ABSTRACT

Cell death is an essential biological process for physiological growth and development. Therefore, this process has different types of cell death and the main three are: apoptosis, autophagy and necrosis. In addition, cell death is related to manifestations of various diseases and treatment of systemic diseases in the areas of general health, such as cancer and periodontitis, in addition to viruses. In this study, the importance of cell death for the organism and its relationship with various human diseases, such as the new coronavirus 2 respiratory syndrome (SARS-CoV-2), both in clinical manifestations and in possible treatments, such as tumor necrosis agents (anti-TNF), to improve the response rates of patients with inflammatory diseases or the importance of lymphocytic apoptosis, promoted by SARS-CoV-2 by increasing the expression of Fas. Through this study it was possible to identify the importance of cell death for the organism and how it can interfere in human diseases; thus, enable the biotechnological application in the development of specific drugs and therapies.

Keywords: Apoptosis; necrosis; autophagy; Health.

RESUMO

A morte celular é um processo biológico essencial para o crescimento e desenvolvimento fisiológico. Diante disso, esse mecanismo possui diferentes tipos de morte celular e os três principais são: apoptose, autofagia e necrose. Além disso, a morte celular está relacionada a manifestações de várias doenças e tratamento de doenças sistêmicas nas áreas de saúde geral, como câncer e periodontite, além de vírus. Este estudo, demonstra a importância da morte celular para o organismo e sua relação com várias doenças humanas, como a nova síndrome respiratória do coronavírus 2 (SARS-CoV-2), tanto em manifestações clínicas quanto em possíveis tratamentos, como agentes de necrose tumoral (anti-TNF), para melhorar as taxas de resposta de pacientes com doenças inflamatórias ou a importância da apoptose linfócita, promovida pela SARS-CoV-2, aumentando a expressão de Fas. Através deste trabalho, foi possível identificar a importância da morte celular para o organismo e como ela pode interferir na doença humana e assim, possibilitar a aplicação biotecnológica no desenvolvimento de medicamentos e terapias específicas.

Palavras-chave: Apoptose; Necrose; Autofagia; saúde
INTRODUCTION

Cell death is an essential biological process for physiological growth and development. Three classic forms of cell death - apoptosis, autophagy, and necrosis - exhibit distinct morphological characteristics by activating specific signaling pathways (Chen, Kang and Fu, 2018). Apoptosis, necrosis or autophagy is the mode of cell death that defines the response of surrounding cells and organs (Messner et al., 2016). As these pathways become more thoroughly characterized, interesting molecular links have emerged between them, some still controversial and others implying the physiological and pathophysiological roles that these pathways of death play (Lalaoui et al., 2015).

Cell death is important not only in homeostasis, as mentioned above, but also in pathologies such as cancer, any mistake made by a metastatic cell during these cell events can lead to cell death (Su et al., 2015). Generally speaking

Generally there are two types of programmed cell death: apoptosis and necrosis (Zimmermann and Green, 2001). According to the Zimmermann & Green, necrotic cell death is considered an accidental type of death, that the cell suffers damage that results in the death of cell groups within a tissue (Zimmermann and Green, 2001). As necrosis cells show “swollen”, with increase in volume of whole cells and also increase of endoplasmic and Golgi apparatus, and as a final result occurs cells rupture and release their contents in the extracellular environment, causing inflammation (Carneiro, José; Junqueira, 2012).

In contrast, apoptosis is controlled cell death that makes the rules for many cellular processes possible, that embryonic development and tissue maintenance (Allan and Clarke, 2009). In this process, the cells contract, condense and form apoptotic bodies that are phagocytized by macrophages and, thus, prevent the cytoplasmic content from spilling over (Alberts, 2017).

Autophagy is a process of cell component self-degradation in which double-membrane autophagosomes capture organelles or cytosol moieties and fuse with lysosomes or vacuoles to break through resident hydrolases (He and Klionsky, 2009). This process is positively regulated in response to extracellular and intracellular stress and to signals such as hunger, deprivation of growth factors, RE stress, and pathogen infection (He and Klionsky, 2009).

Is known that programmed cell death is a regulated mechanism that serves to eliminate undesirable and irreparably damaged cells, with the least possible reaction from the host. In the case of viral infections, according to (V. Kumar, Jon Aster, 2016) the loss of cells infected by cell death in most cases due to apoptosis induced by the virus or by the host’s immune response. In the case of the new coronavirus 2 respiratory syndrome (SARS-CoV-2) caused by the covid-19 virus that has spread around the
world causing a pandemic the viral cycle occurs through the protein S quarters that radiate the lipid envelope. (Cheng et al., 2007; V. Kumar, Jon Aster, 2016; Fedson, Opal and Rordam, 2020). In this case, the Protein S subunits can connect to the angiotensin-binding enzyme 2 (ACE2) leading to cell death after binding to the ACE2 protein. (Cheng et al., 2007; Liu et al., 2020; Lu et al., 2020; Shi et al., 2020).

CHEN e colab (chen et al., 2020) suggests that SARS-CoV-2 induces cell apoptosis through deregulation of pro-inflammatory cytokines, such as TNF-α and IL-6, promotes cell necrosis and apoptosis.

Based on the authors Chen et al (Chen, Kang and Fu, 2018), cell death has specific characteristics and is a crucial process during development, providing homeostasis and immune regulation of multicellular organisms, and various pathologies can deregulate this process. Cell death may be due to infection as part of the defense mechanism, however some pathogens have developed strategies to control host cell death. In this context, autophagy has longer survival, followed by apoptosis, with necrosis with shorter survival. Autophagy is instinctively induced before apoptosis, when cells are stimulated by stress, but if inhibited or ineffective in cell control, apoptosis is induced to prevent necrosis (Kusano and Ferrari, 2000).

Apoptosis

Apoptosis is a cellular process that directs cell suicide by following two major pathways: cytochrome c released from mitochondrial or through activation of the death receptor (Agnello et al., 2015). The entire process of apoptosis takes about an hour from the beginning, and the form of the initiation is very varied, and are broadly grouped with physiological or non-physiological steps (Goma, 1979). This biochemical pathway is characterized by chromatin condensation, DNA fragmentation and apoptotic body formation, but cell death and proliferation are deeply connected (Anazetti and Melo, 2007).

Caspases

Caspases are expressed as inactive zymogens in virtually all animal cells and are activated in cells destined to undergo apoptosis (Garrido and Kroemer, 2004). These proteases target several hundred proteins for restricted proteolysis in a controlled manner that minimize damage and destruction to neighboring cells and prevent the release of immunostimulatory molecules (Taylor, Cullen and Martin, 2008). Regardless of the actual route for caspase activation, all pathways lead to activation of the major effector caspases, caspase 3, caspase 6 and caspase 7. These enzymes perform much of the proteolysis that is seen during the cell destruction phase (Taylor, Cullen and Martin, 2008), those involved in the initiation of apoptosis are caspases 8 and 9, while caspases 3, 6 and 7 are responsible for the execution of the process (McIlwain, Berger and Mak, 2013).
Activation Paths

The process of apoptosis or programmed cell death can be triggered by intrinsic or extrinsic pathways. The extrinsic pathway is dependent on the interaction of cell death receptors, such as the Fas receptor (FasR) and Fas ligand (FasL) (Bergantini et al., 2005). In the initiation of the process the proteins FADD adapter protein and procaspase-8 form a death-inducing signaling complex (DISC) (Taylor, Cullen and Martin, 2008). DISC consists of an adapter protein and primer caspases and is essential for induction of apoptosis (Peter and Krammer, 2003).

In DISC, procaspase-8 is activated by self-hydrolysis (Wang and Tjandra, 2013), therefore caspase 8 is activated or by cleaving the Bid protein. Thus, the truncated Bid (tBid) will translocate to mitochondria, resulting in conformational changes in proteins Bax and Bak and their oligomerization to pore formation in the mitochondrial outer membrane (Fan et al., 2005).

The intrinsic pathway is a second pathway of activation, this activation is known as mitochondrial-dependent pathway, triggered primarily by non-receptor stimuli, including cytokine deprivation, DNA damage and cytotoxic stress, but may also be activated by death receptors (Shiozaki, Chai and Shi, 2002). This pathway can be activated through various cellular stresses that leads to the release of cytochrome c from mitochondria and apoptosome formation, comprising APAF1, cytochrome c and ATP, resulting in activation of caspase-9 (McIlwain, Berger and Mak, 2013). And as already presented, caspase 9 is one of those responsible for the execution of apoptosis death.

After both activation pathways, the apoptotic cell quickly disappears from the tissue without generating an inflammatory response, as they are digested by phagosomes without causing an inflammatory response in the body (Brass, 1997).

Adapter proteins

For the apoptosis process, it is necessary to adapt proteins, which consist of connections between cell death effectors, caspases and cell death regulators, death receptors and members of the Bcl-2 family (Salvesen and Dixit, 1999). These bonds take the form of physical associations between members of the three classes of molecules, with the adapter proteins that interconnect caspases and the apoptosis regulators.

 Associations between adapter proteins and caspases or members of the tumor necrosis factor receptor (TNFR) family are characteristically mediated by homotypic interactions between domains known as the death domain, the death effector domain, and the caspase recruiting domain (Strasser, Connor and Dixit, 2000). TNFR family members have pleiotropic action, depending on the type of cell and the other signals the cell receives, these receptors can trigger proliferation, survival,
differentiation or death (Wallach et al., 1998). Among the proteins mentioned, there is the protein P-53 that acts when apoptosis is caused by DNA damage. The genes Puma and Noxa stand out for induced by this transcription of proteins BH3-only and pro and anti-apoptotic members of the Bcl-2 family necessary to initiate apoptosis (Villunger et al., 2012).

**BCL-2 proteins**

The Bcl-2 family and related cytoplasmic proteins are the main regulators of apoptosis, as they promote cell survival by inhibiting the necessary adapters for the activation of cell-disrupting proteases (Caspases) (Adams and Cory, 1998). The Lymphoma 2 (BCL-2) family of proteins is one of the major pro and anti-apoptotic regulators, as cells are kept in a delicate balance - disorders that can irreversibly go toward cell death or allow a cell to escape apoptosis (Knight et al., 2019).

**Necrosis**

Necrosis has been considered only as an uncontrolled form of cell death, but there is evidence that the execution of necrotic cell death can be finely regulated by a set of signal transduction pathways and catabolic mechanisms, for example Tumor necrosis factor receptor 1 (TNFR1), Fas/CD95 and TRAIL-R; and Toll-like receptors (TLR3 and TLR4), that have been shown to cause necrosis, in particular in the presence of caspase inhibitors (TNFR1, Fas/CD95) (Festjens, Vanden Berghe and Vandenabeele, 2006). This cell death has already been considered passive and disorganized, however it is currently known as an alternative form of programmed cell death, because it may be induced by ligands that bind to plasma-specific membrane receptors, regulation by genetics, epigenetics, and pharmacological factors (Levine and Kroemer, 2008). Furthermore, inactivation of caspases causes a change in apoptosis or cell death morphologies with mixed necrosis and apoptosis or total necrosis (Kroemer et al., 2009), whose activation may have important biological consequences, including induction of an inflammatory response (Edinger and Thompson, 2004).

Necrosis is characterized by cytoplasmic granulation and cell swelling, which results in plasma membrane and organelle rupture (Kim-Campbell, Gomez and Bayir, 2017). Also according to the authors, it can lead to secondary local inflammation.

Necrotic cell death has a prominent role in multiple physiological and pathological configurations, and given that it can occur in a regulated manner, various triggers may induce regulated necrosis, including alkylation DNA damage, excitotoxins, and death receptor binding (Galluzzi et al., 2012). Also according to the article, necrosis can also be induced by stimulating death receptors with tumor necrosis factor (TNF) or other agonists.

A necropse, which is a more common form of regulated necrosis, and occurs...
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independently of caspase, can be triggered by treatment with TNF alone without the presence of a pan-caspase inhibitor (Andreas Linkermann, M.D., and Douglas R. Green, 2018), was being dependent on Non-specific serine/threonine protein kinase (Kroemer et al., 2009). A necropse occurs as a type of cell death that can be prevented by inhibition of Receptor-interacting serine/threonine-protein kinase 1 (RIP1), through genetic or pharmacological methods. That enzyme have function in a variety of cellular pathways related to both cell survival and death (Degterev et al., 2005).

**Autophagy**

Autophagy is an intracellular degradation system that distributes cytoplasmic constituents to the lysosome (Levy et al., 2018). It consists of a self-degrading process in response to various stresses, including nutrient reduction, organelle damage, hypoxia, reactive oxygen species (ROS), Endoplasmic reticulum stress (ER stress), and drug treatment (Chen, Kang and Fu, 2018). According to the authors, for autophagy to occur, there are four main steps: initiation, nucleation, autophagosome fusion and lysosoma, and hydrolization. An autophagy can be differentiated into 3 types: macroautophagy, microautophagy, and companion-mediated autophagy. The term “autophagy” usually indicates macroautophagy unless otherwise specified (Mizushima, 2005). Macroautophagy is an evolutionarily conserved stress-responsive process that eliminates superfluous or potentially dangerous cytosolic entities (for example, damaged mitochondria and invading pathogens) by sequestration in double-membrane vesicles (autophagosomes) that will be delivered to lysosomes for degradation (Levine and Kroemer, 2019). Microautophagy, the non-selective lysosomal degradation process that directly involves cytoplasmic loading on a boundary membrane through autophagic tubes, which mediate both invagination and vesicular scission in the lumen (Li, Li and Bao, 2012).

Chaperone-mediated autophagy (CMA) is a selective type of autophagy whereby a specific subset of intracellular proteins is directed to the lysosome for degradation (Juste and Cuervo, 2019). Also according to the authors, proteins are translocated to the organelle lumen through a lysosomal membrane receptor complex, eliminating damaged and altered proteins.

This review paper stresses the importance of studying and understanding the mechanisms of cell death and their action between systemic pathologies applied in various areas of health, and at the molecular level. For understanding its functioning can help in the treatment, or even use the types of cell death as an apparatus for etiology of these diseases. In this way, the objective was the analysis of bibliographic productions recorded in journals attached to the PubMed and LILACS databases on concepts and differences in cell death types.
and their relationship with general and dental health from 2015 to 2019.

Cell death and its concept applied in general health

Several studies and research can be found in the literature and related areas demonstrating the importance of biochemical and biological mechanisms of cell death (Figure 1 and Table 1 - Supplementary material).

Cell death, especially when programmed, is an essential genetic and biochemical pathway for metazoans (Danial and Korsmeyer, 2004). According to the same researchers, an intact death path is necessary for successful embryonic development and maintenance of normal tissue homeostasis. There are three classic forms of cell death: apoptosis, autophagy, and necrosis, which exhibit distinct morphological characteristics by activating specific signaling pathway, which illustrates the relationship between the three types of cell death (Figure 2) (Chen, Kang and
Apoptosis is characterized by a series of dramatic disturbances in cell architecture that contribute not only to cell death but also prepare cells for phagocyte removal and prevent undesirable immune responses (Taylor, Cullen and Martin, 2008). Apoptotic cells may be characterized by specific morphological and biochemical changes orchestrated by a family of cysteine proteases known as caspasases (Zimmermann and Green, 2001). This biological phenomenon, besides playing an important role in the control of several vital processes, is associated with numerous diseases, such as câncer (Ivana Grivicich, Andréa Regner, 2007).

Therefore, we can determine different aspects related to Cell Death and, in particular, those related to health. Because this process causes cellular morphological changes inhibiting or causing pathologies.

In health, program cell death or apoptosis acts as the first identified regulated cell death pathway and plays a crucial role in the development of the immune system and its return to homeostasis after T or B cell responses (Behar and Briken, 2019). When apoptotic cells are not efficiently encompassed by macrophages, they undergo secondary necrosis and release intracellular materials that represent a damage-associated molecular pattern, which can lead to lupus-like systemic autoimmune disease (Nagata, 2018). According to Behar & Briken (Behar and Briken, 2019) in efferocytosis some pathogens prevent macrophage activation and thus facilitate their dissemination. Still according to the same researchers, many obligate intracellular bacterial pathogens and some intracellular facultative bacteria inhibit apoptosis, preventing efferocytosis and avoiding innate host defenses. Under normal and healthy conditions, infected cells that undergo apoptosis are swallowed by macrophages. After efferocytosis, most non-pathogenic bacteria are destroyed by the macrophage. However some human pathogens have hijacked the macrophage to survive and disperse the disease, bypassing the defense
mechanism, as shown in figure 3.

Figure 3: Defense mechanism of the linked antibacterial host: (a) Infected cells that undergo apoptosis are swallowed by macrophages; (b) there is the inhibition of cell death (that is, apoptosis) by pathogenic bacteria (Behar and Briken, 2019).

Moreover, according to Tiwari and colleagues (Tiwari et al., 2015) apoptosis causes the elimination of more than 99% of the germ cells in the ovarian cohort due to follicular atresia, showing the involvement of mitochondria-mediated pathways and death receptors in the apoptosis of mammalian oocytes, whose involves both mitochondria-mediated (intrinsic), as well as cell surface death receptors-mediated (extrinsic) pathways, as shown in figure 4a. In non-mitochondrial factors (Fas L-mediated pathway), they are specific death receptors shows the pro-apoptotic ligands (FASL and TNFa) that bind to their respective receptors and activate death receptors on the cell surface. Activation of death receptors followed by caspases leads to apoptosis mediated by the death receptor. However, in mitochondrial factors (Mitochondria-mediated pathway), increased levels of reactive oxygen species (ROS) due to decreased levels of cAMP and cGMP in oocytes and increased level of cytosolic free Ca2+, that can raise H2O2 generation and modulate expressions of Bax/Bcl2 ratio in mitochondria membrane and thereby membrane potential. As a result, change in the mitochondria membrane potential triggers cytochrome c release in the cytoplasm of a cell, that activate upstream and downstream caspases in oocytes, leading to several biochemical and morphological changes associated with oocyte apoptosis. Also according to the same study, less than 1% of germ cells, which culminate in oocytes, still suffer apoptosis during the final stages of oogenesis and deplete ovarian reserve in most mammalian species, including humans. Thus, it is possible to conclude that there are several forms of cell death related to apoptosis of mammalian oocytes, as summarized in figure 4b. In this case, several factors may be related to the of oocyte apoptosis such as premature disruption of gap junctions, that signal molecules (Ca2+, cAMP and cGMP), oxidants (NO, H2O2 and OH-), maturation promoting factor (MPF) destabilization, Meiotic competency, Oocyte aging, survival factors, proapoptotic factors (Bax, cytochrome c, caspases 8 and 9), BH3-only proteins and apoptotic factors (caspase 3 and DNA fragmentation), Caspase 3, DNA Frag DNA Fragmentation, Cytochrome c and Caspases 8 and 9 (Tiwari et al., 2015). Therefore, according to Cheng et al. Cheng et al. (Chen, Kang and Fu, 2018) the existence of various regulated cell death pathways implies the complexity of cell death programs, but also provides new therapeutic targets.
Figure 4: a) Hypothetical schematic diagram showing the involvement of mitochondria-mediated pathways and death receptors in apoptosis of mammalian oocytes; b) Schematic representation showing various players of oocyte apoptosis such as premature disruption of gap junctions (Tiwari et al., 2015).

For MEI, Y. et al. (Mei et al., 2015) autophagy is an important factor in the development of cardiovascular diseases such as atherosclerosis, ischemia, cardiac reperfusion, cardiomyopathy, heart failure and hypertension. Thus, we can state that knowledge of autophagy as an adaptive or maladaptive response would provide possibilities for the prevention and treatment of cardiovascular diseases.

Studies by Martin et al (Martin et al., 2015), have shown that autophagy may be a primary target for the treatment of neurodegenerative diseases involving protein aggregation, such as Huntington’s disease, where an expansion of the polyglutamine tract in the N-terminus of the huntingtin protein, which leads to protein aggregation. According to the data obtained by these researchers, there is evidence to suggest that the N-terminus of the huntingtin protein is not simply a passive passenger in autophagy, but may also be an important regulator of autophagy, acting as a support for autophagosome transport and biogenesis, causing mutations in various motor proteins and autophagy regulators, which also lead to neurodegenerative disease with Huntington disease-like phenotypes.

In necrosis, for Chen et al. (Chen, Kang and Fu, 2018), most of the knowledge originated from investigations of Tumor Necrosis Factor (TNF) signaling. While the works of Olesen et al. (Olesen et al., 2016) found that TNF inhibitors were successful in treating intestinal disease. According to their research, Tumor Necrosis Factor inhibitors have proven efficacy in inflammatory bowel disease, as they affect the signaling of this factor, thereby suppressing the production of proinflammatory cytokines and other mediators, resulting in reduced inflammation and inflammation, decreased cell activation,
proliferation, leukocyte recruitment and angiogenesis, and subsequent promotion of mucosal healing. Despite this, it is not possible to fully understand the mechanisms of action of TNF inhibitors, since they work through tools mediated by blocking TNFR activation performed by TNF, as shown in figure 5 and by mechanisms dependent on the binding to tmTNF. In the figure, it is observed the intestinal permeability that was reduced due to the low levels of IEC apoptosis and reduced TJs permeability (Olesen et al., 2016). Then, there is an increase in the frequency and activity of Treg cells, a reduction in the expression of inflammatory mediators in immune cells and induction of apoptosis in immune cells. In addition to improving response rates of anti-TNF antibody treatment, Billmeier et al. (Billmeier et al., 2016) says that in addition to pharmacokinetic reasons, it is mandatory to better understand the mechanism of action of these agents, such as tumor necrosis factors, to unravel the main signaling pathways involved.

Figure 5: 1) There is a decrease in IEC apoptosis and a reduction in the permeability of TJs due to decreased apoptosis; 2) The frequency and permeability of Treg cells increases; 3) reduced expression of inflammatory mediators in various immune cells; 4) inference of apoptosis in immune cells (IEC, intestinal epithelial cell; IL-1β, interleukin-1β; mAb, monoclonal antibody; MAC, macrophage; sTNF, soluble TNF; T cell; TJ, watertight junction; tmTNF, transmembrane TNF; TNFR, TNF receptor; Treg, regulatory T cell.) (Olesen et al., 2016).

**Cell death and câncer**

A relationship between cancer and cell death was discussed in a paper by Ferreira et al. (Ferreira et al., 2011), which demonstrated several apoptosis inducing and inhibiting agents recognized as weapons to combat diseases caused by cell proliferation and death disorders. With this, Ivana et al. (Ivana
Grivicich, Andréa Regner, 2007) concluded that many molecules are involved in the control of apoptosis activation pathways, among which are antiapoptotic and pro-apoptotic proteins, in addition to caspases, which play an important role in controlling various vital processes, and is associated with numerous diseases, such as cancer. Nagata’s work (Nagata, 2018) has shown that an anticancer drug (venetoclax) developed through apoptosis research has been approved by the US Food and Drug Administration for the treatment of chronic lymphocytic leukemia. The same effects are pointed out by Lok et al. (Lok et al., 2019), in which venetoclax demonstrated a potent and selective BCL2 inhibitor, synergy with endocrine therapy in preclinical models of RE-positive breast cancer. However, as explained by Finlay et al. (Finlay et al., 2017), cancer cells regularly acquire resistance to programmed cell death, or apoptosis, which not only supports cancer progression but also leads to resistance to therapeutic agents. Since, according to Pfeffer et al (Pfeffer and Singh, 2018).

The apoptotic pathway is typically inhibited by a wide variety of means, including overexpression of anti-apoptotic proteins and underexpression of proapoptotic proteins, as a cellular inhibitor of apoptosis protein 1; cIAP2, cellular inhibitor of apoptosis protein 2; ML-IAP, melanoma inhibitor of apoptosis protein; NAIP, neuronal apoptosis inhibiting protein; TNF, tumor necrosis factor, relevant to the survival and apoptosis of tumor cells shown in figure 6, where the interaction of intracellular signaling of The inhibitor of apoptosis protein (IAP) related to cell survival and apoptosis occurs, this inhibitory scheme is appropriate for apoptosis signaling pathways and is relevant for the achievement of tumor cell survival and apoptosis (Finlay et al., 2017). The dashed lines in figure 6 indicate possible degradative events, with blue mediated by ubiquitin and black mediated by caspase.
Deregulated malignant cell apoptosis remains an attractive target in cancer therapy; however, according to the authors Koff et al. (Koff, Ramachandiran and Bernal-Mizrachi, 2015) much work needs to be done to realize the full potential of such approaches as most therapies remain in the preclinical stages, and several recent clinical trials have been affected by dose limiting effects or for disappointing answers. However, according to the same researchers, promising results remain enthusiastic about these approaches, and other efforts should focus on maximizing power while minimizing side effects.

The works of Mowers et al. (Mowers, Sharifi and Macleod, 2017) showed the role of autophagy in cancer metastasis, which is of particular interest given, according to these authors, the scarcity of effective therapeutic options for metastatic disease. Although autophagy was originally considered a tumor suppressor factor. Isaka et al. (Isaka et al., 2017) demonstrate that cancer employs autophagy to survive under metabolic stress. Specifically, Mowers et al. (Mowers, Sharifi and Macleod, 2017) explained that autophagy has been shown to be involved in modulating tumor cell motility and invasion, cancer stem cell viability and differentiation, epithelial-mesenchymal transition, tumor cell numbness, and escape from immune surveillance, with emerging roles in establishing the pre-metastatic niche and other aspects of metastasis. In summary, Mowers et al. (Mowers, Sharifi and Macleod, 2017) identified an increasing number of articles with several critical functions for autophagy in all cancer metastases, offering the opportunity to define specific points in the metastatic cascade, which involve the physical translocation of cancer cells to microenvironments that enable them to survive in conditions, according to the study, the emergent functions of autophagy in metastases include a role in establishing the pre-metastatic niche; in addition to promoting the survival of tumor cells, escaping immune surveillance and other aspects necessary to ultimately develop a open metastasis (Mowers, Sharifi and Macleod, 2017). Figure 7 exemplifies the role of autophagy in the metastatic cascade. Autophagy then increases as tumor cells gradually invade, this in turn occurs due to increased cell motility, EMT, a stem cell phenotype, secretion of pro-migratory factors, release of MMPs, resistance to medications and escape from immune surveillance at the primary site where in some cases they may be tumors. At the secondary
site, autophagy occurs so that the tumor cells remain and a state of dormancy, probably due to their ability to stimulate quiescence and a stem cell phenotype, linked to the survival of tumor cells and drug resistance.

Figure 7: Schematic illustrating roles of autophagy in the metastatic cascade (Mowers, Sharifi and Macleod, 2017).

Rabiee et al. (Rabiee et al., 2019) claims that in the early stage of cancer progression, apoptosis is the main mechanism of cell mortality and, later, autophagy would be the main mechanism of cell survival. According to the study by Rabiee et al. (Rabiee et al., 2019) that autophagy acts both as cell death and survival mechanisms at the onset of cancer progression with the cell survival approach.

In contrast Isaka et al (Isaka et al., 2017), has assumed that autophagy provides alternative energy or nutrient supply to cancer cells under unfavorable conditions. Thus, the autophagy suppressing drug may act as cancer therapy.

When it comes to cell death by necrosis, to Harald tumor necrosis factor, besides being an extraordinarily pleiotropic cytokine with a central role in immune homeostasis, inflammation and host defense, has relevance in the immune surveillance of tumors. It also plays crucial roles in the development and progression of tumors. Therefore, for Micic et al. (Micic et al., 2019), the risk of new cancer or cancer recurrence among patients with a history of cancer and use of anti-tumor necrosis factor therapy is similar to the risk with non-biological disease modifying therapies.

**Cell death and oral diseases**

Periodontal pathologies and their relationship with cell death were discussed by Loreto et al. (Loreto et al., 2015) the authors stated that apoptosis plays a key role in dental remodeling related to damage repair. In the studies by Taskan et al. (Taskan et al., 2019) this statement was exemplified by oleuropein, which
is a potent phenolic compound that may play a crucial role in the prevention of periodontal disease, as it has successfully decreased alveolar bone loss as a result of decreased osteoclastic activity, inflammation and apoptosis and increased osteoblastic activity. In addition, LI et al. (Li, Tong and Ling, 2019) demonstrated that osteoblast apoptosis is critical for the development and repair of bone destruction in case of persistent apical periodontitis, as it has shown that clinically isolated strains of E. faecalis can induce apoptosis in MC3T3 osteoblasts.

Gums represent a potential therapeutic target for intervention in the management of chronic periodontal disease, as according to Castro et al. (Castro et al., 2017), efficient plasma clearance or elimination of apoptotic cells is essential for the resolution of inflammation and tissue restoration. Chen et al. (Chen et al., 2019) diz state that several pathological factors, including periodontal pathogens, cytokines, and drugs may lead to periodontal ligament apoptosis responsible for periodontitis. Already the works of Palareti et al. (Dyah Listyarifah1,2, Ahmed Al-Samadi3, Abdelhakim Salem1,3, Ahmad Syaify4, Tuula Salo3,5, Taina Tervahartiala3, Daniel Grenier6, Dan C. Nordström7, Timo Sorsa3,8, 2016) demonstrated evidence of increased apoptosis is seen in periodontitis, and may be associated with destruction of periodontal tissue caused by increased cell death, release of danger signals and subsequent stimulation of proinflammatory processes.

**Cell death caused by viruses**

In humans, billions of cells die every day, as part of the body’s natural processes, overproduced cells and cells damaged by microbial infection or mechanical stress, and the type of cell death that occurs in the physiological environment, called programmed cell death (Nagata, 2018). One of the defenses against intracellular infection in animals is responsible for the death of hosted cells before the parasite can replicate and kill the cell in the path of other infections. Thus, cell death also triggers innate and adaptive immune responses. (Green et al., 2009).

Particularly in viral infections, the loss of infected cells occurs largely due to virus-induced apoptosis (such as adenovirus and HIV infections) or the host's immune response (such as viral hepatitis)(V. Kumar, Jon Aster, 2016). Furthermore, according to or author, another important host that responds to viral infections is the cytotoxic T lymphocytes used for viral infections, which cause an apoptosis of infected cells to eliminate infection reservoirs. Recently, a new respiratory syndrome coronavirus 2 (SARS-CoV-2) caused by the covid-19 virus (2019-nCoV) recently appeared in China and has a virus similar to the SARS coronavirus that spread internationally in 2003, infecting more than 8,000 people, killing almost 800. Currently, covid-19 infection spread across the world, causing widespread
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social and economic disruption (Fedson, Opal and Rordam, 2020). The viral life cycle of this new virus occurs through the quarters of the S protein that radiates the lipid envelope. An S protein is a class I fusion protein that has the amino terminal of the carboxyl terminal in the S1 and S2 subunits, being connected by a fusion peptide (Cheng et al., 2007). In addition, Protein S has 1104 to 1273 amino acids and contains an S1 amino (N) -terminal subunit and a carboxyl (C) -terminal S213 subunit (Figure 8) and the S1 subunit (receptor-binding domain - RBD) has the ability to connect to Angiostensin 2-binding enzyme (ACE2) (Liu et al., 2020). The virus 2019-nCoV causes cell death after binding the protein ACE2 and spreads, causing cell damage, death and complications in infected tissues, such as liver cells, cardiac cells, vascular endothelium, testis and kidney (Cheng et al., 2007; Shi et al., 2020).

Figure 8: illustrates the structural diagram of the SARS-CoV, MERS-CoV and SARS-CoV-2 peak glycoproteins and the S1 and S2 subunits, which were divided by the S. FP protein cleavage sites, shows the fusion peptide; HR, shows heptad repeat 1 and heptad repeat 2; RBD demonstrates the receptor binding domain, which contains the connection to the nucleus in the external subdomain; SP, indicates the signal peptide (Liu et al., 2020)

In the case of cell death, SARS-CoV-2 induces, for example in lymphocytes, through the intensification of Fas signaling, and is a highly cytotoxic virus, its persistence in the secondary organic lymphoid can induce lymphocytopenia. To confirm this possibility the autors Chen et al. (chen et al., 2020) used the staining method at the TUNEL site, display what type of cancer and lymphocytes (LNs) infected by viruses manifest strong apoptosis, while apoptotic cells in tissues from undetectable age, coming to the conclusion that that SARS-CoV-2 induces cell apoptosis. However, the SARS-CoV-2 virus does not directly infect lymphocytes, so the persistence of an old virus can constitutively activate T cells and B cells in the spleen and LNs, use-induced cell death (AICD), which is mediated by Fas/FasL signaling (chen et al., 2020).

In addition, deregulation of pro-inflammatory cytokines such as TNF-α and IL-6 has been reported to promote cell
necrosis and apoptosis. (Chen et al., 2020). Since IL-6 interleukin has a wide effect on cells in the immune system and in those that do not belong to the system (Hunter and Jones, 2015). The exposure to viral Spike protein (S) can trigger transcription of the Il6 gene in macrophages in in vitro tests, resulting in high levels of IL-6 in vivo from SARS-CoV-infected macrophages (Chen et al., 2020). Therefore, the author requests that IL-6 derived from macrophages cause lymphocytic apoptosis, necrosis and could improve Fas expression.

**CONCLUSION**

In this study it was possible to conclude that the cell death is fundamental for the maintenance of the organism homeostasis, since it defines the cellular response caused when there is an imbalance in the extracellular and intracellular means, often resulting in pathologies. Among the listed diseases, the types of cell death and their agents are extremely important in metastatic cancer and may cause cellular morphological changes inhibiting or allowing the evolution of this disease, besides actively participating in the performance of some tumor suppressor drugs. Another extremely important point was to highlight cell death in systemic pathologies, since any cell damage and failure in the process of cell death can lead to such pathologies as inflammatory bowel disease, lupus, cardiovascular disease, efferocytosis and microbial infection, especially for viruses. Cell death in these cases may contribute to block or contribute to the advancement of these diseases. Therefore, cell death by apoptosis, necrosis and autophagy are necessary scientific knowledge for future studies in the treatment and control of pathologies, since their mechanisms morphologically alter cells and maintain tissue balance and homeostasis, and any alteration can cause diseases. serious. Moreover, understanding the functioning of each type of cell death allows the development of drugs and therapies to control future and existing pathologies, and perhaps even cure current diseases.

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**OBSERVAÇÕES:**

1. Os autores declaram não existir conflitos de interesse de qualquer natureza.

2. As imagens no presente artigo são de total responsabilidade dos autores.

**NOTES:**

1. The authors declare that there are no conflicts of interest of any kind.

2. The images in this article are the exclusive responsibility of the authors.

**Supplementary material**

**TABLE 1 - Supplementary material: Data related to the studies of the selected articles.**
Cell death and its concept applied in general health and microbiological action: literature review

| Article | Intervention | Conclusion |
|---------|--------------|------------|
| Chen, Kang and Fu, 2018 | The study was a literature review made through the analysis of articles published in the last 10 years, about different types of cell death. It addresses the the specific mechanisms involved in each type of death and their consequences, demonstrating the impact of different types of cell death on disease treatment. | The authors concluded that the three types of cell death: apoptosis, autophagy, and necrosis, which were previously classified as independent, were now considered as interconnected processes with overlapping signaling pathways in response to different stresses. Thus implying the complexity of cell death programs and also providing new therapeutic targets. |
| Behar and Breiten, 2018 | This article provided a literature review on Efferocytosis (apoptotic cell involvement), which reviewed articles published in the last 10 years, presenting an overview of known bacterial effectors, their host cell targets and their importance for the virulence of human pathogens. | The authors concluded that many bacterial pathogens actively inhibit host cell apoptosis, which allows them to avoid the antibacterial effects of efferocytosis. |
| Tovar et al., 2015 | The article presented a bibliographic review made by analysis of articles published in the last 10 years, showing that eotaxin apoptosis induces depletion of the ovarian reserve, directly affecting the reproductive outcome of mammals, such as humans. | They concluded that eotaxin apoptosis is a major cause for ovarian germ cell depletion and has a direct negative impact on female fertility. |
| Bolmster et al., 2019 | This article presents a literature review with analysis of articles from the last decade, reviewing the different aspects related to the mechanism of action of tumor necrosis factor (TNF) inhibitors in the treatment of inflammatory bowel disease to Antitumor necrosis factor (TNF) therapy. | It was possible to conclude by the authors that, in order to improve response rates of anti-TNF antibody treatment, in addition to pharmacokinetic reasons, it is mandatory to better understand the mechanism of action of these agents, namely, tumor necrosis factors, to unravel the main routes of treatment. Signaling involved. |
| Olsen et al., 2016 | This article is a literature review that discusses available data on biologic treatment with tumor necrosis factor (TNF) inhibitors. In order to identify mechanisms of importance for its effectiveness in inflammatory bowel disease. | TNF inhibitors have proven efficacy in inflammatory bowel disease, affecting the signaling of this factor only suppressing the production of proinflammatory cytokines and other mediators. This resulted in reduced inflammation and decreased cellular activation, proliferation, leukocyte recruitment and angiogenesis, and subsequent promotion of mucosal healing. |
| Komaki et al., 2017 | The article was a systematic review and meta-analysis of direct and network meta-analyses that evaluated the outcome of pregnancy and maternal complications with the use of tumor necrosis factor-a in women with immunomodulated diseases. | The authors concluded that female patients with immune-mediated diseases treated with tumor necrosis factor-a (TNF-α) had a significantly higher risk of premature birth, miscarriage, and low birth weight compared to the general population, but achieved comparable results with non-carriers. |
| Singh et al., 2018 | The article was written through a systematic survey conducted through January 24, 2017, which identified randomized controlled trials or observational studies in adults to assess the association between obesity and response to tumor necrosis factor-a (TNF-α) agents. | The researchers' conclusion was that obesity is an unreported predictor of lower response to Anti-tumor necrosis factor (TNF) agents in patients with selected immune-mediated inflammatory diseases. |
| Sasi et al., 2015 | The article consisted of a literature review, part of the volume entitled “Autophagy and protein quality control in cardiovascular disease.” Which highlighted the dual role of autophagy in the development of cardiovascular disease. And how the full recognition of autophagy as an adaptive response provides new strategies for cardiovascular disease prevention. | They concluded that the definition of the mechanisms of autophagy pathways in different cell types in the cardiovascular system. And the importance of autophagosomal degradation of organelles, such as endoplasmic reticulum and mitochondria, during oxidative stress, which may produce new therapeutic approaches for the treatment of cardiovascular disease. |
| Keenan, 2015 | This article is a literature review, studying studies that seek attempts to identify specific inducers or inhibitors of autophagy and how to use them for therapeutic correction when there is dysregulation. | They concluded that autophagy inhibitors, which are targeted to specific cell types or tissues, thus allowing a new specific type of therapeutic intervention. |
| Martin et al., 2015 | The article portrayed a literature review that analyzed articles published in the last 10 years, seeking to integrate the newly described roles of wild-type Huntington (HdhQ171), as well as altered autophagy in Huntington’s disease. | The researchers concluded that the Huntington N-terminal Tract is not simply a passive passenger in autophagy, but is also an important regulator, acting as a scaffold for the transport of autophagosomes and biogenesis. |
| Mevors, Sharif and Macleod, 2017 | This review was a bibliographic study that analyzed publications from the last ten years, presenting an overview of how autophagy modulates cancer metastasis. In addition to discussing the importance of new findings for the management of the disease. | They concluded, in short, that autophagy had a number of critical functions throughout cancer metastasis, offering the opportunity to define specific points in the metastatic cascade where autophagy inhibitors can be targeted to reduce cancer mortality rates. |
| Rotinova et al., 2018 | The article represented an applied research that analyzed the cultivation of human Proliferating cell nuclear antigen (PCNA) and prostatic cancer cell line LNCaP. This cell line was grown in steroid-free medium and treated with Albinizone A (AA) and therefore evaluated the potential | The authors then concluded that Albinizone A (AA) activated autophagy as a cytoprotective mechanism and specific cancer cell line LNCaP and targeting autophagy enhances the antitumor effect of the compound. |
| Reference                    | Summary                                                                                       | Conclusion                                                                                     |
|-----------------------------|------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------|
| (Nagata, 2018)              | The article analyzed the reasons why cells suffer cell death, and analyzes the types of programmed cell death: necrosis and apoptosis, emphasizing the clearance of cells in the process of cell apoptosis. For this, articles published in the last 10 years were analyzed. | They concluded that the way apoptosis is triggered, it is understood that necrosis, previously considered a process of accidental death, is also programmed and categorized into pyroptosis and necroptosis. And that the approval of an anticancer drug developed through apoptosis research for the treatment of chronic lymphocytic leukemia is the initial step to elucidate the molecular mechanisms of efferocytosis. |
| (Mabu et al., 2019)         | The present study showed an applied research that investigates the effect of acidosis on the contribution of apoptosis, necrosis and autophagy to MDCA - MB 231 cells to better understand the mechanisms of cancer disease. | From the study approached, the authors concluded that eventually, in the early stage of cancer progression, apoptosis is the main mechanism of cell mortality and, later, autophagy would be the main mechanism of cell survival. |
| (Genica et al., 2017)       | The present article was a literature review, which analyzed articles from the last decade, reporting the relationship between autophagy and cancer. In addition to addressing cancer modulating autophagic therapy. | They concluded that autophagy provides alternatives, energy, or nutrient supply to cancer cells under unfavorable conditions. |
| (Finnay et al., 2017)       | The present article consisted of a literature review that gathered articles from about 10 years ago, and dealt with approaches performed for tumor cell apoptosis induction for therapeutic purposes, review of the BCL-2 protein family and the current study of IAPs as targets for anti-cancer therapy. | Since IAPs are at the nexus of cancer cell survival and, conversely, apoptosis, the authors concluded that while clinical application of IAP antagonists has not yet produced the desired drug, the continued development of next-generation agents and potent combinations is a good omen for the future. "Inhibiting inhibitors" is seen as a viable anti-cancer strategy. |
| (Su et al., 2015)           | The article presented a review and literature based on articles published in the last ten years, and reviewed recent advances in understanding the mechanisms by which major apoptosis, autophagy and necroptosis regulators participate in cancer metastasis and discusses crosstalk between apoptosis, autophagy and necroptosis involved in the regulation of cancer metastasis. | They concluded that the types of programmed cell death are natural barriers that prevent malignant cells from surviving and spreading. And the more we understand about the specific roles, mechanisms and regulators of apoptosis, autophagy and necroptosis and their interaction with cancer metastasis, the best therapeutic strategies can be developed for cancer treatment. |
| (Mate et al., 2019)         | This paper addressed a systematic review and meta-analysis of observational studies, including patients with a history of cancer exposed to anti-tumor necrosis factor therapy, assessing the risk of new cancer or cancer recurrence by September 2015. | It was concluded by the authors that the risk of new cancer or cancer recurrence among patients with a history of cancer and use of anti tumor necrosis factor (anti-TNF) therapy is similar to the risk with non-biological disease modifying therapies. These results support the use of antiTNF drugs in selected populations, despite previous cancer diagnosis. |
| (Lok et al., 2019)          | This study is a preclinical case study combining BCL2 inhibitor venetoclax with trastuzumab in a phase Ib clinical trial to demonstrate that apoptosis targeting could represent a promising new strategy in the treatment of breast cancer. | It was concluded by the researchers that in the first clinical study to evaluate venetoclax in a solid tumor, the combination of venetoclax with endocrine therapy had a tolerable safety profile and elicited remarkable activity in ER and apoptotic protein BCL2 positive metastatic breast cancer. These findings support further investigations of apoptosis targeting combination therapy for patients with BCL2 positive tumors. |
| (Koff, Ramachandiran and Iyeral-Mirza, 2015) | The article consisted of a literature review that analyzed the latest findings in the regulation of apoptosis and possible mechanisms for resealing tumor cells to therapy, published in the last decade. | It was concluded by the authors that while dysregulated malignant cell apoptosis remains an attractive target in cancer therapy, much work needs to be done to realize the full potential of such approaches. |
| (Li, Tong and Ling, 2019) | The article consisted of a research applied to the dental area, which sought to explore the effect of E. faecalis on apoptosis in MG63-E1 osteoblastic cells through an in vivo model. For this, the nature of mouse MG63-E1 osteoblastic cells was analyzed. From the analyzed article, they concluded that clinically isolated strains of E. faecalis can induce apoptosis in MG63 osteoblasts, which can be attributed to the regulation of the interaction between Bel-2 and Bax in the Bel-2 family. These findings may provide information on the development and repair of PAP periodontal bone destruction. |
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| (Castro et al., 2017) | The article studied was a research applied to dentistry, which characterize the immune clearance of apoptotic cells and their modulation by ginsenosides. Because, efficient clearance of apoptotic cells is essential for the resolution of inflammation and tissue restoration. In studies have examined the capacity of ginsenoside-treated macrophages to migrate towards and phagocytose apoptotic cells. They concluded that lysine ginsenosides treatment reduced surface expression levels of CD14, a key macrophage receptor for apoptotic cells, which resulted in reduced macrophage interactions with apoptotic cells. Additionally, while apoptotic cells and their derived secretome were shown to inhibit TNF-a-induced expression by P. gingivalis lipopolysaccharide. The authors demonstrated that ginsenoside preparations induced a rapid inflammatory response in macrophages that was resistant to the anti-inflammatory effects of apoptotic cells or their secretome. |
| (Chen et al., 2019) | This paper analyzed the Cardiolipin-induced apoptosis of periodontal ligament cells (PDLCs), and the authors have suggested that is an important pathogenic factor of periodontitis. Because the mitochondrial abnormalities are closely linked to OS and act as the main players in apoptosis. The authors confide in this study that significant reduction in viability and increased apoptosis were observed in H2O2-treated hPDLCs. They also noted that H2O2 also induced mitochondrial dysfunction, judging by increased mitochondrial reactive oxygen species amounts, and decreased mitochondrial membrane potential as well as ATP levels. In conclusion, these paper, the OS-induced apoptosis of hPDLCs may be mediated by mitochondria-dependent pathway. |
| (Zhang et al., 2015) | This paper portrayed a case-control study that investigated how a high glucose environment influences the osteogenic capacity of periodontal ligament stem cells (PDLSCs) and the autophagy function in this process. It was explored whether the osteogenic capacity of PDLSCs could be protected by autophagy. The authors then concluded that high glucose inhibited PDLSC activity and regulated cellular function protected by autophagy. Self-regulation of autophagy partially reversed the adverse effect of high glucose conditions on PDLSCs. |
| (Yang et al., 2019) | The article portrayed a research applied to dentistry, which evaluated through Hypoxia-induced generation of reactive oxygen species in mitochondria and changes in mitochondrial membrane potential were evaluated, respectively, by Mitotracker and JC-1 fluorescence dye signaling, the connection between mitochondria and hypoxia-induced apoptosis in osteoblasts. It also identifies whether simvastatin alleviates bone resorption in apical periodontitis by modulating autophagy-related apoptosis. The authors concluded from the results that autophagy is a prerequisite for hypoxia-induced osteoblast apoptosis and inhibition of simvastatin osteoblast apoptosis, at least partially by inhibiting autophagy. Modulation of osteoblast autophagy may help decrease inflammation-associated bone loss and has its potential as an adjunctive therapy in apical periodontitis. |
| (Song et al., 2017) | This paper presented a literature review that analyzed publications from the last 10 years and sought to relate programmed cell death in periodontitis. The authors concluded by the researchers that apoptosis was in fact reported to have a role in periodontitis. However, the role of autophagy in periodontitis needs further verification. Moreover, the implication of necrosis or pyroptosis in periodontitis remains unknown. They recommend future studies, which will unravel the pivotal role of PCD in periodontitis, allowing us to prevent, diagnose, and treat the disease, as well as predict its outcomes. |
| (Loreto et al., 2019) | This paper is a research applied to dentistry that analyzed immunohistochemical study explored the localization of TRAIL, DR5, Bel-2 and Bax, the main proteins involved in apoptosis, in teeth with advanced caries. To evaluate TRAIL, DR5, Bel-2 and Bax immunoreactions twelve permanent carious premolars were embedded in paraffin and processed for immunohistochemistry. The permanent premolars (10 with gross cavities and 2 healthy teeth), collected after extraction at the Department of General Surgery and Medical-Surgical Specialties of the University of Catania (Italy). Activation of the apoptotic process in decayed teeth was investigated to gain insight into its molecular mechanisms. The authors concluded that embossedness an adoption routes are activated in dental caries, and showed that TRAIL and DR5 were overexpressed in dentin and in pulp vessels and microvascular cells; strong Bax immunostaining was detected in disintegrated dentinal tubules close to the lesion, and Bel-2 staining was weak in some dentin areas under the cavity or altogether absent. These findings suggest that both apoptosis pathways are activated in dental caries. However, according to the authors, additional in vitro studies on odontoblast cultures will be needed to obtain more information on the apoptotic mechanisms and studying the progresses and progress of the apoptotic pathways and their inhibition, using the identification of drugs that may influence this process. |
| (Jiang, Li and Zuo, 2019) | The article was analyzing articles from the last 10 years illustrating the effect of autophagy on the pathogenesis of periodontal disease. It was concluded, according to the authors, that autophagy has been shown to have multiple regulatory effects on the pathogenesis of periodontal disease. Regulatory effects are mainly |
Cell death and its concept applied in general health and microbiological action: literature review

| Reference          | Summary                                                                                                                                                                                                 | Conclusions                                                                                                                                                     |
|--------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Tang et al., 2018  | The study was a case study that evaluated the effect of 1,25-dihydroxyvitamin-D3 (1,25VitD3) on neuropathic apoptosis in patients with type 2 diabetes mellitus and periodontitis, and the mechanism of the signaling pathway relevant for p38-MAPK in this in vitro process. | The researchers concluded that 1,25VitD3 could promote peripheral blood neuropathic apoptosis in patients with type 2 diabetes mellitus and PD by activating the p38-MAPK signaling pathway in vitro. |
| Taskin et al., 2019| The article presented a case-control study that evaluated the effect of oleuropein on ligature-induced alveolar bone loss. In this regard, osteoblastic, osteoclastic activity, inflammatory markers and apoptosis were evaluated. | The authors concluded that oleuropein successfully decreased alveolar bone loss as a result of decreased osteoclastic activity, inflammation and apoptosis, and increased osteoblastic activity. |
| Chen et al., 2020  | The article is an experimental study, which investigates an infeccteptin, common in patients infected with coronavirus respiratory syndrome 2 (SARS-CoV-2), through a spleen and lymph node inspection (LNI) of six post-mortem use cases. | The authors noted that SARS-CoV-2 could directly affect a secondary lymphoid to induce cell death. In addition, the in situ staining of TUNEL illustrated that viral infection leads to lymphocytes in cases of apoptosis mediated by viral antigens inducing positive Fas regulation. And that SARS-CoV-2 can also promote lymphocyte necrosis, through macrophages that produce cytokine IL-6. |
| Cheng et al., 2007 | This study is a comprehensive literature review on the coronavirus of severe acute respiratory syndrome (SARS) (sars-cov), seeking to understand taxonomy and virology of sars-cov; viral life cycle; sequence of the molecular and epidemiological evolution of virus sars; molecular evolution; epidemiological characteristics; clinical resources; histopathological and histological changes in SARS; immunological profiles; immune response and susceptibility to hosting; laboratory diagnosis of sars-cov infection; clinical management and antivirals; infection control and laboratory safety; passive immunization and development of a sars-cov vaccine. | The authors concluded that, despite the control numbers for the control of SARS, there are still terms in terms of the molecular basis of physical stability and transmission of this virus, as well as doubts about a molecular and immunological basis of pathogens of human diseases. And as the coronavirus class undergoes genetic recombination, it can lead to new genotypes and outbreaks. |