Cell death and its relationship to viral infections: What are the ways to fight viruses?

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Abstract

Cell death is a crucial process for maintaining homeostasis and the development of the organism. They are mainly characterized by apoptosis, necrosis and autophagy, being complex processes and essences for the immune system and balance of the human organism, especially when there are infectious agents such as viruses. Therefore, a bibliographic review was carried out seeking to deepen the knowledge of cell death applied to viruses, and its possible action against COVID-19, demonstrating the action and importance of understanding and understanding cell death pathways and applying their results as therapeutic targets. The results obtained showed the individual action of cell deaths against the virus in the immune system and emphasized the understanding of cell death pathways as fundamental for the development of drugs and therapies for viral control for already known viruses and for new viruses, such as Covid -19.

Keywords: Apoptosis; Necrosis; Autophagy; Virus;

Introduction

Cell death is an essential biological element for the process of physiological growth and development of the organism (CHEN; KANG; FU, 2018). There are three classic forms of cell death: apoptosis, autophagy and necrosis, which define the response of the surrounding cells and organs in response to impulse, thus maintaining the organism's homeostasis (MESSNER et al., 2016).

Cell death can be programmed or accidental, programmed cell death results in lytic processes or non-lytic morphology, depending on the signaling pathway involved (JORGENSEN; RAYAMAJHI; MIAO, 2017). Among the classic types of cell death, two are programmed, namely, apoptosis and necrosis (ZIMMERMANN; GREEN, 2001). The autophagy consist a physiological process of the cell, in the form of self-degradation of cellular components in response to extracellular changes and intracellular stress (HE;

KLIONSKY, 2009). Figure 1 illustrates the types of cell death and their morphological characteristics mentioned (NIKOLETOPOULOU et al., 2013).

Apoptosis is a cellular process that directs the cell to cellular suicide, following two major pathways: mitochondrial or activation of the death receptor (AGNELLO et al., 2015).

The death receptor activation pathway is called the extrinsic pathway, and depends on the interaction of cell death receptors, such as the Fas receptor (FasR) and Fas ligand (FasL) (BERGANTINI et al., 2005). While the mitochondrial pathway, also called the intrinsic pathway, is triggered mainly by non-receptor stimuli, including deprivation of cytokines, DNA damage and cytotoxic stress, but it can also be activated by death receptors (SHIOZAKI; CHAI; SHI, 2002).

In order for apoptosis to occur, the caspase pathways are activated, which are inactive proteases and present in practically all animal cells; these biochemical cascades are activated in cells destined for apoptosis (GARRIDO; KROEMER, 2004). The caspases minimize damage and destruction to neighboring cells, in addition to preventing the release of immunostimulatory molecules, making the process restricted to the injured cell (TAYLOR; CULLEN; MARTIN, 2008). In sequence after the programmed death is triggered, the apoptotic cell quickly disappears from the tissue without generating an inflammation, as they are digested by the phagosome without causing an inflammatory response in the body. (BRASS, 1997).

Necrosis is a pathological cell death process that can be induced by ligands that bind to the specific plasma membrane, by receptors, genetic regulation, epigenetics, and pharmacological factors (QUEIROZ et al., 2020). In it, granulation of the cytoplasm and cell swelling occurs, which results in the rupture of the plasma membrane and the organelle, causing leakage of the intracellular content due to physical damage to the cell (KIM-CAMPBELL; GOMEZ; BAYIR, 2017).

Therefore, the host cell death has been demonstrated in several cases of viral infections, since these microorganisms, especially viruses, can trigger the cell death process (LABBÉ; SALEH, 2008). In addition, in viral infections such as that caused by COVID-19, there are a no specific drug treatments so far (KHEDKAR; PATZAK, 2020), understanding the pathways of cell death can serve as promising options for the development of treatment (FAKHRI et al., 2020a).

Therefore, understanding the functioning of cell deaths can help in the treatment, or even the knowledge of disease control and etiology.

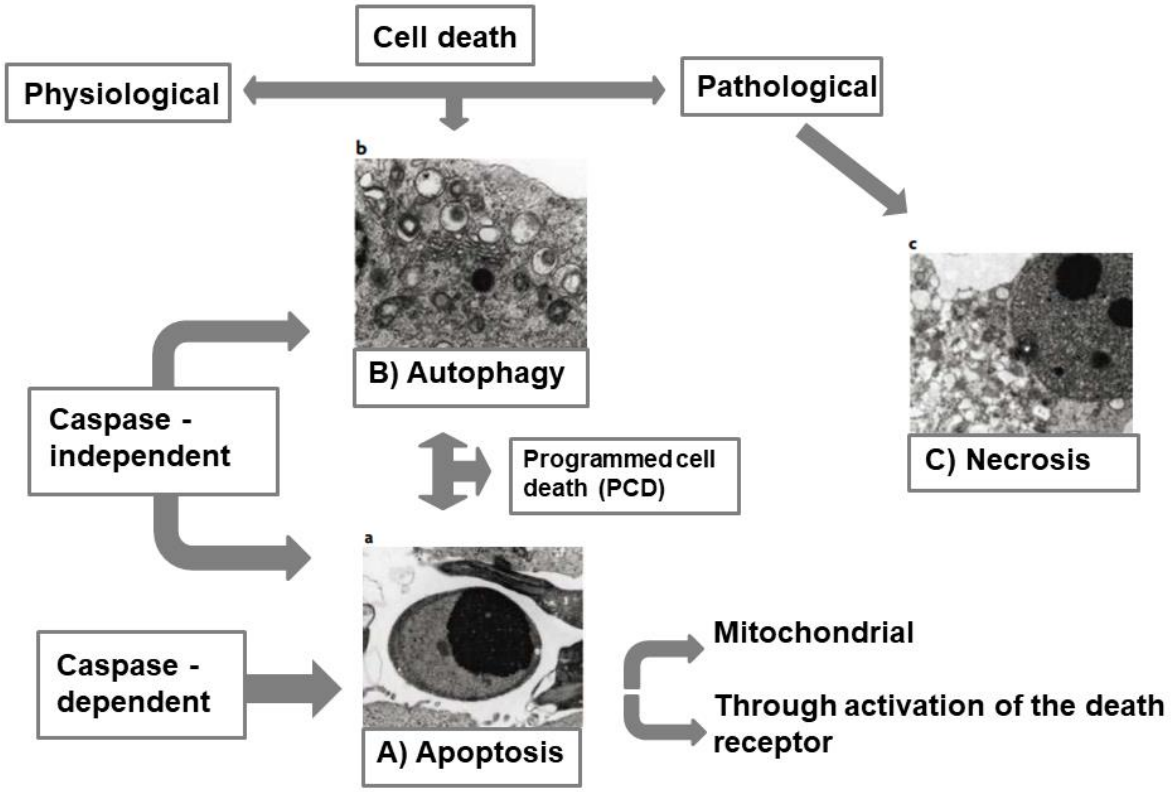

Figure 1: Mechanisms of necrosis, apoptosis and autophagy showing a diagrammatic of the different types of cell death. PCD: programmed cell death. Morphological characteristics of a) apoptotic cell b) an autophagic cell, c) a necrotic cell. (Electromicrograph images adapted from KROEMER et al., 2008. Scale bar: 1 mm) (KROEMER; LEVINE, 2008).

Materials and methods

The present study corresponded to an integrative literature review, carried out from March to October 2020. For this purpose, the articles were searched in the Google Scholar, SciELO and PUBMED databases. To search for content in the described databases, Research in banks of data was performed using “Cell death” as the central theme and with subdivisions: “Cell death in viroses”. The articles were based on descriptors created by the Virtual Health Library developed (http://decs.bvs.br/homepage.htm) from MeSH - Medical Subject Headings of the US National Library of Medicine (NLM), which allows the terminology in common in Portuguese, English and Spanish. The descriptors were: Cell Death; Virus.

To complement the database, a manual search of references was also carried out to identify eligible studies. The inclusion criteria for the articles selected for this research were: “Articles published in journals indexed in the databases mentioned above”; “Articles published in Portuguese, English or Spanish"; “Articles published in the period from 2005 to 2020”. In this sense, no restrictions were applied to the sample of studies and articles not related to the descriptors of the pre-established theme were excluded.

Results and discussion

Cell death caused by microorganisms: Pathways of cell death activation by viroses

In viral infections, for an infected cell to be eliminated from the body, it needs to be phagocyte (NAINU; SHIRATSUCHI; NAKANISHI, 2017). For this to occur, apoptosis of infected cells must occur allowing the elimination of viruses as an innate immune response (NAINU; SHIRATSUCHI; NAKANISHI, 2017). Still, according to the author, this mechanism is effective against most types of viruses and seems to be conserved among multicellular organisms (NAINU; SHIRATSUCHI; NAKANISHI, 2017). Based on this precept, the induction of cell death by apoptosis contributes to the cytopathic effects of viral infection, and its morphological characteristics are frequently observed in cells that suffer direct viral cytotoxicity, as in the case of the new corona virus and Human Immunodeficiency Virus infection 1 (HIV-1) (CHEN et al., 2020a; PATEL; GORES, 1998; SILVA, 2016).

This is because the initial response to viral infection starts from the innate response of immunity through the death of virus-infected cells, mediated by cytotoxic T lymphocytes and natural killer cells (BARBER, 2001; PAROLIN; MESSIAS REASON, 2001). Figure 2 shows the viral modulation of apoptosis due to death receptors caused by viral infection (ZHOU et al., 2017). The second host defense-mediated response is also triggered, involving the induction of a family of cytokines known as interferons (IFNs), which are essential to initiate and coordinate a successful antiviral response (CHAWLA-SARKAR et al., 2003). These molecules stimulate adaptive immunity through cytotoxic T cells and induce a series of intracellular genes that directly prevents virus replication and cytolysis, thus favoring apoptosis (BARBER, 2001). Figure 3 demonstrate how viruses are destroyed through innate immune response. In the initial phase of viral infections, these infections are controlled by type I interferons (IFN-α and IFN-β), macrophages and Natural Killer cells (NK)(MACHADO et al., 2004).

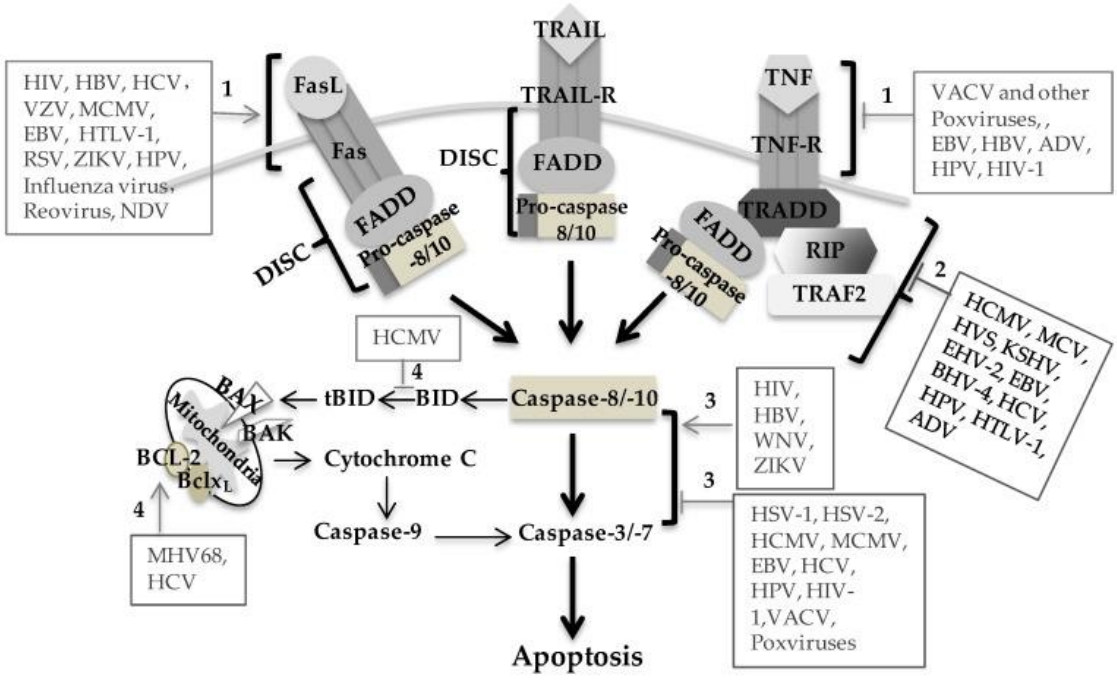

Figure 2: Viral modulation of apoptosis mediated by death receptor. The death receptors Fas, TRAIL-R and TNF-R form DISC by binding to their ligands, activate a cascade of caspases and subsequently initiate extrinsic apoptosis. Activation of caspase-8 can cleave BID into tBID and bind to the mitochondria-

mediated intrinsic apoptosis pathway. A virus infection regulates a death receptor-mediated extrinsic apoptosis, mainly by means of virus-encoded proteins. Regulatory ones involve: (1) an expression and function of regular receptors / death ligands; (2) interfere with the formation and function of the DISC; (3) regulation of caspase activities; (4) regulation of the expression and function of pro-apoptotic and anti-apoptotic proteins. A black arrow represents a signal induction; the gray arrow represents the virus-induced signal; the gray T bar represents the signal inhibited by viruses (ZHOU et al., 2017).

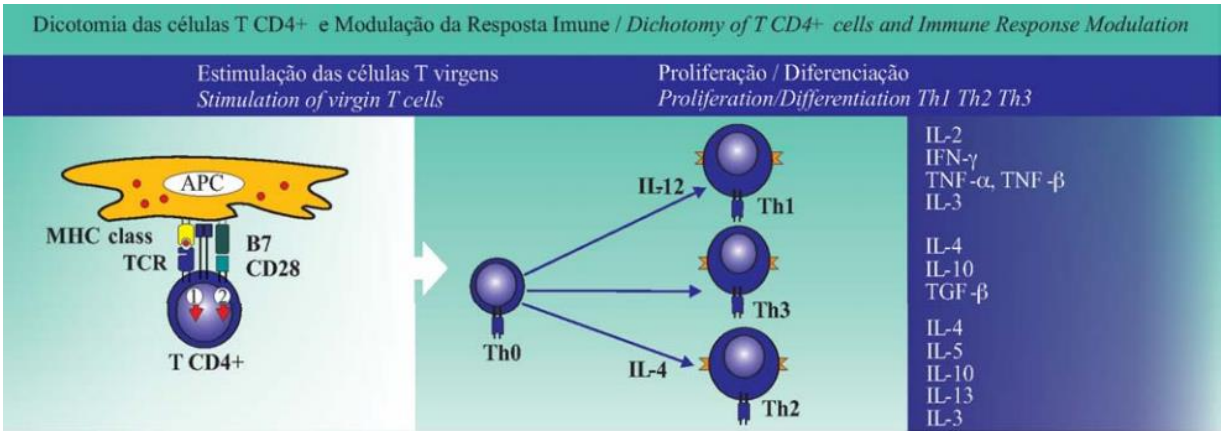

Figure 3: Mechanisms of antiviral activity of innate immunity (MACHADO et al., 2004).

These factors occur because the main death effect or mechanism of cells infected by the virus is mediated by cytotoxic T lymphocytes and "natural killer" cells, being then guides to the extrinsic pathway of apoptosis, which, through the death of the infected cell, prevents the spread of the vírus (PAROLIN; MESSIAS REASON, 2001). The extrinsic pathway is dependent on the binding of ligands (TNF, FasL) to their death domain receptors present in the plasma membrane, when the cell is infected by a virus (PATEL; GORES, 1998; QUEIROZ et al., 2020). In this case, death receptor-mediated apoptosis represents an efficient mechanism by which the virus can induce cell death and spread the progeny, which plays an important role in viral pathogenesis and provides a potential therapeutic target.

In the case of autophagy, like apoptosis, it can work with antiviral ability to suppress virus infection (AHMAD; MOSTOWY; SANCHO-SHIMIZU, 2018; DELORME-AXFORD; KLIONSKY, 2020; QUEIROZ et al., 2020). However, some viruses can usurp and exploit autophagy machinery to support replication (AHMAD; MOSTOWY; SANCHO-SHIMIZU, 2018). In addition, selective autophagy controls several human viral infections in vitro, leading to the elimination of viral pathogens or antigens and the survival of the host cell. The study by AHMAD *et* al., Demonstrated that autophagy plays an important role in the control of cytokines in HIV-1 infections and influenza A virus (IAV) infection, allowing studies to prevent prolonged and excessive inflammation harmful to the host caused by these viroses (AHMAD; MOSTOWY; SANCHO-SHIMIZU, 2018). Such facts, allow to investigating the control of viral infections, and to formulate new therapeutic options for treatment.

Viral infection and tissue damage:

Viruses are capable of inducing apoptosis and necrosis of various types of cells after they enter the host, including T cells, endothelial and epithelial cells; through vascular leakage mediated by pro-

inflammatory cytokines and chemokines and T cell responses (MACHADO et al., 2004). According to the same authors, in many of these situations there is a hypersensitivity reaction with an exaggerated and unmodulated immune response those results in tissue damage due to the cytopathic effect of the virus, hypersensitivity reaction and autoimmune phenomena (MACHADO et al., 2004). This leads to the protective immune response to a weakened state, which allows the virus to spread and promote massive tissue destruction (SHI et al., 2020).

Consequently, damaged cells induce innate inflammation that is largely mediated by pro-inflammatory macrophages and granulocytes, as well as the release of reactive oxygen species and proteases (MIMS; NASH; STEPHEN, 2001). These defense cells, when attempting to destroy the virus, will cause mass destruction of all surrounding alveolar cells, which may cause anoxia or necrosis in the tissues irrigated by these vessels (MIMS; NASH; STEPHEN, 2001; SHI et al., 2020). The figure 4 shows how these pathologies associated with viral infection may be related to the cytopathic effects of the virus, hypersensitivity reaction and autoimmune phenomena (MACHADO et al., 2004).

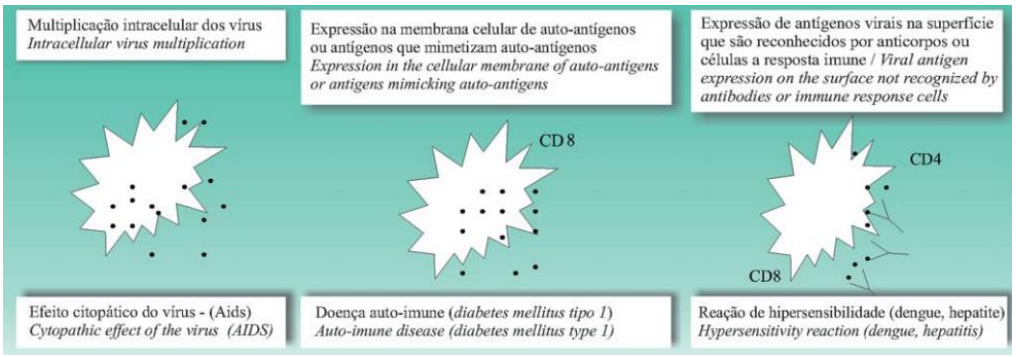

Figure 4: Effects of pathologies associated with viral infections on cells (MACHADO et al., 2004).

In the case of COVID-19 infection, according to Liu et al., The interaction between virus and host cell occurs through the ACE2 protein, found in a variety of organs such as the lungs and liver (LIU et al., 2020). From this connection, damaged cells induce innate inflammation in the organs with a higher incidence of ACE2, through a cytokine storm mediated by pro-inflammatory macrophages and granulocytes, promoting tissue damage (SHI et al., 2020; ZHANG; SHI; WANG, 2020). Figure 5 shows the cytokine storm produced by Sars-cov-2, where the virus inhibits innate immunity via interferon, increasing the viral load, which causes the cytokine storm, worsening the patient's general condition (ANTONIO et al., 2020).

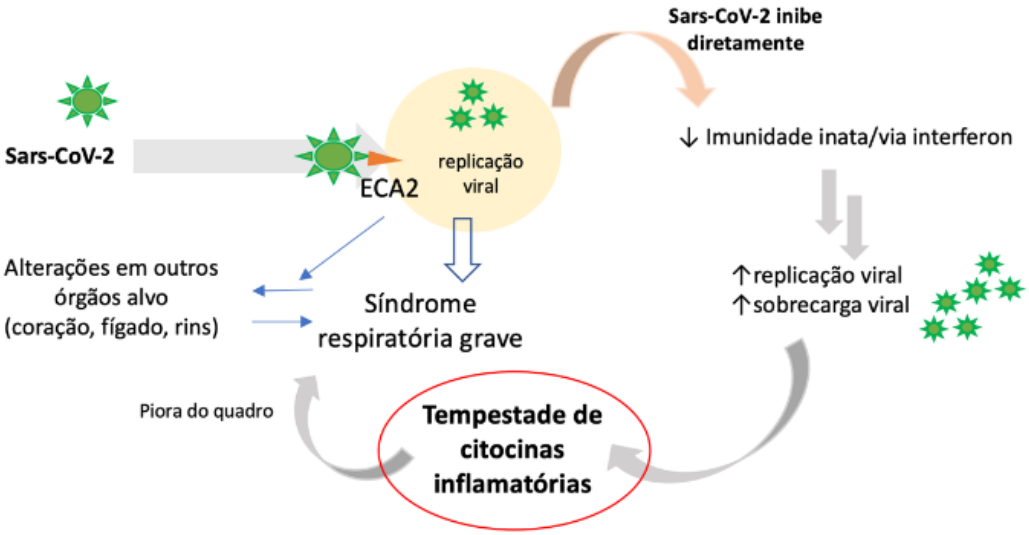

Figure 5: SARS-CoV-2 infection and cytokine storm production. The virus fuses into the host cell by recognizing the ECA2 receptor, which releases its genetic material for viral replication. During this process, the virus inhibits innate immunity via interferon, increasing the viral load, which causes the cytokine storm, aggravating the patient's general condition (ANTONIO et al., 2020).

Terpos *et* al. demonstrated that lymphocytes express the ACE2 receptor on their surface, so SARS-CoV-2 can directly infect these cells and ultimately lead to their lysis. This cellular damage characterizes cell death and tissue degradation (TERPOS et al., 2020).

In addition, according to the same authors, the cytokine storm is characterized by markedly increased levels of interleukins and tumor necrosis factors alpha (TNF-alpha), which can promote lymphocyte apoptosis, impairing the defense against the virus and increasing tissue damage (TERPOS et al., 2020).

Furthermore, studies of FAKHRI *et* al. 2020 emphasize the crucial role of oxidative stress, inflammation, apoptosis, autophagy, in triggering the pathogenesis and complications of COVID – 19 (FAKHRI et al., 2020a). What emphasizes the need to understand the pathways of cell death so that there is the development of drugs that control the progress of the infection, as shown in the study by FAKHRI et al., 2020 which, through the study of the steroid astaxanthin, sought to deregulate the autophagy harmful to the organism and apoptosis reduction contain the inflammatory complications of COVID-19 (FAKHRI et al., 2020b).

The same occurs in studies to control Ebola, which in addition to the disturbance of the immune system, infects vital organs, such as the liver, spleen and kidneys, where it kills the cells that regulate coagulation, chemical and fluid homeostasis and responsiveness. Immunological (JACOB et al., 2020). In this case, for IBA *et* al., 2020, finding drugs that can regulate apoptosis would be essential to help control infection (IBA et al., 2020).

Cell death and the relationship with Covid-19

SARS-CoV-2, or Covid-19, has been manifesting since December 2019, causing a pandemic, and generating symptoms since mild, such as cough and loss of taste and smell, as severe, as lymphopenia and

severe acute respiratory syndrome (CHEN et al., 2020b; RODRIGUEZ-MORALES et al., 2020; ZHENG, 2020). Studies indicate that contamination with this agent can cause prolonged cytokine and chemokine responses, resulting in immune defects and the death of some patients (TAGHILOO et al., 2020).

Feldmann *et* al. (FELDMANN et al., 2020) suggested an anti-TNF therapy applied to patients with COVID-19 on hospital admission to prevent progression to the need for intensive care support, aimed at reducing inflammation. As well as the study of drugs aimed at the proliferation of lymphocytes through inhibition of apoptosis, such as corticosteroids (WALSH; SEXTON; BLAYLOCK, 2003), can inhibit a lymphopenia and also compensate the lymphocyte count in critically ill patients with this viral disease, increasing immunity and a chance of cure for these patients (FATHI; REZAEI, 2020).

Among the studies on drugs and the complications caused by SARS-CoV-2, studies on FAKHRI *et* al., 2020 claim that oxidative stress, inflammation, interference with apoptosis and autophagy, are responsible for the pathogenesis and complications of COVID-19. These authors seek the development of drugs with a potential anti-inflammatory, antioxidant and anti-apoptotic effects, as well as the modulation of autophagy (FAKHRI et al., 2020a).

In addition, the literature states that manipulations of the response to cell stress induced by coronavirus due to the cytokine storm could be a powerful approach in combating the pathogenesis of COVID-19 in patients with severe pneumonia or multiple organ failure (HAMMOCK et al., 2020).

COVID-19 causes severe acute respiratory syndrome as a complication in some patients (RODRIGUEZ-MORALES et al., 2020). Guler e*t*., al (GULER; SIDDIQUI; FAREED, 2020) show that the relationship between COVID-19 and apoptotic pathways contributes to the focal pathogenesis observed in the lungs and is involved in the progression of the severity of this complication. This, according to the authors, occurs due to the increase in D-dimer in view of the apoptotic processes that target the endothelial cells of the vascular structure, resulting in triggered coagulopathy and in the final result of the increased D-dimer, which increases the rate of mortality of infected patients.

Therefore, the understanding of cell death pathways and their action against the viral agent and in the immune system allows the development of drugs that use the modulation of cell death processes as a defense tool of the host organism and tissues against viral infections and their possible complications.

Conclusion

With the bibliographic survey presented, it was possible to conclude that cell death is fundamental for the maintenance of the organism's homeostasis, since it defines the cellular response caused when there is an imbalance in the extracellular and intracellular media. In the case of cell death caused by viral pathogens, the literature states that this bioprocess acts to block the progress of these diseases, and to contribute to the development of drugs, since their pathways are used as regulatory instruments that act against the viral agent and help the immune response. Thus, we can conclude that scientific knowledge of cell deaths due to apoptosis, necrosis and autophagy, are necessary for future studies in the treatment and control of pathologies, allowing the study and development of drugs and therapies to control existing, future and perhaps even pathologies cure current illnesses like COVID-19.

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