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Research Article

Ferropanoptosis in Neurocysticercosis: Implications for Novel Therapeutic Drug Development-a Comprehensive Review

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Abstract

Background: Ferroptosis (Fp), a newly reported Regulated Cell Death (RCD) associated with iron independence lipid peroxidation (LP), has become a fundamental process involved in the neuropathological basis in the comorbidity of NCC/COVID-19 and PANoptosis represent a group of different RCD and Programmed Cell Death (PCD) as we reported previously. *Taenia solium* (Ts), the larval form of the pig tapeworm, is the primary cause of the preventable and eradicable zoonotic parasitic disease Cysticercosis (Ct), which is primarily observed in individuals residing in underdeveloped nations. However, because to unregulated migration and globalization, the number of carriers in wealthy nations is steadily rising. In this investigation, we seek to learn more about the pathophysiology of neuropsychiatric symptoms in individuals suffering from Neurocysticercosis (NPNCC). Drug development strategies aimed at targeting ferropanoptosis in NCC are promising. Potential therapeutic approaches include: Iron chelators: Compounds that sequester iron ions, reducing their availability for catalyzing lipid peroxidation and subsequent cell death.

Antioxidants: Substances that counteract lipid peroxidation and oxidative stress, thereby protecting neurons from ferroptotic damage.

Lipid peroxidation inhibitors: Molecules that inhibit the enzymatic pathways involved in lipid peroxidation, preventing neuronal membrane damage.

Combination therapies: Synergistic approaches combining iron chelators with antioxidants or lipid peroxidation inhibitors to maximize neuroprotective effects.

Recent advances in understanding ferropanoptosis and its role in NCC highlight the potential for personalized medicine approaches tailored to individual patient profiles and disease stages. Future research should focus on clinical trials to validate the efficacy and safety of these novel therapeutic strategies, ultimately improving outcomes and quality of life for NCC patients globally.

Method: Using a comprehensive search strategy, we looked for published medical subject heading (MeSH) terms such as "neurocysticercosis", "pathophysiology of Fp/NCC", "immunology of FPANp" OR "dysfunctional mitochondria in FPANp", "necroptosis/apoptosis/pyroptosis/autophagia/NCC."

Results: Peer review was conducted on all of the chosen studies, and we were unable to locate any literature discussing the pathophysiology of FPANp in NCC.

Remarks and closing thoughts: We postulated that the pathophysiology of FPANp in patients with NCC is influenced by malfunctioning mitochondria, oxidative stress, neuroinflammation, Fp, and PANp.

Keywords: Drug development strategies; Therapeutic approaches; Neurocysticercosis; Ferroptosis; PANoptosis; Oxidative stress; Dysfunctional mitochondrial; Cytokine storm; Neuroinflammation; Programmed cell death; Regulated cell death; Necroptosis; Apoptosis; Pyroptosis; Autophagia

List of Abbreviations

(Acetyl-CoA) Acetyl Coenzyme A; (ADP) Adenosine Diphosphate; (AGE) Advanced Glycation End-products; (AHSG) Alpha-2-Heremans-Schmid Glycoprotein; (AMPK) Adenosine Monophosphate Protein Kinase; (AO) Antioxidant; (AP) Apoptosis; (APH) Autophagia; (ARNTL) Aryl Hydrocarbon Receptor-like Nuclear Translocator; (AT Case) Aspartate Transcarboxylase; (ATP) Adenosine Triphosphate; (BAK) BCL-2 Homologous Antagonist; (BAX) BCL-2 Associated X-Protein; (bHLH-PAS) Basic Helix–Loop–Helix/Per-ARNT-SIM; (BMAL1) Basic Helix–Loop–Helix ARNT-like 1; (Ca^{2+}) Calcium Ions; (CAD) Dihydroorotase; (CK1ε) Casein Kinase I Isoform Epsilon; (CLR) C-Type Lectin Receptors; (CNCD) Chronic Non-Communicable Diseases; (CNS) Central Nervous System; (COX) Cytochrome C Oxidase; (CPS2) Carbamoyl-Phosphate Synthetase 2; (CRY) Cryptochrome; (CRY 1) Cryptochrome Circadian Regulator 1; (CRY 2) Cryptochrome Circadian Regulator 2; (CVD) Cardiovascular Diseases; (DAMP) Damage-associated Molecular Pattern; (DNA) Deoxyribonucleic Acid; (ECT) Electron Transport Chain; (ER) Endoplasmic

Reticulum; (ETF) Electron-transferring Flavoprotein; (FA) Fatty Acid; (FAD) Flavin Adenine Dinucleotide; (FAO) Fatty Acid Oxidation; (FAS) Factor-Associated Suicide Receptor; (FasL) Factor-associated Suicide Receptor; (FKBP FK506) Binding Protein; (FLT-3) FMS-like Tyrosine Kinase; (FP) Fluorescence Polarization; (FTL) Ferritin Light Chain; (FtMt) Mitochondrial Ferritin; GABA Gamma Aminobutyric Acid; (GAPDH) Glyceraldehyde-3-Phosphate Dehydrogenase; (GLUT) Glucose Transporter; (GPX4) Glutathione Peroxidase 4; (GSH) Glutathione; (GSSG) Glutathione Disulfide; (GTP) Guanosine Triphosphate Hydrolases; (H2O2) Hydrogen Peroxide; (HD) Huntington Disease; (HIF1) Hypoxia-Inducible Factor 1; (hsCRP) High-sensitivity C-Reactive Protein; (HSP) Heat Shock Protein; IFNAR1: Interferon-A/*B* Receptor Subunit 1; (IFN) Interferon; (IFNAR1) Interferon-A/*B* Receptor Subunit 1; (IKK) Inhibitor of Nuclear Factor Kb Kinase; (IPMK) Inositol Polyphosphate Multikinase; (IL) Interleukin; (IL) Intermittent Living; (IMM) Inner Mitochondria Membrane; (JAK/STAT) Janus Kinase/ Signal Transducer and Activator of Transcription; (LDH) Lactate Dehydrogenase; (LDL) Low-density Lipoprotein; (LGI) Low-grade Inflammation; (LOF) Loss of Function; (LPS) Lipopolysaccharide; (m-L-LDL) Mitochondrial Lactate Dehydrogenase; (MAM) Mitochondria-associated Membrane; (MAVS) Mitochondrial Antiviral-signaling Protein; (MCP) Monocyte Chemoattractant Protein; (MCT) Monocarboxylate Transporters; (MCU) Mitochondrial Ca^{2+} Uniporter; (MDP) Mitochondrial Derived Proteins; (MetS) Metabolic Syndrome; (MFF) Mitochondrial Fission Factor; (Mfn) Mitofusin; (miRNAs) microRNS; (MLKL) Mixed Lineage Kinase Domain-like Protein; (MMPT) Mitochondrial Membrane Permeabilization Transition; (MOM) Mitochondrial Outer Membrane; (MOTS) Mitochondrial 12s Ribosomal RNA Type C Open Reading Frame; (mPTP) Mitochondrial Permeability Transition Pores; (mRNA) Messenger RNA; (MSR) Mitochondrial Stress Response; (MT1) Melatonin 1; (mtDNA) Mitochondrial DNA; (MTHFD2) Methylenetetrahydrofolate Dehydrogenase 2; (mTOR Mechanistic Target of Rapamycin; (NA) Noradrenaline; (NAC) N-Acetyl-Cysteine; (NAD) Nicotinamide Adenine Dinucleotide; (NAD^+) Nicotinamide Adenine Dinucleotide; (NADL) Non-alcoholic Fatty Liver Disease; (NADPH) Nicotinamide Adenine Dinucleotide Phosphate; (NcRNAs) Non-coding RNAs; (Np) Necroptosis; (NF-κB) Nuclear Factor Kappa B; (NGF) Nerve Growth Factor; (NLR) NOD-Like Receptors; (NLRP3) NLR Family Pyrin Domain Containing 3; (NNT) Nicotinamide Nucleotide Transhydrogenase; (NPAS2) Neuronal PAS Domain Protein 2; (NPY) Neuropeptide Y; (NR1D) Nuclear Receptor Subfamily 1 Group D; (NR1D1) Nuclear Receptor Subfamily 1 Group D1; (NR1D2) Nuclear Receptor Subfamily 1 Group D2; (NRF2) Nuclear Factor Erythroid 2-Related Factor 2; (OCR) Oxygen Consumption Rates; (OM) Outer Mitochondria Membrane; (ONOO) Peroxynitrite; (OPA1) Protein optic atrophy 1; (OXPHOS) Oxidative phosphorylation; (PAMPS) Pathogen-associated Molecular Patterns; (PARP) Poly ADP Ribose Polymerase; (PD) Parkinson Disease; (PDC) Pyruvate Dehydrogenase Complex; (PDc) Pyruvate Dehydrogenase Complex; (Per 1) Peroxisome 1; (Per 2) Peroxisome 2; (Per 3) Peroxisome 3; (PGC-1α) Peroxisome Proliferator-Activated Receptor Gamma Coactivator-1 Alpha; (Pi) Inorganic Phosphate; (PI3K) Phosphatidylinositol 3-Kinase-Protein Kinase B; (PINK) PTEN-Induced Putative Kinase 1; (PKC-β2) Protein Kinase C Beta 2; (PPARγ) Peroxisome Proliferator-Activated Receptor-γ; (Pp) Pyroptosis; (PRR) Pattern-Recognition Receptors; (RIPK1) Receptor-Interacting Protein Kinase 1; (RIPK2) Receptor-Interacting Serine/ Threonine Kinase 2; (RIPK3) Receptor-Interacting Protein Kinase 3; (shRNA) Short Hairpin Ribonucleic Acid; (siRNA) Small Interfering Ribonucleic Acid; (ROR) Receptor Tyrosine Kinase-Like Orphan Receptor 1; (ROS) Reactive Oxygen Species; (SCN) Suprachiasmatic Nucleus; (SGLT2) Sodium-Glucose Cotransporter-2; (SIRT) Sirtuin; (SNP) Single Nucleotide Polymorphisms; (SOCS1/3) Cytokine Signaling 1 and 3; (SOD) Superoxide Dismutase; (sORF) Short Open-reading Frames; (STING) Stimulator of Interferon Genes; (T1D) Type 1 Diabetes; (TCA Cycle) Tricarboxylic Acid Cycle; (TFAM) Transcription Factor A, Mitochondrial; (TFB2M) Transcription Factor B2, Mitochondrial; (TGF) Transforming Growth Factor; (TLRs) Toll-Like Receptors; (TNF) Tumor Necrosis Factor; (TNFR1) Tumor Necrosis Factor Receptor 1; (TLR3) Toll-Like Receptors 3; (TLR4) Toll-like Receptors 4; (TRADD) Tumor Necrosis Factor Receptor-Associated Death Domain; (TRAF2) Tumor Necrosis Factor Receptor-associated Factor 2; (UCP2) Mitochondrial Uncoupling Protein 2; UDP-GlcNAc UDP-N-Acetyl-Glucosamine; (UPR) Unfolded Protein Response; (VEGF) Vascular Endothelial Growth Factor; (wt-mtDNA) Wild-type Mitochondrial DNA

Introduction

Neurons and Glial Cells (NGC) constitute the fundamental units of the Central Nervous System (CNS), essential for neurophysiological functions and immune defense against pathogens. The pathophysiology of many neurological disorders involves various forms of Programmed Cell Death (PCD). Recently, Ferroptosis (Fp), characterized by iron-dependent Lipid Peroxidation (LP), has emerged as a critical mechanism in these processes. This review explores the role of ferropanoptosis in Neurocysticercosis (NCC) and its implications for developing innovative therapeutic drugs. Fp's involvement in the neuropathogenesis of NCC has gained prominence, especially in the context of concurrent comorbidities like COVID-19, as previously highlighted in our research. The dysregulation of iron metabolism and subsequent lipid peroxidation not only exacerbates neuronal damage but also influences the immune response within the CNS. Understanding these mechanisms presents an opportunity to target Fp pharmacologically for therapeutic benefit in NCC [1-3]. The mechanism, genomics, and morphology of Fp have been proven to be different from the well-known Programmed Cell Death (PCD) such as Apoptosis (Ap), Necroptosis (Np), Autophagy (Aph), Pyroptosis (Pp), scorching death and PANoptosis (PANp)

[4]. Although significant efforts and many studies have been made on the activities and mechanisms of Fp, some specific functions/mechanisms and related regulatory activities still need to be fully proven, requiring better-planned designs and in-depth investigations. Over the past few years, shreds of findings have shown the close relationship between Fp and ischemiareperfusion diseases [5]. However, few studies report the role of Fp in infectious diseases, even though Fp might be a new therapeutic target for developing more accurate adjuvant treatments against inflammatory/infectious diseases [6]. The most common cause of Cysticercosis (Ct), a parasitic condition that can be eradicated but is preventable, is a cestode infection caused by the larval form of the swine tapeworm *Taenia solium* (Ts). This disease is primarily observed in individuals residing in underdeveloped nations. With the exception of the hair, nails, bone tissue, epidermis, cartilage, and adrenal gland, CT can infect any internal organ in humans or pigs. Once a human definitive host consumes contaminated unfreeze or undercooked-pork flesh containing *T. cysticercus*, an adult tapeworm develops in the small intestine. The oncospheres hatch in the gut mucosa of pigs and humans who consume eggs or proglottids. They then pierce the intestinal wall and spread to nearly every part of the body, with the exception of thing membranes, narrow cavities, hair, nails, cartilage, bone tissues, and the adrenal gland. Neurocysticercosis is the term for the condition caused by parasite invasion of the brain parenchymal, ventricular system, subarachnoid space, spinal cord, or optic nerves, which results in cysticerci. Less frequently occurring symptoms and signs include headache and epileptic seizures/epilepsy [7–11]. Within Intraparenchymal NCC (INCC), Epilepsy (Ep) and Epileptic Seizure Disorder (ESD) are the most prevalent symptoms. In the rural communities of Mthatha, South Africa, we conducted over 10 epidemiological studies, and the results confirmed that NCC is the primary cause of secondary epilepsy. First-line Antiseizure Medication (ASM) and Antiepileptic Medications (AED) showed excellent response rates in all ES and Ep [1-3,7-21]. Similarly, difficulties from Status Epilepticus (SE) arise when there is no accessible AED because to COVID-19 limits or for other reasons, such as limited finances or noncompliance. In spite of this, throughout the previous 25 years, no patients in our region had ever presented with refractory epilepsy due to NCC without any other explanation. The most often used AEDs are carbamazepine and valproic acid, while benzodiazepines are the most commonly used ASM. Levetiracetam is not available in rural regions and is only utilized in tertiary facilities [22-25]. As previously stated, the adult tapeworm's final host is humans (taeniasis). On the other hand, the cysticercus (larval form), a cyst-fluid-filled membrane vesicle with an eccentric scolex inside, can be carried by humans and pigs as intermediate hosts. These cysts travel to the intestines, where scolex evaginates, after being consumed by undercooked, contaminated hog flesh. Two crowns of hooks hold them to the intestinal mucosa wall, preventing peristaltic movement from expelling them. One or 2 parasites at most mature into a 2 meter-4 meter long tapeworm at the gut, which is made up of 1200 proglottids, a neck, and a scolex. Between 600 and 2000 viable eggs are contained in gravid proglottids, which defecate on consecutive days and then fall into the ground. The incidence/prevalence of NCC is noticeably high in poor countries or economically disadvantaged regions within wealthy countries (like our area), where access to clean and safe water is scarce and is primarily caused by poor sanitation, poor food and personal hygiene, poor educational health, high levels of poverty, and free-roaming pigs with access to human faeces contaminated by Ts eggs. The embryos are discharged from the egg into the stomach and pass through the gut mucosa to the blood flow, which delivers them to the target tissues where they are converted into cysticerci when the proglottids or eggs are consumed by contaminated water, food, or by the faecal-oral route. Pigs are susceptible to developing porcine cysticercosis, just like humans. The disease is widespread in developed nations without free-range pigs and even in locations where the 4 phases of cysticercus in the brain parenchymal have been identified. Person-to-person transmission is a fairly common mode of transmission, explaining how non-eaten pork individuals become sick [18]. The autoimmunity, meningeal lymphatic, glymphatic drainage, and the role of activated OLG/OPC/NG2 in the pathogenesis of NCC clinical manifestations, including neuropsychiatric manifestations, complications, outcome, and mortality rate, were recently reviewed as novel aspects of NCC associated with COVID-19 and HIV. As previously reported, the activation of astrocytes and Microglia (Mg) is crucial to NCC neuro-inflammatory pathways, either directly or indirectly, as a result of their production of inhibitory glial scars, induction of BBB disrupting proteinases, and release of pro-inflammatory cytokines. We have discussed how pro/anti-inflammatory cytokines/chemokines, Mg, Oligodendrocytes (OLG), Pericytes (Pc), Oxidative Stress (OS), and other autoimmune components contribute to the pathophysiology of NCC. But we never looked into the This review's primary goal is to provide answers to the following research questions:

1. What is the current understanding of the Fp's pathophysiology in neurocysticercosis (FpNCC)?
2. Is the pathophysiology of the colloid/nodular-fibrotic stage of NCC influenced by the combined effects of Fp and PANp (FPANp)?

Material and Methods

In order to find articles published between January 31, 2003, and July 31, 2023, we conducted a thorough search of EMBASE, Medline, the Cochrane Library, Scopus, PsycINFO, Global Health, and the Health Management Information Consortium. This was followed by a manual search of pertinent journals.

This review synthesizes current knowledge on FpNCC, explores potential therapeutic strategies targeting ferropanoptosis, and discusses future research directions to improve outcomes for patients with neurocysticercosis. By elucidating the intricate interplay between ferroptotic

pathways and parasitic infection in the CNS, this review aims to pave the way for innovative treatments that mitigate neurological damage and improve patient prognosis.

This content integrates the concept of ferropanoptosis into the context of neurocysticercosis, emphasizing its implications for drug development and therapeutic strategies.

Search strategy for this review

Using the chosen databases, a thorough online search of manuscripts published between January 1, 2000, and July 31, 2023 was carried out. To investigate the Fp/PANp in NCC and the role that magnesium plays in this pathogenic process, 2 searches were conducted. As a result, we looked through every article pertaining to the topics covered by the search criteria "OS/NCC," "Dysfunctional Mt and NCC" [MeSH], "PANp and NCC" [MeSH], "pathophysiology of NCC" [MeSH], "mitochondrial disorder and Np/Fp/PANp" [MeSH]. The studies that were pertinent to these problems were then all recognized. Furthermore, we went over each included manuscript's references, bibliographies, and citations very carefully. After that, we conducted extensive searches through MEDLINE (Ovid), Scopus (Elsevier), Global Health, CINAHL, Cochrane Library, Health Management Information Consortium, Web of Science (Clarivate Analytics), and EMBASSY. Choosing the original research studies associated with our search approach was the main goal. We chose full-text authored in Spanish, Portuguese, and English after a precise, trustworthy peer-review procedure. We only included parts that fell within the current work scope, and all publications were retrieved using MeSH, as previously mentioned.

Our systematic approach involved targeted searches across multiple databases to explore the intersections of Ferropanoptosis (Fp/PANp) in Neurocysticercosis (NCC) and the potential therapeutic implications of magnesium (Mg) in this pathological process.

Exclusion and inclusion criteria

Additionally, we chose quasi-experimental or randomized controlled trials that were published in peer-reviewed publications and were associated with the search method. Nevertheless, certain research was disregarded if it assessed treatments for vascular issues, other infections, or parasite illnesses with etiologies distinct from *T. solium* infection. Furthermore, only adult patient studies published in English, Spanish, or Portuguese were included in the study. Documents presenting original data on IS related to NPNCC and confidence, defined as the lack of substantial biases, were acceptable for inclusion. Because further details on the approach were required, conference proceedings, textbooks, and published abstracts were not included. Rejected were case series involving fewer than 20 individuals, review papers lacking original data, and letters to the editor or editor without an original date.

Study selection

In order to do the literature search, we looked up every paper using its title and abstract. Articles were independently reviewed for eligibility by LdeFIV and HFS. A consensus-building debate was held to decide which research were included, mainly in cases where there was uncertainty.

Quality appraisal

Selection bias, study design, health status, blinding procedure, reasons for dropouts or withdrawals, and data collection techniques were the 4 categories of study quality that were evaluated. Furthermore, a methodological quality assessment was conducted independently by LdeFIV and subsequently confirmed by HFS.

Data extraction

To collect research data about the study design, patient demographics, methodologies, measuring instruments, assessment timing, and outcomes, a data extraction system was created. An Excel® spreadsheet was used for the screening procedure. Furthermore, vital details regarding the intervention for research involving secondary data analysis were taken from the original paper or a previously published document. The data extraction was carried out independently by LdeFIV and HFS; the authors' discussion led to the consensus.

Methods of analysis

Following an initial synthesis of the extracted data using textual descriptions to ascertain the features of the chosen studies, the data were sorted, clustered, and tabulated for presentation.

Study and cohort selection

In order to determine inclusion criteria, we choose case reports that are both prospective and retrospective, cross-sectional studies, cohort studies, casecontrol studies, case series, reviews, controlled clinical trials, and meta-analyses that provide data.

Data collection process

Using Microsoft Excel, the chosen data is taken out of each manuscript using a standardized coding system. Mt/NCC, Mt/RCD/OS/FPANp/NCC, clinical symptoms, population size, age distribution, and, when relevant, the investigations conducted to corroborate the final diagnosis were among the information gathered. When there was doubt about how to interpret the chosen data or how to apply it, we examined the circumstances until we could come to an understanding. When details about the study design or the reported results were ambiguous or absent in the reviewed article, the corresponding authors of a few chosen primary studies were emailed.

Data synthesis and analysis

In several articles, the 12 index was used to summarize

the overall variability in proportion to between-study variation, although the Cochran's Q test was employed to evaluate homogeneity across trials. When necessary, our investigation made use of aggregate data.

Quality assessment of selected publications

The Jadad scoring system was first used to screen all studies for bias. This approach is primarily used to evaluate the methodological quality of controlled trials, specifically in relation to randomization, masking, and accountability-withdrawals. Additionally, only individuals who had Jadad scores of ≥ 4 were added to the evaluation.

Results

Literature search

3871 manuscripts in all met the requirements for the first screening round due to their high quality. The quantity of articles chosen from each database and included in the degree of bibliographic research, together with the primary explanations for exclusions, are displayed in Figure 1. During the screening process, approximately 75% of the manuscripts were rejected. The remaining papers (n=0) were all eliminated in the following phase since they failed to provide clinical proof of the pathophysiology of Fp/NCC or FPANp/NCC analysis, or they failed to support the neuroimaging-based diagnosis of NCC. Because of this, the papers that did not address the pathophysiology of FPANp in NCC were not included in this review. All of the chosen research were published after peer review from the start, and no one satisfied all of the requirements for inclusion on FPANp in NCC. Consequently, no thorough evaluation of FP/PANp in patients presenting with NCC has yet been conducted. Below is a flow chart for the literature search.

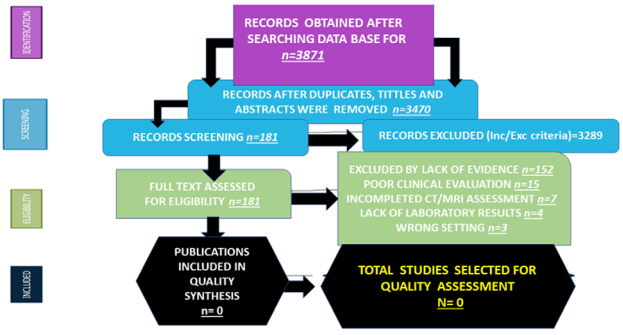

Figure 1: Flow diagram of the selected articles

Study characteristics

Because this study did not address bioethical considerations, the ethics committee did not consider examining it. 791% of the studies were released within the last 4 years. 49.44% of people in South Africa were HIV positive, and 592% of those people were female. The majority of investigations (42.1%) were carried out in the United States and Canada, with Asia (39.5%), Europe (12.7%), and Africa [5.7] following closely behind. 77.3% of research concentrated on adults over the age of 18. There were 3871 publications in all, 181 after duplicates were eliminated, 0 after the complete text was removed, 0 for quality synthesis, and 0 for quality evaluation.

Comments and concluding remarks

We recently discussed the part that playedby PC, Mg, OS, OLG/OPC, PCD, RCD, and PANp in NCC, and many accompanying graphical illustrations were delivered into the medical literature [22-27]. After a compressive review of the medical literature, Regarding the combined function of Fp and PANp in NCC instances, we were unable to locate any published articles. However, we identified that both CD mechanisms could influence its clinical manifestations, outcomes, and mortality rate. For more than 20 consecutive years, the vesicular (stage 1) pathological stage of presentation at the brain parenchymal, which is characterized by a translucent wall with transparent fluid and a viable invaginated scolex with intact membrane, no-host immunological reaction, and consequently no Neuroinflammation (NI) around the cysts, is where we grouped our series of cases with NCC. Stage 2 colloidal: Here, we observe the parasite's dying process, which often occurs before 5 years after entry and is characterized by a thick-walled cyst, murky fluid, and a degenerating scolex that triggers an inflammatory reaction in the host. In comparison to the CSF density, the intra-cystic fluid becomes opaque at this point. The ruptured membrane releases liquid antigens that harm the blood-brain barrier and cause vasogenic oedema around the cyst. At this point, the direct and indirect effects of the released parasite's antigen make the neurological symptoms more noticeable. Stage 3: Granular/nodular Reduce the area around the perilesional oedema, and the cyst starts to retreat, but the enhancement is still there and is characterized by a thicker-walled cyst with a deteriorated scolex and minimal inflammatory reaction. Determined (phase 4): Perilesional oedema may occur in certain instances, the cyst's structural features vanish, and the remaining material becomes a rough, calcified nodule Figure 2 [1-30].

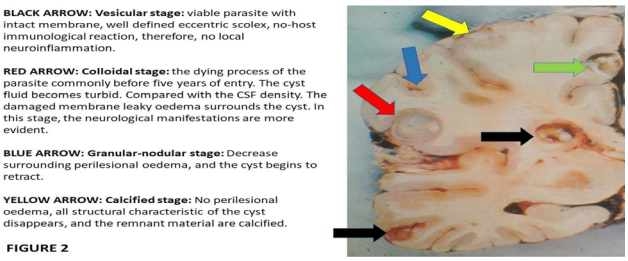

Figure 2: Coronal section of both cerebral hemispheres showing all stages of *T. solium* NCC

This systematic search strategy enabled us to compile a comprehensive overview of the current understanding of ferropanoptosis in neurocysticercosis and its implications for novel therapeutic drug development. By synthesizing findings from diverse sources and languages, this review aims to contribute valuable insights into potential therapeutic targets and strategies for combating NCC-related neurological complications.

Within the content of our hypotheses, we recommend the medical terminology of FPANp for a regulated variety of CD induced by several/different types of stimuli and composed by elements present in other forms of CD like Aph, Ap, Np, PANp, Pp, and Fp; that in our opinion are typically seen in people affected by *T. solium* NCC during the colloid/nodular-fibrotic stage with multifocal lesions with associated Mg polarisation to M1-pro-inflammatory overproduction/M2-host defence and anti-inflammatory response, anti-pathogenic/antitumor effect/dysfunctional Mt leading to OS/increased ROS production and PCD among other factors but also highly implicated in the pathogenesis of many pathological and neurophysiological process, triggering malignant progression/inhibition, remarkable tissue injury, uncontrolled inflammatory cascade response, disorder chronicity, and on top of that, without acting as a specific detrimental process only as has been proposed by Keng Ye, et al. for cases of Fp [31]. Our hypothesis on the pathophysiology of FpNCC is described below.

Recently, we reported that apart from all situations causing OS, such as osmotic stress, calcium overload, drug stimulation and heat stress, other conditions characterised by IRI can promote Np, which combined with PANp leads FPANp if the signalling pathway involving ligand-receptor binding like Fas ligand/FAS, interferon-gamma (IFN-γ)/IFNAR1, double-stranded RNA/Toll-like receptor 3 (TLR3), double-stranded DNA/Z-DNA binding protein 1 (ZBP1), and TNF-α/TNFR are expressed and working together according to our hypothesis [23].

We speculate that osmotic stress can stimulate the RIPK3 kinase directly and promote Np by increasing the Na^+/H^+ exchanger SLC9A1. At the same time, Np can also happen after activating ZBP1 *via* Heat Shock Transcription Factor 1 (HSF1) by heat stress in patients with NCC. However, further studies must confirm this speculation due to insufficient solid evidence.

Based on previous reports, we hypothesised that RIPK3 can be bonded by activated ZBP1, which recruits and phosphorylates MLKL almost immediately and translocates phosphorylated MLKL oligomerises to the plasma membrane, where it executes Np by breaking the NC/GC membrane. We documented before that TNF is a central component of the Mg polarisation into M1 binding with TNFR1 producing other pro-inflammatory cytokines through membrane-bound complex (complex I), which include RIPK1, cIAP1/2, TNFR1-associated Death Domain (TRADD), TNFR-associated factor 2 (TRAF2), and Linear Ubiquitin Chain Assembly Complex (LUBAC) as reported by Choi, et al. (2019) [32]. We also speculate that NGC in NCC may afford several different choices for selected outcomes after the formation complex I and how they survive or die by PCD/RCD (Ap/Np/Aph/Pp/PANp/Fp) according to the predominancy of the post-translational status changes of RIPK1 (phosphorylation/ubiquitination) as is shown in Figure 3.

Other author confirmed the same but based on their findings from different studies [33-35]. In that graphical hypothesis shown is represented that in the intermediate domain of RIPK1, then LUBAC and the complex I components cIAP1 can catalyse the polyubiquitination of Lys63 in cases of NCC as have been confirmed in 2013 by other authors under different circumstances [36,37].

While other investigators reported that polybiquinated RIPK1 could scaffold other elements such as those composed of NEMO, IKKα, IKKβ and IKK complex plus the TAK complex composed by TAK1-binding protein (TAB)1/2 and Tat-associated Kinase 1 (TAK1) [38,39].

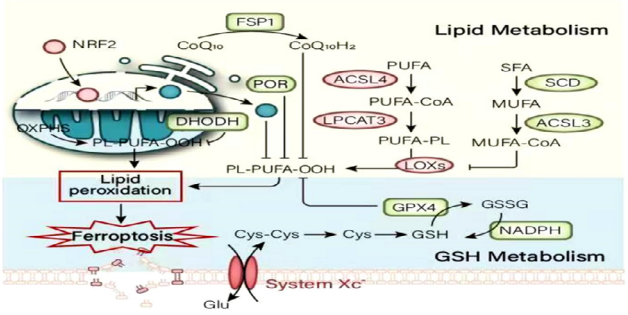

Figure 3: Hypothetical graphical mechanism of ferroPANoptosis (FPANp) from Lipid Peroxidation (LP) in cases presenting NCC at the colloid/nodular-fibrotic stage.

Abbreviations: LO: Alkoxyl radical; L-OH, lipid alcohol; L–H, lipid; LOOH: Lipid hydroperoxide; LOO•: Epoxy peroxyl radical, plus dysfunctional mitochondria, and necrosome complex and its components. RIPK1: Receptor-interacting serine/threonine-protein kinase 1 functions which is a cellular pathway related to both death and cell survival. RIPK3: Receptor-interacting serine/threonine-protein kinase 3 is an enzyme; MLKL: Mixed lineage kinase domain like pseudo kinase is a protein that is encoded by the MLKL gene; TLR 3/4: Tolllike receptor are proteins that play a vital role in the innate immune system

The correlation between the Nuclear Factor-kappa B (NF-κB) and the pathogenesis of NCC was recently documented, and its pathway activation by IKK complexes and TAK was adequately represented [27]. We now hypothesised that this mechanism could stimulate many pro-inflammatory expressions and pro-survival genes which promote NC/GC survival around the *T. solium* cysticercosis lesion at the colloid/nodular-fibrotic stage.

Other investigators confirmed that RIPK1 can be deubiquitinated in the absence of cIAP1/2 or LUBAC after binding to a Second Mt-Derived Activator of Caspase (SMAC) mimetics and under these circumstances then TNF-α leads CD *via* Ap/Np, and the situation of RIPK1 ubiquitination can be modified by many deubiquitinating enzymes plus deubiquitinating process done by deubiquitinating enzymes of Np or FPANp in cases of NCC according to our hypotheses [40,41] (Figure 3).

In 2013, Moquin, et al. (2013) confirmed that Cylindromatosis (CYLD) can promote RIPK1 expression in the necrosome [42]. On the other hand, CYLD and A20 have been proven to be 2 remarkable inflammatory signalling modulators in different conditions. We commented before that they have the unique capacity to separate the K63 polyubiquitin chain from NF-κB complex proteins to support one-second cytosolic complex II formation and to begin the regulated

CD mechanism either Ap or Np as have been supported by other investigators [43-45]. Based on these findings, we hypothesised that a similar mechanism happens during the regulated CD FPANp at the colloid/nodular-fibrotic stage of *T. solium* NCC. In Figure 3, we hypothetically Illustrate the role of A20 in cases infected by the pig tapeworm *T. solium*, including its properties to interrupt the formation of RIPK1–RIPK3 complexes, inhibit ubiquitination of RIPK3 and lead FPANp, taking into consideration the findings reported by Onizawa, et al. (2015) which also proposed and anti-inflammatory effect [46].

Additionally, we hypothesize that in cases where NCC is present at the colloid/nodular-fibrotic stage, RHIM–RHIM interactions of RIPK3 are essential for the phosphorylation of MLKL as the primary executor of Np, and ESCRT-III plays a crucial role in plasma membrane rupture and repair.

Brief comments on Ferroptosis/PANoptosis in neurocysticercosis

Recently, some investigators from Guangdong Medical University in China confirmed that the regulatory CD process such as Ap, Aph, and Np are strongly associated with infectious diseases, while Fp, which is characterised by iron-dependent lipid peroxidation, is tightly related to the regulation of infectious disorders like malaria, cryptococcal meningitis, tuberculosis, and COVID-19 [4].The sole form of CD driven by LP that is dependent on iron is Fp, which is regulated by lipid metabolism, iron processing, and redox homeostasis-a process also referred to as multifactorial NC/GC metabolic pathways implicated in NI response [47]. Iron-dependent LP, which is highly regulated by lipid metabolism, redox balance, and iron processing, is the only kind of CD that is driven by Fp. Through multiple Neuronal and Glial Cell (NC/GC) metabolic pathways, these activities jointly contribute to Neurocysticercosis (NCC) and affect the Neuroinflammatory (NI) response. It is essential to comprehend how Fp is regulated and modulated in NCC since this provides new opportunities for therapeutic approaches. By focusing on the particular pathways connected to Fp, new medications that reduce the inflammation and neuronal damage brought on by NCC (Figure 4).

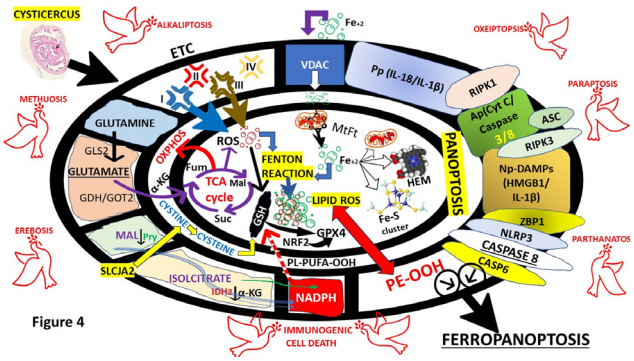

Figure 4

Figure 4: Graphical hypothesis on the Mt pathways engaged in FPANp combining PANoptosis, Ferroptosis, oxidative stress, and other regulated cell death programs around. Abbreviations: CoQ10, coenzyme Q10; ETC, electron transport chain; FSP1, ferroptosis suppressor protein 1; Fum, fumarate; GDH, glutamate dehydrogenase; GLS2, glutaminase 2; GOT2, glutamic-oxaloacetic transaminase 2; IDH2, isocitrate dehydrogenase 2; IMM, inner mitochondrial membrane; Pyr, pyruvate; membrane; IMS, intermembrane space; α-KG, α-ketoglutarate; Mal, malate; MtFt, mitochondrial ferritin; NOX4, NADPH oxidase 4; OMM, outer mitochondrial Suc, succinate; TCA cycle, tricarboxylic acid cycle; VDAC, voltage-dependent anion channel. GPX4, Glutathione Peroxidase 4 is a selenoprotein Coding gene being one of the most relevant AO mediators able to reduce complex hydroperoxides into their respective alcohols and the main regulator of Fp; NFR2, Nuclear factor erythroid 2-related factor 2, encoded by the NFE2L2 gene; GSH, Glutathione, is a tripeptide composed of cysteine, glycine, and glutamic acid and an endogenous component of cellular metabolism; Mt, mitochondria is involved in iron accumulation, mtROS production, glutaminosis, regulation of redox status, lipids/amino acids metabolism, modulation of NC/GC antioxidant capacity triggering FPANp pathways

One of the most important characteristics of Fp is Lipid Peroxidase (LP), which is produced through a sequence of biochemical reactions involving the Free Radical (FR), which targets lipids with carbon-carbon double bonds, primarily Polyunsaturated Fatty Acids (PUFAs). Additionally, FR (•OH) is produced excessively due to an excess of ferrous iron, which leads to the production of LP, which destroys the fluidity and integrity of the lipid bilayer cell membrane, causing cell injury, damage, or death.

Fp was first identified in 2012 and distinguished against other types of CD, such as Ap, Aph, Np, Pp, and PANp, by its iron deficiency, LP, and closed relationship to immune mediators such as Damage-Associated Molecular Patterns (DAMPs), proinflammatory cytokines, and NC/GC metabolism, which includes amino acids. It is generally accepted that in all cells exposed to chemical/ physical harmful environments (detergents, lasers, bacteria-derived membrane perforators, some immune elements), the integrity of the cell membrane is damaged/ lost. As a result, regulated CD lyses these cells, and we postulated that FPANp is the most common PCD in NCC cases at the colloid/nodular-fibrotic stage (Figure 4). Our hypothesis was that during the colloid/nodular-fibrotic stage of *T. solium* NCC, FPANp could improve NI's response to antigens released from the parasite's dying process. It could also function as an inhibitor for innate immunity by interacting with membrane translocation and increasing MLKL oligomerization, which activates the NLRP3 inflammasome and produces IL-1β, which affects host defense and ultimately results in a dysfunctional NGC network from survived/reprogrammed NGC [23,25]. We also reported that during the comorbidity of NCC/ COVID-19, many regulated CD pathways such as AP, Np, Pp, Aph, PANp, and now FPANp can be expressed, leading to an inevitable inflammatory cytokine storm and multi-organ failure [1-3,5]. In comorbidity of NCC/HIV/AIDS, we hypothesised that the PCD is also linked to ZBP1 and recruitment of RIPK3. We hypothesised that the released antigens, pro-inflammatory cascade and induced FPANp mechanism also serve to enhance the immunological host reaction and secondary injured nearby parasitic chain reaction, which will kill the host with many cystic lesions or lead to multiple complications due to Mg/M1 activation, overproduction of FR(ROS)/OS, and FPANp expression in other areas of the CNS. Our main hypotheses are graphically represented in Figures 3 and 4.

According to Christopher, et al. (2023) Np is a regulated caspase-independent type of necrotic CD resulting in NI phenotype involved in multiple medical disorders characterised by the interaction of RIPK1 (scaffolding functions), RIPK3(-dependent Ap) and MLKL (final effector of necroptosis), leading to the rupture of the plasma membrane, chromatin condensation, cellular swelling/lysis/loss of its contents all induced by TLR3/4, TNF, TNFR1, Fas, NOD, NLRs, IFNAR1, and ZBP1 [48]. We hypothesised that adding it to dysfunctional NF-κB pathway, caspase 3-8, RIPK1, RIPK3, and MLKL pseudo-kinase, TRADD, TRAF2, cIAP1/2, LUBAC, TAK1, FADD expression the result is FPANp, NI and CNS injury.

Based on our proposal, the NCC colloid/nodular stage is tightly associated with PANop as a predominant Regulatory Cell Death Program (RCDP). But as we can see in Figures 3 and 4, another RGDP is distinguished by an iron-dependent lipid peroxidation known as Ferroptosis (Fp), which plays a role in the pathophysiology of NCC [4]. However, we hypothesized that the most well-known key component in the regulation of Fp (selenoprotein), known as Glutathione Peroxidase 4 (GPX4), May have the capacity to reduce the intracellular level of LP *via* lipids detoxification supported by Glutathione (GSH-cofactor) assisting to GPX4 to transform toxic elements such as lipid hydroperoxides into non-toxic elements like lipid alcohols in cases with NCC. On top of that, we also speculate that a diminished level of GSH can cause the inhibition of GPX4 and delete the NCC patient's capacity to fix LP, leading to the occurrence of combined Fp and PANp, which we called FPANp, as shown in Figure 4.

Discussion

However, numerous other CD kinds have been verified. The most widely recognized CD types in the scientific community are parthanatos (a CD that results from overactivation of the DNA repair enzyme poly PARP1 ([ADP-ribose] polymerase 1), erebosis (a new CD mechanism during homeostatic turnover of gut enterocytes), methuosis (a non-apoptotic type of PCD in which the cytoplasm is occupied by fluid-filled vacuoles that originate from cytoplasmic vacuolation (macropinosomes) and paraptosis (a pH-dependent cell death process characterized by damage and Mt). Moreover, the ability of an immunogenic CD to boost immunological responses to certain immunotherapy protocols and to activate the host immune system (Figure 4). We hypothesized that disordered mental states have a role in each of them. Again, let us emphasize the role these double-membrane-bound organelles play in energy production, metabolic pathways, age-related disorders, network control, unfolded protein response, mitophagy, cellular balance (mitohormesis), and, ironically, even in both unprogrammed and programmed CD. Drawing from prior research, we postulate that, as previously noted, OXPHOS, LP, and PANp initially target Polyunsaturated Fatty Acids (PUFA) during the dying phase (colloid stage) of NCC [26].

Conclusion

Ultimately, we postulated that the pathophysiology of the pericystic symptoms during and after the colloid/nodular-fibrotic stage of *T. solium* intraparenchymal NCC is significantly influenced by the combined effects of Fp and PANp. To the best of our knowledge, this is the first study of its kind to be published in the medical literature, thus further well-designed research is required to confirm or refute our theories.

Declarations

Consent for publication

We acquired the authorized, informed consent of our patient before publishing any information, including test results. All information is freely available upon request to any reader who may be interested.

Availability of data and material

By contacting the Corresponding Author, all data supporting this study are readily available.

Ethical Approval

No ethical approval request for this study was made by the WSU/NMAH Ethical Committee.

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Competing Interest

The authors confirm that they had no financial, commercial, or other relationships that would have given rise to a conflict of interest throughout the course of this work.

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Authors Contribution

HFS and LFIV are the study's concept and design. Data obtained through HFS and LdeFIV literature searches. LdeFIV/HFS analyzed the acquired data in addition to the initial and final drafts of this study. The paper was revised by HFS and LFIV, under HFS's supervision. Writing a manuscript: HFS and LFIV. The publication of this version has been approved by both writers. Anonymity proclamation: The names, initials, and other identifying concerns of this patient were kept anonymous, as all authors attest to. Consequently, total anonymity.

References

1. H.F. Sibat, Racemose neurocysticercosis long

COVID and brainstem dysfunction: A case report and systematic review, Clin Schizophr Relat Psychoses, 15S(2021).

2. H.F. Sibat, Neurocysticercosis, epilepsy, COVID-19 and a novel hypothesis: Cases series and systematic review, Clin Schizophr Relat Psychoses, 15(2021).
3. H.F. Sibat, People living with HIV and neurocysticercosis presenting Covid-19: A systematic review and crosstalk proposals, Clin Schizophr Relat Psychoses, 15(2021).
4. L. Xiao, H. Huang, S. Fan, B. Zheng, J. Wu, et al. Ferroptosis: A mixed blessing for infectious diseases. Front Pharmacol, 13(2022):992734.
5. H.F. Sibat, Comorbidity of neurocysticercosis, HIV, cerebellar atrophy and SARS-CoV-2: Case report and systematic review, Clin Schizophr Relat Psychoses, 15(2022).
6. B.R. Stockwell, X. Jiang, W. Gu, Emerging mechanisms and disease relevance of ferroptosis, Trends Cell Biol, 30(2020):478–490.
7. H.F. Sibat, L.F.I. Valdes, Pseudo seizures and epilepsy in neurocysticercosis, Electron J Biomed, 2(2003):79-87.
8. H.F. Sibat, M.D.I.V. LdeF, Vascular dementia type binswanger's disease in patients with active neurocysticercosis, Rev Electron Biomed, 1(2003):32-42.
9. F.S.H.I.V. LdeF, Insular neurocysticercosis: Our finding and review of the medical literature, Inte J Neurol, 5(2006):2.
10. H.F. Sibat, L.D. Cowan, H. Carabin, I. Targonska, M.A. Anwary, et al. Accuracy of serological testing for the diagnosis of prevalent neurocysticercosis in outpatients with epilepsy, Eastern Cape Province, South Africa, PLoS Negl Trop Dis, 3(2009):e562.
11. H.F. Sibat, I.V. LdeF, J. More-Rodriguez, Parasitic zoonoses of the brain: Another challenger, Inte J of Neurol, 12(2009):9-14.
12. H.F. Sibat, I.V. LdeF, Treatment of epilepsy secondary to neurocysticercosis, Novel Treat Epilepsy InTech, 2011.
13. H.F. Sibat, L.F.I. Valdés, Clinical features of epilepsy secondary to neurocysticercosis at the insular lobe, Novel Asp Epilepsy InTech, 2011.
14. H.F. Sibat, Epilepsy secondary to parasitic zoonoses of the brain, Novel Asp Epilepsy InTech, 2011.
15. H.F. Sibat, M. Salazar-Campos, L. Ibanez-Valdes, Cysticercosis of the extraocular muscles: Our experience and review of the medical literature, Internet J Neurology, 14(2001):1.
16. H.F. Sibat, L.F.I. Valdes, Introduction to cysticercosis and its historical background, InTech, 2013.
17. H.F. Sibat, L.F.I. Valdes, What is a low frequency of the disseminated cysticercosis suggests that neurocysticercosis is going to disappear? InTech, 2013.
18. H.F. Sibat, L.F. Valdes, Uncommon clinical manifestations of cysticercosis, InTech, 2013.
19. L.F.I. Valdes, H.F. Sibat, Psychogenic nonepileptic seizures in patients living with neurocysticercosis, InTech open, 2018.
20. L.F.I. Valdes, H.F. Sibat, Subarachnoid cysticercosis and ischemic stroke in epileptic patients, InTech open, 2018.
21. E.V. Noormahomed, N. Nhancupe, J. Mufume, R.T. Schooley, H.F. Sibat, et al. Neurocysticercosis in epileptic children: An overlooked condition in Mozambique, challenges in diagnosis, EC Microbiology 17(2021):49-56.
22. H.F. Sibat, L.F.I. Valdes, The role of pericytes in neurocysticercosis: Comprehensive review and novel hypotheses, Clin Schizophr Relat Psychoses, 2013.
23. H.F. Sibat, L.F. Valdés, New hypotheses on the role of microglia in ischemic reperfusion injury secondary to neurocysticercosis and a comprehensive review, Clin Schizophr Relat Psychoses, 2023.
24. H.F. Sibat, L.F.I. Valdes, Role of oxidative stress in neurocysticercosis, J Drug Alc Res, 17(2023).
25. H.F. Sibat, L.F.I. Valdes, Novel hypotheses on the role of oligodendrocytes in neurocysticercosis: Comprehensive review, Clin Schizophr Relat Psychoses, 17(2023).
26. H.F. Sibat, L.F. Valdés, Novel hypotheses on the role of microglia and panoptosis in neurocysticercosis, Clin Schizophr Relat Psychoses, 17(2023).
27. L.F.I. Valdes, T Dubula, H.F. Sibat, Neuropsychiatric manifestations of neurocysticercosis: A comprehensive review, J Drug Alc Res, 2023.
28. H.F. Sibat, L.F. Valdes, Comorbidity of spinal cord neurocysticercosis and tuberculosis in a HIV-positive patient, Int J Neurol, 7(2006):5-10.
29. L.F.I. Valdes, H.F. Sibat, Meningeal lymphatic vessels and glymphatic system in neurocysticercosis: A systematic review and novel hypotheses, Clin Schizophr Relat Psychoses, 17(2023).
30. A.R. Jadad, R.A. Moore, D. Carroll, C. Jenkinson, Assessing the quality of reports of randomized clinical trials: Is blinding necessary? Control Clin Trials, 17(1996):1–12.
31. K. Ye, Z. Chen, Y. Xu, The double-edged functions of necroptosis, Cell Death Dis, 14(2023):163.
32. M.E. Choi, D.R. Price, S.W. Ryter, A.M.K. Choi, Necroptosis: A crucial pathogenic mediator of human disease, JCI Insight, 4(2019):e128834.

33. A.J. Pradhan, S. Chitkara, R.X. Ramirez, V. Monje-Galvan, Y. Sancak, et al. Acylation of MLKL impacts its function in necroptosis, ACS Chem Biol, 19(2024):407-418.

34. A.T. Ting, M.J.M. Bertrand, More to life than NF-κB in TNFR1 signaling, Trends Immunol, 37(2016):535–45.

35. A. Annibaldi, S.W. John, T.V. Berghe, K.N. Swatek, J. Ruan, et al. Ubiquitin-mediated regulation of RIPK1 kinase activity independent of IKK and MK2, Mol Cell, 69(2018):566–80.e565.

36. Y. Dondelinger, M.A. Aguileta, V. Goossens, C. Dubuisson, S. Grootjans, et al. RIPK3 contributes to TNFR1-mediated RIPK1 kinase-dependent apoptosis in conditions of cIAP1/2 depletion or TAK1 kinase inhibition, Cell Death Differ, 20(2013):1381–92.

37. K. Keusekotten, P.R. Elliott, L. Glockner, B.K. Fiil, R.B. Damgaard, et al. OTULIN antagonizes LUBAC signaling by specifically hydrolyzing Met1-linked polyubiquitin, Cell, 153(2013):1312–26.

38. Y. Dondelinger, S. Jouan-Lanhouet, T. Divert, E. Theatre, J. Bertin, et al. NF-κB-independent role of IKKα/IKKβ in preventing RIPK1 kinase-dependent apoptotic and necroptotic cell death during TNF signaling, Mol Cell, 60(2015):63–76.

39. J. Geng, Y. Ito, L. Shi, P. Amin, J. Chu, et al. Regulation of RIPK1 activation by TAK1-mediated phosphorylation dictates apoptosis and necroptosis, Nat Commun, 8(2017):359.

40. S.L. Petersen, L. Wang, A. Yalcin-Chin, L. Li, M. Peyton, et al. Autocrine TNF alpha signaling renders human cancer cells susceptible to smac-mimetic-induced apoptosis, Cancer Cell, 12(2007):445– 56.

41. T. Douglas, M. Saleh, Post-translational modification of OTULIN regulates ubiquitin dynamics and cell death, Cell Rep, 29(2019):3652–63.e3655.

42. D.M. Moquin, T. McQuade, F.K.M. Chan, CYLD deubiquitinates RIP1 in the TNFα-induced necrosome to facilitate kinase activation and programmed necrosis, PLOS ONE, 8(2013):e76841.

43. Z.J. Chen, Ubiquitination in signaling to and activation of IKK, Immunol Rev, 246(2012):95–106.

44. M. Lork, K. Verhelst, R. Beyaert, CYLD, A20 and OTULIN deubiquitinases in NF-κB signaling and cell death: So similar, yet so different, Cell Death Differ, 24(2017):1172–83.

45. D. Priem, G. van Loo, M.J.M. Bertrand, A20 and cell death-driven inflammation, Trends Immunol, 41(2020):421–35.

46. M. Onizawa, S. Oshima, U. Schulze-Topphoff, J.A. Oses-Prieto, T. Lu, et al. The ubiquitinmodifying enzyme A20 restricts ubiquitination of the kinase RIPK3 and protects cells from necroptosis, Nat Immunol, 16(2015):618–27.

47. L. Deng, S. He, N. Guo, W. Tian, W. Zhang, et al. Molecular mechanisms of ferroptosis and relevance to inflammation, Inflamm Res, 72(2023):281–299.

48. C.R. Gardner, K.A. Davies, Y. Zhang, M. Brzozowski, P.E. Czabotar, et al. From (tool) bench to bedside: The potential of necroptosis inhibitors, J Med Chem, 66:2361–2385.