

Necroptosis Signaling Pathways and its Pharmacological Implications in Chronic Inflammatory and Infectious Diseases: A Mini Review

Rumpa Banerjee¹, Adrija Chatterjee² and Abhijit G Banerjee^{3*}

¹Eminent College of Pharmaceutical Technology, India

²Eminent College of Management & Technology, India

³Genomic Bio-Medicine Res. and Inc., Chhattisgarh (CGBMRI), Durg, India

***Corresponding author:** Abhijit G Banerjee, Genomic Bio-Medicine Res. and Inc, Chhattisgarh (CGBMRI), Durg, CG-491001, India

ARTICLE INFO

Received: 📅 October 14, 2024

Published: 📅 October 24, 2024

Citation: Rumpa Banerjee, Adrija Chatterjee and Abhijit G Banerjee. Necroptosis Signaling Pathways and its Pharmacological Implications in Chronic Inflammatory and Infectious Diseases: A Mini Review. Biomed J Sci & Tech Res 59(2)-2024. BJSTR.MS.ID.009265.

ABSTRACT

Introduction: Necroptosis is a state of a cell wherein, necrosis occurs but in a programmed way. Basically, necroptosis is a mediator between necrosis and apoptosis where cells can undergo programmed necrosis when apoptosis signaling is inhibited by some external factors like pathogen or some genetic mutation. Apoptosis or Programmed Cell Death (PCD) is an end of cellular life controlled by programmed signaling. Apoptosis takes place by producing apoptotic bodies, which are capable of engulfing the cell itself before these can spread their content on to neighboring cells and causing damage to them. Here some, programmed and sequential cellular changes, occur including blebbing, cell shrinkage, and chromatin condensation etc. Generally, apoptosis is a caspase (a protease enzyme) -dependent process, but necrosis is promoted due to injury or infection. Current review work is focused on an alternative form of programmed cell death known as 'Necroptosis' as a target, and the findings have pharmacological implications for various inflammatory diseases, with or without infection. In this review, we have focused on the interplay of relationships between apoptosis and necroptosis signaling mechanisms at the molecular level, that might address targets of potential intervention.

Methods: Literature review was carried out in the Pubmed database utilizing the keywords mentioned below and boolean operator functions. A total of 38 articles were finally reviewed that were available in full-text, in English and appeared in the last two decades.

Results and Discussion: The type of inflammatory cell death is an important factor in various chronic inflammatory disorders and infectious diseases. Both the apoptosis and the necroptosis can be activated upon stimulation, via the Tumor necrosis factor- α (TNF- α or TNF α) and TNF Receptor-1 (TNFR1) and is mainly mediated by receptor interacting protein (RIP1-RIP3) coupling involving the RIP homotypic interaction motifs (RHIM). This effect is mediated by RIPK3 in the necroptotic signaling pathway, wherein RIP1 participates as an accessory molecule in the signaling complex.

Conclusion and Implications: Various natural and synthetic compounds having inhibitory or modulatory effects on the necroptotic signaling pathways is discussed. The structural implications of ligand – protein interactions may provide a basis for future drug development or repurposing strategies.

Keywords: Necroptosis; Inflammation; Receptor Homotypic Interaction Motif (RHIM); Advanced Glycation End Products (AGE); Necrostatin-1 (Nec-1)

Abbreviations: RHIM: Receptor Homotypic Interaction Motif; RIP: Receptor Interacting Protein; TNF: Tumor Necrosis Factor; PCD: Programmed Cell Death; NGF: Nerve Growth Factor; TRADD: TNF Receptor-Associated Death Domain; RIP: Receptor-Interacting Protein; FADD: FAS-Associated Protein with A Death Domain; RSO: Reactive Oxygen Species; RHIM: RIP Homotypic Interaction Motif; AGE: Advanced Glycation End; ETC: Electron Transport Chain

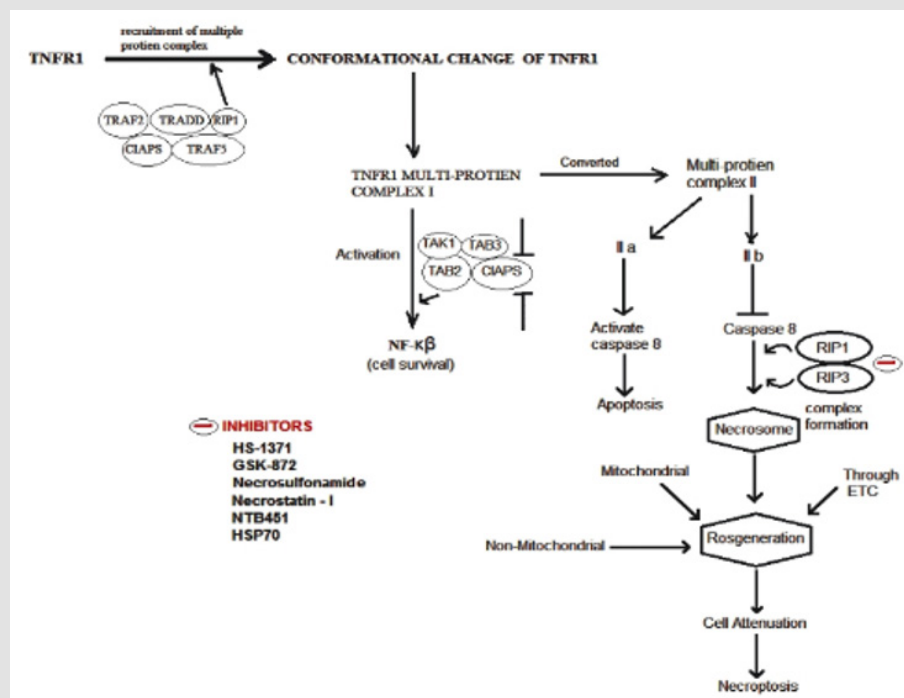


Figure 1: Overview of the molecular and pharmacological aspects of the necroptosis cycle.

Introduction

Apoptosis is a type of programmed cell death occurring through signal transduction. Although extracellular death domain ligands carrying cytokines have the power to initiate apoptosis, the fate of apoptosis is mainly dependent upon caspase activation. Caspase, a cysteine-aspartic protease enzyme family, has an important role in "apoptosis". Cysteine in the active site of the enzyme, has a nucleophilic attack site that cleaves the target molecule after aspartic acid [1,2]. These caspases are functionally classified into three types: initiator caspases (caspase 2, caspase 8, caspase 9, and caspase 10), executioner caspases (caspase 3, caspase 6, and caspase 7); and inflammatory caspases (caspase 1, caspase 4, caspase 5, caspase 1, caspase 12, and caspase 13) [3]. When these initiator caspases get a signal, then these initiator molecules proceed in a chain reaction to activate executioner caspases [4].

The Initiation of Apoptosis

Apoptosis is regulated at two phases i.e., namely, extrinsic: that involves the interaction of an external death domain ligand with the death receptor and the activation of caspase 8 and caspase 10, and intrinsic: that leads to the release of mitochondrial cytochrome C via the activation of caspase 9 [5]. In addition to the extracellular death domain signal, it is seen that caspase activation is directly proportional to the presence or absence of some amounts of nerve growth

factor (NGF), for example, Neurotrophins are trophic factors that inactivates the apoptotic regulator protein. This trophic factor works on pro-apoptotic and anti-apoptotic interaction. If this factor is absent, then pro-apoptotic protein Bad binds to anti-apoptotic proteins from the Bcl-2 family and thus prevents Bcl-2 from interacting with membrane bound pro-apoptotic protein Bax. Then, Bax forms an ion-channel through which mitochondrial cytochrome-C is released into the cytosol where these Cytochrome-C binds to the adapter protein Apaf-1, that leads to the activation of caspase-9, initiating the formation of the multiprotein complex apoptosome, which promotes "apoptosis". On the other hand, the necroptotic pathway is extensively characterized by the ligation of the external death domain of the inflammatory cytokine – Tumor necrosis factor- α (TNF- α) to Tumor necrosis factor receptor-1 (TNFR-1) [6]. Once TNFR-1 gets stimulated, then TNFR-1 undergoes conformational changes and allows the formation of TNFR-1 multiprotein complex-I, which leads to the NF- κ B activation pathway (cell survival), or TNFR-1 multiprotein complex-II, which leads to caspase-dependent apoptosis whereas; TNFR-1 multiprotein complex-IIb, that leads towards the caspase-independent process termed as necroptosis [7].

Results

The literature search on medical database - Pubmed, resulted in 38 articles found to be acceptable for review after meeting inclusion and exclusion criteria.

Discussion

Following sections address sequentially the parameters of molecular cascades responsible and targets & current interventions worthy of discussion.

Interplay Role of the TNFR-1 Signaling Pathway Between Cell Survival, Apoptosis and Necroptosis

TNFR-1 Elicits Discrete Molecular Signals Related to Cell Survival, Apoptosis and Necroptosis

The binding of TNF-alpha to TNFR-1, allows the recruitment of multiple proteins like, TNF receptor-associated death domain (TRADD), receptor-interacting protein-1 (RIP-1), cellular inhibitor of apoptosis protein (cIAPs), and TNF receptor-associated factor 2 and factor 5 (TRAF-2 and TRAF-5), to form the TNFR-1 multiprotein complex-I [7]. RIP-1 is a death domain -containing serine/threonine kinase. It exhibits two conformational states, an open or closed state. In the closed state, the T-loop blocks the activation loop or T-loop to inhibit its catalytic effect, but autophosphorylation of Ser-161 in the activation loop helps to become an open active kinase state [8]. The cIAPs that mediate Lys-63 polyubiquitinylation to RIP-1 helps to dissociate RIP-1 from the TNFR-1 complex and recruit transforming growth factor-beta-activated kinase-1 (TAK-1), which induce the binding of TAK-1 binding to protein-2 and 3 (TAB-2 and TAB-3), which together leads to the activation of the NF-kB pathway [9,10]. But, the inhibition of cIAPs blocks the NF-kB pathway and prevents RIP-1 polyubiquitination, thus promoting the conversion of complex-I to multiprotein complex-II that contain TRADD, Fas-associated protein with a death domain (FADD), caspase-8 and RIP-1 [11,12]. This caspase-8 shuts down the activity of RIP-1 by proteolytic cleavage and leads to the activation of classical extrinsic caspase. Once the caspase-8 is inhibited at least one additional protein, RIP-3, is added to form multi-protein complex [13,14]. Like the RIP-1 family, RIP-3 is also an important component for necroptosis signaling. In addition to having an 'N'-terminal kinase domain, RIP-3 also has a 'C'-terminal RIP homotypic interaction motif (RHIM), which interacts with RIP-1 forming a necrosome complex, similar to the apoptosome, and this interaction makes sure that both RIP-1 and RIP-3 phosphorylates each other by sharing their respective kinase activities [15].

Execution of Necroptosis

As the necrosome complex (the RIP1-RIP3 interaction complex) determines how to initiate the necroptotic cell death, so the regulation of necroptosis is determined by the generation of mitochondrial Reactive Oxygen Species (ROS) generated by NADPH oxidase and Nox-1, causing over activation of Poly (ADP-Ribose) Polymerase (PARP-1), triggered by DNA damage.

Mitochondrial Reactive Oxygen Species (ROS) Generation

Mitochondrial-dependent ROS generation is directly linked to mitochondrial respiratory chain bursts. RIP3, a component of the necrosome, activates glycogen phosphorylase (PYGL) to induce glycogenolysis, where the end product, glucose-1-phosphate, goes through the glycolytic pathway to produce glucose-6-phosphate, which can be converted to pyruvate, which in turn is the substrate in the production of acetyl Co-A, to run the Tricarboxylic acid cycle [13,14]. This RIP3-mediated metabolic pathway is prone to the production of methylglyoxal (a cytotoxic compound), but the main source of generation of cytotoxic compound occurs when phosphate elimination occurred from glyceraldehydes phosphate, di-hydroxyacetone, and dihydroxyacetone phosphate. The exact function of this compound is unclear, but the recent work on this compound has revealed that methylglyoxal, covalently bound to the free amino group of a protein molecule alters their function to form Advanced Glycation End product (AGE), which favors the formation of ROS. Furthermore, these AGEs inactivate the glycolytic pathway due to dysfunction of mitochondrial protein, which attenuates the cell [15].

Involvement of the Electron Transport Chain (ETC) in ROS Generation

The ETC is a series of complex biochemical reactions in which electrons are transported from one complex to another via carrier protein through oxidation-reduction. The last acceptor of electrons is the oxygen molecule. In mutated condition, if this oxygen molecule is prematurely reduced, then it results in production of superoxide radicals, Hydroxyl radicals (OH⁻), leading to the chromosomal aberration (mainly DNA strand breaks). This free radical has the ability to initiate lipid peroxidation, a process where electrons from the lipid bi-layer of the cell membrane are eliminated, resulting in cell damage [16].

Non-Mitochondrial ROS Generation

It occurs when the plasma membrane produces NADPH oxidase-Nox1, which is recruited by RIP1 [17]. However, it is reviewed that RIP1 is not the main factor responsible for NADPH oxidase dependent Nox1 activation. The functioning of the NADPH oxidase Nox1 is dependent when Riboflavin Kinase (RFK) combines with TNFR1 on the combination of riboflavin kinase (RFK) with TNFR1 and TRADD [18]. RIP1-RIP3-mediated signal activates JUN-N-terminal kinase to degrade ferritin, to form a labile iron pool [19]. Ferritin is an iron-binding protein. It acts as a storage of non-toxic iron and agent for nontoxic iron, and due to its ferroxidase activity, it converts iron from ferrous (Fe²⁺) to ferric (Fe³⁺), which remains in stable form [20]. Free iron from the labile iron pool catalyzes the formation of reactive oxygen species, which is why it is highly toxic to cells and can be taken up by mitochondria through mitoferrin, a mitochondrial iron transporter [21].

Involvement of lysosomal Membrane Permeabilization (LMP) in Necroptosis Execution

The necrosome (RIP1-RIP3) elicited signal elicits sphingomyelinase activity. Sphingomyelinase is a DNase1 superfamily enzyme, which works on sphingomyelin to generate ceramide, and this breakdown of sphingomyelin occurs in an acidic chamber, similar to lysosomal compartments [22]. Ceramide, the structural lipid molecule of the plasma membrane of a cell, can be converted to sphingosine by ceramidase activity through the salvage pathway, and thereafter the sphingosine is ready to be discharged from the lysosome. Sphingosine opens the calcium ion channel to generate cytosolic free Ca^{2+} waves [23]. These cytosolic free calcium waves induce two bio-signaling pathways (one calcium-dependent calpain cascade and the other cytosolic phospholipase A2-mediated lipid peroxidation) to change the lysosomal membrane permeabilization [24].

Regulation of Calpain in Cellular Damage

Calpain, a calcium-dependent protease, is a heterodimer (calpain I and calpain II) that has a large catalytic subunit and a small regulatory subunit. The N-terminal region of the catalytic subunit has a proteolytic cleavage site which is active on the enzyme-substrate reaction. It is seen that nuclear lamin of both the "A" and "B" type act as a substrate of calpain [25]. The Lamin protein is a structural unit of the nucleus that helps to maintain the nuclear shape. Calpain cleaves this lamin protein, which is anchored to chromatin allowing chromatin condensation. It is known that calpain attack on Lysosomal Associated Membrane Protein2 (LAMP2) through proteolytic cleavage activity; as a result, lysosomal membrane permeability changes, which induces the leakage of cytotoxic hydrolase enzymes into the cytosol [26]. All cytosolic free calcium waves and the presence of free radicals and reactive oxygen species (ROS) are collectively responsible for the generation of Mitochondrial Permeability Pore Complex (MPTP). Szabo et al., explored the mitochondrial permeability pore complex (MPTP) formed by voltage-dependent anion channel (VDAC) molecules, found that, a free Ca^{2+} molecule binds to the Ca^{2+} -binding site on the MPTP, and this can cause the pore complex to open [27].

This leads to the decrease in mitochondrial membrane permeability and transmembrane potential is lost [28]. Loss of transmembrane potential inhibits the ATP production through the hydrolysis of ATP synthase [29]. Simultaneously, the opening of the MPTP arrests the adenine nucleotide translocase activity, which shuts down the ADP/ATP exchange across the mitochondrial membrane [30]. This depletes stored ATP to make up for the basic need of free energy in cells, which causes energy deficit conditions. Once the mitochondrial membrane permeability drops, that leads the translocation of Apoptosis Inducing Factor (AIF) from mitochondria to nucleus and this triggers Poly (ADP) Ribose Polymerase hyper activation followed by DNA single strand break, resulting in programmed cell death. Once PARP detects single strand DNA nicks, PARP depletes the stored ATP

of Cell in an attempt to repair the damaged DNA, which leads to cell lysis [31].

Apoptosis Versus Necroptosis in Individuals with Normal Development and Chronic Inflammation-Dependent Diseases

Development is a process whereby unnecessary and damaged cells or tissues are removed through natural ways; for this reason "apoptosis" is considered to be involved in morphogenesis during development. In contrast, from the abovementioned studies it is seen that necroptosis is an accidental death of any cell or tissue from injury. So it is very important to suppress necroptosis during development. From the above studies, we also know that RIP1-RIP3 is a crucial component to initiate necroptosis (Figure 1). So, the protease activity of caspase-8 plays an important role in suppressing the RIP1-RIP3 kinase activity. During early embryogenesis, it has been proven that any aberration or deletion of RIP1-RIP3 decreases the lethality in caspase-8- or FADD- mutant mice. Cell death caused by any genetic mutation, injury or neurodegeneration is the significant feature of human disease. Neurodegeneration results in the loss of neuronal cells, both structurally as well as functionally. The discovery of Nec1 (a RIP1 inhibitor) made it possible to provide protection against excitotoxicity, conferring the implication of the importance of RIP1 kinase in neurodegenerative diseases. So, to elicit the interest in the pathology of neuro-degenerative diseases, RIP1 kinase is considered to be a druggable target. Excitotoxicity, oxidative stress, and mitochondrial malfunction thus causes neurodegenerative diseases such as Huntington's disease or retinal degeneration through RIP1 activity. Necroptosis is also an important component of acute respiratory disease syndrome (ARDS) in COVID-19 patient's that progress to a severe stage [32] through upregulation of the host RIP3 [33].

Huntington's disease is a genetic disorder due to an autosomal dominant mutation in the Huntington gene, which provides information about the Huntington protein (HTT) but for; this single-gene mutation causing the expansion of trinucleotide repeats (CAG, Cytosine-Adenine-Guanine) that encodes for polyglutamine, an altered or mutated form of the HTT protein (mHTT), becomes responsible for malfunction and death of neurons. But it is seen that application of Nec1 delays the progression of neuronal cell line death [34]. Age-related macular degeneration is a disorder of retinal pigmented epithelial (RPE) degeneration of the macula. The macula is an oval-shaped pigmented area at the center of the retina of the human eye. Histologically, the macula has two or more layers of ganglion cells. In dry or non-exudative forms, there is deposition of drusen (extracellular protein or lipid) in the macula between the RPE and choroid, resulting in retinal damage over time [35]. Here, we discuss the necroptotic death of RPE cells in response to Sodium Iodate. The use of sodium iodate directly affects the RPE cells, which produces ROS, implicating the RIP kinase activity. If different cell death inhibitors, such as Nec1, Nec5, Nec7 and GSK872, were used before NaIO₃ treatment it was

observed that, these inhibitors were shown to act directly on RIP1 and RIP3, increasing RPE cell viability, despite the effect of NaIO3 treatment. From these observations, it can be safely concluded that RPE cell degeneration occurs mainly through RIP1-RIP3 activity [36]. Necroptosis is also associated with the pathogenesis of periodontitis. Ke et al. in 2016, further reported that *Porphyromonas gingivalis* mediates necroptosis via RIP1, RIP3, and MLKL [37].

Relationship Between Parkinson's Disease and Necroptosis

The key points regarding the relationship between Parkinson's disease and necroptosis are as follows

1. Restriction of necroptosis can reverse the catastrophe of dopaminergic neurons in PD patients.
2. Mitochondrial dysfunction associated with PD.
3. Mutation in the Dynamin-related GTPase Oric Atrophy – 1 (OPA1) gene, a player of transposon involved in mitochondrial fusion and structure, leads to oxidative stress.
4. The pharmacological resolution of the OPA1 gene to normal levels is directly proportional to mitochondrial morphology and functions; the decrease in oxidative stress, and the inhibition of necroptosis.

Thus far, we know that a decrease in the number of dopaminergic neurons is a crucial factor in the progression of Parkinson's disease. However, in recent work, the OPA1 gene has also been shown to be associated laterally with PD. OPA1 (an inner mitochondrial protein) that is directly linked with mitofusins (MFN1 and 2), boost mitochondrial respiratory efficiency to build up the mitochondrial respiratory complex. But, the loss of OPA1, undermines the cristae morphogenesis. Moreover, only mutant OPA1 is not the fundamental factor affecting PD patients phenotypically. Some neurotoxins, such as MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) and rotenone, can be grouped as partners of mutant OPA1. However, the administration of Nec-1 (a necroptosis inhibitor) to PD patients can debilitate the loss of dopaminergic neurons through counter-action with mutant OPA1 neurons and promotes the maintenance of normal OPA1 levels [38].

Recent Developments in Interventions on the Necroptosis Signaling Pathway

Many diseases, such as chronic obstructive pulmonary disease (COPD), and inflammatory bowel disease (IBD), etc. are associated with the hyperactivity of the R1P3 kinase. In normal cells, hyperactivity of R1P3 can result in impulsive necroptosis. However, in cancer cells, R1P3 activity is required to induce necroptosis. Some of the drugs acting as necroptosis inhibitors are as follows:

HS-1371 (PubChem CID: 134817449): This compound is a potent R1P3 inhibitor, which binds directly to R1P3 in a time-dependent and ATP-competitive manner. Although it inhibits TNF-induced

necroptosis, it does not inhibit TNF-induced apoptosis.

GSK872 (PubChem CID: 54674134): This protein is a selective and potent R1P3 inhibitor, which binds the RIP3 kinase domain with high affinity. It acts by inhibiting TNF-induced necroptosis and by TLR3-induced necrosis in fibroblasts. It has minimal cross-reactivity. At high concentrations, it may induce apoptosis.

Necrosulfonamide (Pubchem CID: 1566236): This compound is a sulfonamide group molecule, and a member of the pyrazines and thiophenes. It inhibits the mixed lineage kinase domain-like protein(MLKL), a substrate of R1P3 (the receptor-interacting serine-threonine kinase 3 (R1P3), which is a key signaling molecule in the programmed necrosis (necroptosis) pathway. Even at 5 μ M concentration, necrosulfonamide has no effect on apoptosis induced by TNF- α -induced apoptosis. However, Necrosulfonamide efficiently blocks necrosis in human cells, but not mouse cells.

NECROSTATIN – -1 (PubChem CID: 2828334): This compound is a potent, selective and cell-permeable necroptosis inhibitor with an EC50 of 490 nM in Jurkat cells. It inhibits necroptosis by T-loop-dependent inhibition of R1P1 Kinase.

NTB451 (PubChem ID: 9541170): This compound is a potential inhibitor of necroptosis. It acts by inhibiting the phosphorylation and oligomerization of MLKL, which in turn inhibits the R1P1-R1P3 complex. It showed no effect on the activation of nuclear factor- κ B or apoptotic cell death.

NARINGENIN (PubChem CID: 439246): This compound is a bitter, colorless flavanone found in grape fruits and citrus peels. It is a trihydroxy flavanone and a member of 4'-hydroxyflavanone (the 4'-hydroxyflavanone family) and acts by inhibiting R1P3.

HSP70 (PDB ID: 2KHO): It is a family of Heat Shock Proteins, which protect cells from stress. It binds to proteins and prevents protein degradation and is necessary for the continued persistence of many cancer cells. It acts by suppressing the activity of R1P1 and thus inhibiting necroptosis.

Conclusion

The shared property of kinase activity in RIP1-RIP3 of the necrosome complex mediates the downstream signal of necroptosis. However, very little is understood about the execution of necroptosis, which depends not only on RIP1 kinase activity, but also on the suppression of apoptosis through RIP3 activity. In human disease pathology, the discovery of Nec1 and the modification of RIPK1 helped to decide whether a cell can undergo NF- κ B activation to survive or die through apoptosis or necroptosis mechanism. Genomic studies implicated in cell death have approached this topic clinically, thus providing a wide field of research for future medicines and, compounds of natural origin, which may further help in the design of newer therapeutic modalities for chronic diseases, whether its necroptotic or apoptotic cascades of events are found blocked or inhibited.

Implications for Translation

GSK872 is a potent RIP3 kinase inhibitor, and Necrostatin-1 acts as an RIP1 kinase inhibitor; thus, both ultimately inhibit necroptosis. Compared to Necrostatin-1, GSK872 showed a good docking score while binding to the main protease protein of SARS-CoV-2 in our unpublished work. The Plex View interaction analysis of GSK872 within the SARS-CoV-2 main protease (PDB ID:6Y84) evidently represents the molecular interaction through hydrogen bonding between the N4 ligand atom N4 and Phe3 and hydrophobic interactions involving Phe6 and Phe112. GSK872 and Necrostatin-1 analogs, both show hydrogen bonding interactions with Phe3 and a bond distance of 2.96 and 2.92 Angstroms, respectively (data not shown). Further, wet lab experimental validation of interaction is in progress.

Author Contributions (Credit Nomenclature)

RB and AC performed the literature review on the topic using the keywords cited, writing: original draft of the manuscript, writing: review and editing of the final draft. AGB: Conceptualization, strategized review of literature, supervision of review process and writing: reviewed and edited the final manuscript. form. All the authors have read and approved the final draft for submission of the manuscript, for publication.

Funding

This research did not receive any specific grants from any funding agencies in the public or private sector.

Declaration of Conflict-of-Interest Statements

No conflicts of interest exist between authors towards this collaborative scientific and academic report.

References

- Thornberry NA (1997) The caspase family of cysteine protease. *Br Med Bull* 53(3): 478-490.
- Grutter MG (2000) Caspase: Key players in programmed cell death. *Curr Opin Struct Biol* 10(6): 649-55.
- Lorenzo G, Alejandro LS, Sharad K, Guido K (2016) Caspases Connect Cell-death Signaling to Original Homeostasis. *44*(2): 221-231.
- Sollberger G, Strittmatte GE, Garstkiewicz M, Sand J, Beer HD, et al. (2014) Caspase-1: The inflammasome and beyond. *20*(2): 115-125.
- Craig M Walsh (2014) Grand Challenges in cell death and survival: apoptosis vs necroptosis. *Frontiers Cell dev Biol* 20(2): 3.
- Vandenabeele P, Galluzzi L, Berghe TV, Kroeme G (2010) Molecular mechanisms of necroptosis: An ordered cellular explosion. *Nature Mol Cell bio* 11: 702-704.
- Micheau O, Tschopp J (2002) Induction of TNF Receptor I-mediated apoptosis via two sequential signaling complexes. *Cell* 114: 181-190.
- Dana E, Christofferson, Yuan J (2010) Necroptosis as an alternative form of programmed cell death. *Curr Opin Cell Biol* 22(2): 263-268.
- Han J, Zhong CQ, Zhang DW (2011) Programmed necrosis: backup to & competitor with apoptosis in the immune system. *Nature Immunology* 12: 1143-1144.
- He S (2009) Receptor interacting protein kinase-3 determines cellular necrotic response to TNF α . *Cell* 137(6): 1100-1111.
- Feng S (2007) Cleavage of RIP3 inactivates its caspase-independent apoptosis pathway by removal of kinase domain. *Cell signal* 19: 2056-2067.
- Sun X, Yin J, Starovasnik MA, Fairbrother WJ, Dixit VM, et al. (2002) Identification of a novel homotypic interaction motif required for the phosphorylation of receptor-interacting protein (RIP) by RIP3. *J Biol Chem* 277: 9505-9511.
- Zhang DW (2009) RIP3, an energy metabolism regulator that switches TNF-induced cell death from apoptosis to necrosis. *Science* 325: 332-336.
- Bouche C, Serdy S, Khan CR, Goldfine AB (2004) The cellular fate of glucose & its relevance in type 2 diabetes. *Endocr Rev* 25(5): 807-830.
- Van Herreweghe F (2002) Tumor necrosis factor-induced modulation of glyoxalase1 activates through phosphorylation by PKA results in cell death and is accompanied by the formation of a specific methylglyoxal-derived AGE. *Proc Natl Acad Sci USA* 99: 949-954.
- Li X, Fang P, Mai J, Choi ET, Yang XF, et al. (2013) Targeting mitochondrial reactive oxygen species as novel therapy for inflammatory diseases and cancers. *Journal of Hematology & Oncology* 6: 19.
- Kin YS, Morgan MJ, Choksi S, Liu ZG (2007) TNF-induced activation of the Nox1 NADPH oxidase & its role in the induction of necrotic cell death. *Mol Cell* 26(5): 675-687.
- Yazdanpanah (2009) Ribi flavin kinase couples TNF receptor1 to NADPH oxidase. *Nature* 460(7259): 1159-1163.
- Antosiewicz J, Ziolkowski W, Kaczor JJ, Herman-Antosiewicz A (2007) Tumor necrosis factor- α -induced reactive oxygen species formation is mediated by JNK1-dependent ferritin degradation and elevation of labile iron pool. *Free Radic Biol Med* 43(2): 265-270.
- Arosio P, Levi S (2002) Ferritin, iron homeostasis and oxidative damage. *Free Radical Biology & Medicine* 33(4): 24-38.
- Hentze MW, Munchenthaler MU, Galy B, Camaschella C (2010) Two to tango: regulation of Mammalian iron metabolism. *Cell* 142(1): 24-38.
- Hannun YA, Obeid LM (2002) The Ceramide-centric universe of lipid-mediated cell regulation: stress encounters of the lipid kind, *J Biol Chem* 277(29): 25847-25850.
- Itagaki K, Hauser CJ (2003) Sphingosine1-Phosphate, a Diffusible Calcium Influx factor Mediating Store-operated Calcium Entry, *J Biol Chem* 278(30): 27540-27547.
- Burke JE, Dennis EA (2009) Phospholipase A2 structure/function, mechanism and signaling, *J Lipid Res* 50: S237-S242.
- Momeni HR (2011) Role of calpain in apoptosis; *Cell J* 13(2): 65-72.
- Villalpando Rodríguez GE, Torrigila A (2013) Calpain1 induce lysosomal permeabilization by cleavage of lysosomal associated membrane protein 2. *Biochimica et Biophysica Acta* 1833(10): 2244-2253.
- Szabo I, Zoratti M (1993) Mitochondrial permeability transition pore may compromise VDAC molecules I. Binary structure and voltage dependence of the pore. *FEBS Letters* 330(2): 201-205.
- Ichas F, Mazat JP (1998) From Calcium Signaling to cell death: two conformations for the mitochondrial permeability transition pore. Switching from low-to high-conductance state. *Biochimica et Biophysica Acta* 1366(1-2): 33-50.

29. Stavrovskaya, IG, Kristal BS (2005) The powerhouse takes control of the cell: is the mitochondrial permeability transition a viable therapeutic target against neuronal dysfunction and death. *Free Radical Biology and Medicine* 38(6): 687-697.
30. Halestrap AP, Brenner C (2003) The adenine nucleotide translocase. a central component of the mitochondrial permeability transition pore and key player in cell death. *Curr Med Chem* 10(16): 1507-1525.
31. Moubarak RS, Yuste VJ, Artus C, Bouharrou A, Greer PA, et al. (2007) Sequential activation of poly (ADP-ribose) polymerase1, calpains, and bax is essential in apoptosis-inducing factor-mediated programmed necrosis. *Mol Cell Biol* 27(13): 4844-4862.
32. Shashaty MGS, Reilly JP, Faust HE, Forker CM, Glttner CA, et al. (2019) Plasma receptor interacting protein kinase-3 levels are associated with acute respiratory distress syndrome in sepsis and trauma. a cohort study *Crit Care* 23(1): 235.
33. Nakamura H, Kinjo T, Arakaki W (2020) Serum levels of receptor-interacting protein kinase-3 in patients with COVID-19. *Crit Care* 24: 484.
34. Zhou W, Yuan J (2014) Necroptosis in health and diseases. *Seminars in Cell & Developmental Biology* 35: 14-23.
35. Goodman DM, Parmet S, Lynm C, Livingston EH (2012) Age-Related Macular Degeneration. *JAMA* 308(16): 1702.
36. Hanus J, Anderson C, Sarraf D, Ma J, Wang S, et al. (2016) Retinal pigment epithelial cell necroptosis in response to sodium iodate. *Cell death discovery* 2: 16054.
37. Ke Xiaojing (2016) Manipulation of necroptosis by Por phyro monas gingivalis Porphyromonas gingivalis in periodontitis development, *Molecular Immunology* 77: 8-13.
38. Lannielli A, Simone Bido, Lucrezia Folladori, Alice Segnali, Cinzia Cancellieri, et al. (2018) Pharmacological inhibition of necroptosis protects from dopaminergic neuronal cell death in Parkinson's Disease models. *Cell Reports* 22(8): 2066-2079.

ISSN: 2574-1241

DOI: 10.26717/BJSTR.2024.59.009265

Abhijit G Banerjee. Biomed J Sci & Tech Res



This work is licensed under Creative Commons Attribution 4.0 License

Submission Link: <https://biomedres.us/submit-manuscript.php>



Assets of Publishing with us

- Global archiving of articles
- Immediate, unrestricted online access
- Rigorous Peer Review Process
- Authors Retain Copyrights
- Unique DOI for all articles

<https://biomedres.us/>