNF-α	mtDNA damage in the mitochondrial apoptotic pathway, leading to increased resistance to anticancer drugs
mitochondria activate STING pathway which can lead to apoptosis, necroptosis and pyroptosis	

disease 9 (Cadwell *et al*., 2008), pancreatic disease related to its endocrine activity, or diseases of the kidneys, lungs and the Paget-Kosi's disease (Orzechowski, 2017). It is assumed that autophagy may be a target of therapy under these conditions, as well as in viral infections and neoplastic processes (Dinkins *et al*., 2015; Niedźwiedzka-Rystwej & Deptuła, 2009; Ren *et al*., 2020).

CONCLUSIONS

Mitochondria, as well as PRR receptors and the autophagy process are important elements for health and disease, including viral infections. Table 2 summarizes the contribution of mitochondria under physiological and pathological states.

It can be concluded that the activity of these elements of the macroorganism affects the processes that determine health. Such a state is constantly evolving over time and most likely arises as a result of adaptation to changing environmental conditions, in which the number of stress factors, including microorganisms, grows and changes, which in the context of the role of the immune system may contribute to the improvement of human and animal health protection.

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