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Research Article

Our Hypotheses about the Role of Cuproferropanoptosis in Neurocysticercosis and a Comprehensive Review

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Abstract

Background: Neurocysticercosis (NCC) is a parasitic disease secondary to a cestode infection by the larva form of pig tapeworm Taenia solium (Ts). In this study, we look for publications related to the role played by cuproptosis, ferroptosis and PANoptosis in the pathogenesis of NCC. After reviewing this issue, we formulate some hypotheses regarding their role in this zoonotic and neglected parasitic disease.

Method: We searched the medical literature comprehensively, looking for published medical subject heading (MeSH) terms like "neurocysticercosis", "pathogenesis of neurocysticercosis", "comorbidity in NCC" OR "cuproptosis" OR "necroptosis"; OR "pyroptosis"; OR "ferroptosis"; OR "apoptosis"; OR Programmed cell death"; OR "regulated cell death" and NCC.

Results: All selected manuscripts were peer-reviewed, and we did not find publications related to Cp, Fp, Py, Ap, or NCC.

Comments and concluding remarks: We have hypothesized the role of CUFEPANp on the mechanism of local NC/GC survival/growth in the perilesional cystic area. This review was the first study to comprehensively analyses the association between copper-induced CD and NCC in combination with Fp and PANp, which we named CUFEPANp. Based on this comprehensive review, we delivered several hypotheses on the participation of Cp, Fp, and PANp in NCC. However, future well-designed investigations will support or deny the hypotheses proposed in the present manuscript.

Keywords: Programmed cell death; Regulated cell death; Apoptosis; Necroptosis; Cuproptosis; Pyroptosis; Ferroptosis; PANoptosis; Neurocysticercosis

Introduction

Copper (Cu) is a vital micronutrient and a transition metal for the human body with four oxidation states known as metallic copper, Cu^{+}, Cu^{2+} and Cu^{3+}. Cu is redox-active and easily interconverts between Cu^{+} and Cu^{2+} with the capacity to play a crucial role in various biological processes, including free radical detoxification, Angiogenesis (Ag), cellular iron metabolism, neurotransmitter synthesis, and cellular respiration supported by specific mechanisms to maintain copper homeostasis and regulate Cu metabolism. Dysregulation of Cu metabolism is the leading cause of various diseases, such as Menkes disease caused by Cu deficiency and Wilson disease secondary to Cu overload. At the Mitochondrial (Mt) level, the transfer of Cu ions with different valence states leads to ROS formation, leading to Oxidative Stress (OS), such as decreased cofactor SOD1 activity and increased superoxide anion, which may interfere with the synthesis of iron sulphur clusters to injury countless essential enzymes in cells and damage different types of biological organic molecules like nucleic acids, proteins, and lipids [1].

On the other hand, a high level of Cu is closely related to many malignancies, angiogenesis, tumour proliferation, and metastasis [2-7]. The most critical elements involved in Cu homeostasis maintenance at the cellular level are 1-enzymes guiding copper ion efflux, like Cu-transporting ATPase 1 (ATP7A) and Cu-transporting ATPase 2 (ATP7B); 2-transporters mediating Cu absorption, like Cu transporter receptor 1 (Ctr1) (also known as SCL1A1), Cu transporter receptor 2 (Ctr2), divalent metal transporter 1 (DMT1); 3-biomolecules that sequester and store Cu, such as Metallothionein (MT), glutathione (GSH); 4-Antioxidant protein 1 (Atox1), Cu chaperones such as Copper Chaperone for Superoxide Dismutase (CCS), cytochrome C oxidase Cu chaperone 17 (Cox17), which direct Cu to Cu dependent enzymes and transport Cu to organelles that requiring Cu [1]. Cu also activates some Ag factors such as tumour necrosis factor-alpha (TNF-α), IL-1, IL-6, IL-8, and essential Fibroblast Growth Factor (bFGF), triggering vascular endothelial cell proliferation

and metastasis. Cu directly binds to the Ag growth factor angiopoietin, enhancing its affinity for EC.

Nevertheless, Cu is also remarkably used in industrial production and can become an environmental pollutant at increased concentrations. In the digestive system of humans, dietary Cu is absorbed by the gut while extracellular copper ions remain present in the gut as divalent copper ions. On the other hand, Cu (II) does not upload directly by enterocytes until it is reduced to Cu (I) by binding to the STEAP family of metalloreductase. Cu (I) enters the mucosa of small intestinal tract or other somatic cells mainly through SLC31A2/CTR2 (solute carrier family 31 member 2) and SLC31 Cu osmosis family transporter SLC31A1/CTR1 (solute carrier family 31 member 1). Elevated Cu induces the endocytosis and degradation of the SLC31A1 protein.

On top of that, Cu uptake by SLC11A2/DMT1 (solute carrier family 11 member 2) can be a compensatory mechanism for SLC31A1 deficiency [8]. When Cu ions pass through the cell membrane, then Cu chaperones for Superoxide Dismutase (SOD1-AO) present in the Mt intermembrane space carry it into all cellular compartments, including the nucleus, cytoplasm, Golgi apparatus, and Mt to mediate all cellular processes apart from the regulatory mechanism to keep ROS stability and modulate ROS produced by Electron Transport Chain (ETC) avoiding OS damage caused by Cu overload.

Cytochrome C oxidase Cu chaperone COX17 is the main transport of Cu ions into Mt, while Cu can be transported to the trans-Golgi by Cu chaperone antioxidant 1 Cu chaperone (ATOX1). The Cu-transporting ATPases ATP7A/B play the leading role in the extracellular export of Cu ions [8].

Ceruloplasmin (Cp) is involved in Cu metabolism, which is the primary carrier of Cu, and around 90% of Cu in plasma is found in Cp. Furthermore, Cp is a multi-Cu oxidase that is essential to iron homeostasis. When Fe^{2+} is exported from ferroprotein, the sole iron exporter, Cp promotes cellular iron export by oxidizing iron ions from Fe^{2+} to Fe^{3+}. Although Cp synthesis and secretion are not affected by copper levels, Cu deficiency may decrease Cp stability and activity. Cp is also closely linked to cancer, and studies have indicated that significant Cp gene expression occurs in many tumours and that the overall incidence of cancer is positively correlated with serum Cp levels and may be able to serve as a prognostic marker in some cancers.

Last year, a new type of copper-dependent Cell Death (CD) induced by intracellular Cu termed Cuproptosis (Cp) was reported by Tsvetkov and collaborators [9]. These authors proved that the mechanism of Cp involves a Cu ionophore named "elesclomol," which can bind Cu^{2+} in the extracellular environment and transport Cu^{2+} into the cells. Therefore, Cp is distinct from OS-related CD. Cp results from Mt stress. Here, Cu can directly bind to ester-acylated components of the Tricarboxylic Acid Cycle (TAC) plus subsequent aggregation of Cu-bound lipidated Mt enzymes and loss of iron Sulphur protein clusters, leading to Cp [10]. It is a link between Cu metabolism and Cp. The dysregulation of Cu metabolism in the body, such as Cu overload, may lead to Cp.

Neurocysticercosis (NCC) is a preventable zoonosis/eradicable parasitic disease secondary to a cestode infection of the cerebral parenchymal, intraventricular system, Subarachnoid Space (SAS), cerebellum, brainstem, optic nerve, or spinal cord and the often-clinical manifestations are headache and epileptic seizures/epilepsy among other less frequent symptoms and signs [11-34].

Therefore, this unknown issue raises the following research question: What is the role of Cp and FEPANp in NCC? The principal aid of this review is to answer the previous question.

Materials and Methods

Method

We searched the medical literature comprehensively, looking for published Medical Subject Heading (MeSH) terms like "neurocysticercosis," "pathogenesis of neurocysticercosis," "comorbidity in NCC" OR "cuproptosis" OR "necroptosis"; OR "pyroptosis"; OR "ferroptosis"; OR "apoptosis"; OR Programmed cell death"; OR "regulated cell death" and NCC. We also look at https://www.clinicaltrials.gov/, using the same MeSH terminology but applying filters such as "summary" and "full publication" to those articles published in Spanish, Portuguese, and English.

Inclusion/exclusion criteria and process of screening: The inclusion criteria to be eligible for this review are:

- Patients are approved by their respective Ethical Committee.
- The entire article should be written in English, Spanish, or Portuguese. Although abstracts written in French can be included.
- The central aspects are NCC and PCD, RGC, Ap, Np, Py, Fp, PANp and Cp.
- Manuscript published in a peer-reviewed medical journal.

The exclusion criteria were:

- The manuscript did not refer to issues numbered 3.
- Any manuscript that did not meet the inclusion criteria of an original study;
- Clinical trials with less than 10 cases per treatment arm;
- Medical conference proceedings non accredited by SCOPUS;
- Article written by the same author using the same data or duplicate articles or
- Publication with not corresponding authors.

We did not include in the analysis manuscript any exclusion criteria, and the arising discrepancy among authors was

solved through scientific discussion.

Medical literature searching strategy

We included observational cohort studies, case reports, case series, systematic reviews and meta-analyses, cross-sectional studies, and clinical trials. During the initial search, we looked for inclusive articles published between January 1, 1990, and August 30, 2023. We searched the following databases: Science Direct, Google Scholar, Medline, US National Library, Scopus online databases, Scielo, Search of Sciences, and MedRxiv. As mentioned before, all studies were retrieved by utilizing MeSH. We only included other aspects within the current work scope.

Study and cohort selection

We select case reports, prospective and retrospective cohort studies, controlled clinical trials, reviews, case series, case-control studies, and systematic reviews.

Process of data collection

All information was extracted from each publication using Microsoft Excel in a structured coding scheme. The data collected included NCC, CNS PC, and CNS Ag studies. When any uncertainty related to the interpretation of the obtained data or how it could be used, the authors discussed the situation among them until they reached a unanimous consensus.

Data synthesis

Our investigation used aggregate data where possible.

Quality assessment of included publications

All publications were initially screened for bias using the Jadad scoring system [35]. Jadad scores which ranging from 0 to 5; trials scoring three or greater were considered good quality trials.

Results

Study selection

One of the main aims of this study was to update the scientific information released about these issues. 3,673 manuscripts were retrieved from electronic databases until August 30, 2023. After removing irrelevancy and duplicates, 503 manuscripts were taken for full-text screening. No clinical trials on NCC were found. Of all the selected articles, none delivered some information on the relationship between NCC/PC/Ag. All selected manuscripts were peer-reviewed publications; however, no study met all inclusion criteria on NCC/PC/Ag. Nonetheless, despite efforts to find experimental studies and patient-based investigations related to the pathogenesis of PC/Ag in NCC, including a careful review of the bibliography of selected publications, no studies were found. Therefore, a meta-analysis was not performed.

A flow chart for the literature searched is shown below (Figure 1).

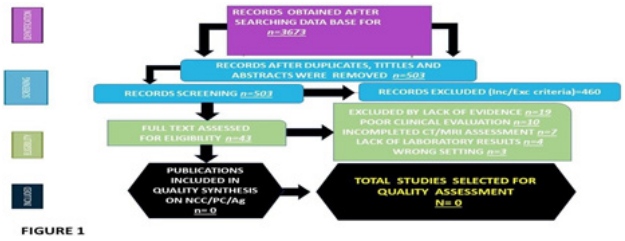

Figure 1: Flow diagram of selected manuscripts

Comments

We found many articles about Cp related to cancer and other disorders, but we did not identify any publications related to Cp/NCC in our comprehensive review; therefore, we do not have any information to disclose from this comprehensive review of the medical literature.

The gross pathological changes in the cerebral hemispheres caused by NCC can be seen in Figure 2.

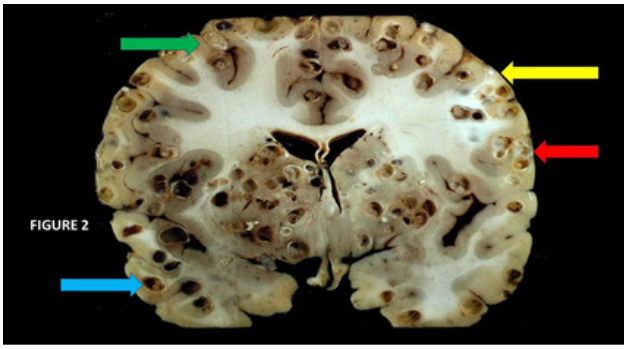

Figure 2: Shows a coronal section of both cerebral hemisphere with all different intraparenchymal NCC stages. BLUE ARROW: Vesicular stage: Viable parasite with intact membrane, well-defined eccentric scolex, no-host immunological reaction, and no local neuroinflammation. RED ARROW: Colloidal stage: The dying process of the parasite commonly before 5 years of entry. The cyst fluid becomes turbid. Compared with the CSF density. The damaged membrane leaky oedema surrounds the cyst. In this stage, the neurological manifestations are more evident, next to this lesion there is another one with important surrounding vasogenic edema. GREEN ARROW: Granular-nodular stage and the cyst begins to retract.

YELLOW ARROW: Calcified stage: No perilesional oedema, all structural characteristic of the cyst disappears, and the remnant material is calcified

This illustration shows the main structural differences between all NCC stages, allowing easily differentiated vesicular, colloid, nodular-fibrotic, and calcified stages, leading to the different clinical manifestations of NCC patients according to the stage of NCC.

For all living species, the inevitable end is death, characterized by the irreversible discontinuation of all biological functions of any critical organ, mainly the brain, the heart, and the lungs, although not all human cells die simultaneously. Some cells die before death, while others die slowly and continue consuming their oxygen and energy after death. Unfortunately, other processes involved in prolonging life, such as tissue repairing/regeneration/

transplantation, will never happen without death. Therefore, we hypothesize that the main triggering factor to perform the healing process/repairing/regeneration/transplantation around the cystic lesion in the CNS is precisely the dying process of the T solium cysticercus at the colloid stage. Recently, we named necrotic tissue an area entirely of cell death until 1972, when John Kerr et al., (1972) proposed the terminology of Ap [36]. However, the Nomenclature Committee on Cell Death has delivered a new classification mainly grouped into unprogrammed cell death and PCD [37] with Aph, Ap, Pp, Np, lysosomal cell death, Fp, Cp, Lysosomal CD (LCD), and PANp being classified as PCD [38].

Notwithstanding, many other types of CD have been confirmed. The CD types commonly accepted by the research community are oxeiptosis, alkaliptosis, paraptosis, methuosis, parthanatos, erebosis and immunogenic CD, and we hypothesized that dysfunctional Mt are involved in all of them. Let us, once more time, highlight the role of these double-membrane-bound organelles in all cellular functions, energy production, metabolic pathways, age-related disorders, network control, cellular balance (mitohormesis), unfolded protein response, mitophagy, and paradoxically even in unprogrammed/programmed CD. Based on the previous publication, we hypothesize that during the dying process (colloid stage) of NCC, polyunsaturated fatty acids (PUFA) are the first targets for OXPHOS, LP and PANp, as we reported before [39].

As has been proved, the main components of the RCD pathways are Ap, Pp, Np, Fp and PANp, which play a crucial role in infection protection, keeping cellular balance and modulating unique processes accompanying malignant diseases and producing billions of CD daily. However, it is not evident due to a cellular process that removes fragmented/CD/Pp cells/Ap cells, better known as efferocytosis. We hypothesized that other types of RCD will be described soon. Novel theories on the pathophysiology of RCD/PCD will also be reported to increase the current comprehension of cell death; as we documented before, the classic character of Ap is the creation of apoptosome after releasing of cytochrome c from Mt, which binds to apoptotic protease activating factor-1 (APAF1) which is a pro-apoptotic factor following by a specific caspase cascade response leading to dysfunctional MtDNA [40]. At the same time, the relevant components of Np are Mixed Lineage Kinase Domain-Like Pseudo Kinase (MLKL), Receptor-Interacting Protein Kinase 1 (RIPK1), and RIPK3. We also documented that RIPK3-mediated phosphorylation leads to MLKL expression, forming oligomers and changing the membrane permeability and CD. Fp is the result of intracellular iron accumulation and LP, as was reported [41].

The brain contains around 9% of the body's Copper (Cu), mainly located at the dopaminergic NC of the Locus Coeruleus (LC) and the substantia nigra and in the mesencephalic region of the brainstem (main productor of norepinephrine), the brain is the third-highest concentration of Cu of any organ. The CU enters the CNS tissue through the Cu transporter located at the BBB and Blood-Cerebrospinal Fluid Barrier (BCB), which regulates Cu homeostasis in the CNS, being it a vital component of NC/GC maturation, development, and functional network. BCB cells stored by ATP7B take up an excessive concentration of Cu and are transported to the CSF or blood flow by ATP7A, as was documented by An and collaborators [40]. After Cu enters the NC, the Cu ions bind to CCS (cellular Cu chaperone), which is transferred to SOD1 and inserts a disulfide bond. As previously cited, Atox1 carry in Cu to Cu- transporting ATPases and is incorporated into Cu-dependent enzymes. If Cu concentration is high, then kinase-mediated kinases phosphorylate Cu-ATPases and relocate their vesicles at the basolateral/apical (ATP7A/ATP7B) membranes. After vesicle fusion, Cu is exported. We hypothesized that glutathione, a well-known element involved in the pathogenesis of NC/GC damaged at the colloid stage of NCC, is involved in modulating the intracellular Cu pool. GC have a higher concentration of Cu than NC under physiological/pathological conditions. At the Mt level, Cu^{+} is supplied to the membrane by a small Cu ligand where SCO1, COX17 and COX11 create two different Cu transport pathways leading to metallization of the Mt CCO complex [An]. Through the LC, Cu modulates rest-activity cycles and regulation of arousal and wakefulness in human beings [40].

Copper entry into the cell binds to cytoplasmic or Mt chaperone proteins, which transfer Cu to specific cellular destinations to perform its programmed functions. Cu chaperone for SOD1 (CCS), a cytosolic chaperone, plays a crucial role in OS. The delivery of Cu to SOD1 requires the mediation of the CCS to detoxify ROS and maintain Cu homeostasis. In cases of NCC, we hypothesize that pericystic lesions are also favored by reduced SOD1 expression, which can cause a remarkable accumulation of superoxide [6]. The role of Cu in NCC has not been studied before. We hypothesize that Cu^{2+} remarkably affects receptor tyrosine kinase-related signaling pathways *via* activating Receptor Tyrosine Kinases (RTK) without binding to the corresponding ligands, HGF and EGF. We speculate that expressed RTK provoke upstream signaling to MET and EGFR, causing the phosphorylation of downstream ERK (extracellular signal-regulated kinase) and ATK (Agammaglobulinemia Tyrosine Kinase) as has been proposed by He Fang et al., (2019) studying the tumour microenvironments [41].

On the other hand, we also considered that Cu^{2+} has the capacity to activate downstream AKT by expressing on PDK1 (3-Phosphoinositide Dependent Protein Kinase 1) or PI3K (Phosphoinositide-3-Kinase), had been revealed by Guo et al., (2021) for the oncogenic signaling pathway to facilitate tumorigenesis [42]. Notwithstanding, Cu acts on MEK1 (mitogen-activated protein kinase 1) and enhances its capacity to phosphorylate ERK1 and ERK2, thus stimulating RAF-MEK-ERK signaling, which we hypothesize plays a relevant role in the injuring process

of the pericystic lesion during the colloid process of NCC. A similar proposal was delivered by Baldari et al. in 2019 for patients affected by cancer of the colon [43]. Figure 3 represents the cellular Cu transport and metabolism.

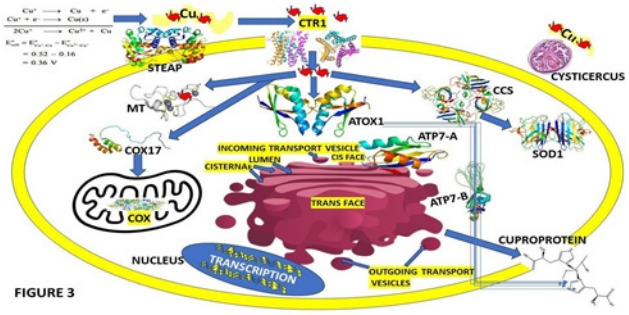

Figure 3: Graphical representation of cellular Cu transport and metabolism. Extracellularly, Cu exists as Cu^{2+}. The cellular reductases protein family STEAP proteins (mainly Steap 2/3/4) reduce Cu^{2+} to Cu^{+}. Cu^{+} is transported into the NC/GC *via* Ctr1, and a segment of Cu^{+} is targeted to cytosolic SOD1 by the CCS (Cu chaperone) to scavenge FR before producing a mitochondria oxidative stress. A fraction of Cu^{+} is delivered by the Cu chaperone Cox17 to Mt Cox to generate ATP. A portion of Cu^{+} is delivered to ATP7A/B of the trans Golgi network by the Cu chaperone Atox1. This Cu metallochaperone protein promotes cuproproteins (CuPrs) secretion and assembly. The remaining excess Cu^{+} is sequestered by MT. There are copper sensors in the nucleus that respond to changes in Cu concentration through regulating MT1 and MT2 gene transcriptions. Abbreviations: SOD1-Superoxide dismutase [Cu-Zn] also named as superoxide dismutase 1 is an enzyme that encoded by the SOD1 gene, located on chromosome 21; CCS-Copper chaperone for superoxide dismutase is a 54kDa; (metalloprotein) responsible for the delivery of Cu to SOD; COX17-Cytochrome c oxidase copper chaperone is a protein which encoded by the COX17 gene. It is the terminal component of the Mt respiratory chain, which catalyzes the electron transfer from reduced cytochrome c to O_2; Atox1-It is a Cu metallochaperone protein encoded by the ATOX1 gene and plays a key role in Cu homeostasis as it delivers Cu from the cytosol to transporters ATP7A and ATP7B; STEAP- is a metalloreductase protein able to convert Fe from an insoluble ferric (Fe^{3+}) to a soluble ferrous (Fe^{2+}) form. STEAP3 is predicted to contain a Di-nucleotide binding domain; ATP7A, also known as Menkes' protein (MNK), is a Cu-transporting P-type ATPase with the capacity to use the energy from ATP hydrolysis to carry Cu (I) across cell membranes. The ATP7A protein is a transmembrane protein and is activated in the gut and all tissues except liver. In the gut, ATP7A regulates Cu(I) absorption by carrying Cu(I) from the gut into the blood; ATP7B is a Cu-transporting P-type ATPase defective in the Cu transport disorder like Wilson disease; MT-Metallothionein is a family of cysteine-rich; Cu^{2+}-exporting ATPase is an enzyme with systematic name ATP phosphohydrolase (Cu^{2+}-exporting); CTR1-High affinity Cu uptake protein 1 is a protein encoded by the SLC31A1 gene. COX-Cyclooxygenase (COX), is an enzyme that is responsible for biosynthesis of prostanoids, including thromboxane and prostaglandins like prostacyclin, from arachidonic acid

On the other hand, FEPANp is a combination of PCD/RCD involved in many physiological and pathological NC/GC processes, including cell homeostasis and the occurrence of permanent CD and even fatal prognosis in cases of massive NCC or damage of CNS vital centre. Cuproptosis (Cp) is a new and different Regulated Cell Death (RCD) caused by Cu ionophores or chelators. This novel discovery will help investigators better grasp the pathogenesis of NCC and shed light on possible therapeutic approaches to critically ill cases of NCC, as has been proposed by Cao et al. for other diseases [44].

Brief comments on Cuproptosis, long non-coding RNAs and NCC

Cp's process and regulation differ from other types of PCD/RCD, such as pyroptosis, apoptosis, necroptosis, ferroptosis, and PANoptosis [45]. According to Ouyang and collaborators, long non-coding RNAs (lncRNAs) are a class of RNA molecules localized in the nucleus or cytoplasm of cells involved in much biological behaviour of malignant diseases such as Ap, cellular differentiation, cell proliferation, and metastasis [39]. Nevertheless, whether and how Cu-related lncRNAs (CRlncRNAs) influence the outcome of NCC remains to be determined, and we did not find confident evidence to formulate a new hypothesis. We hypothesize that lncRNAs are closely associated with the expression of many signaling pathways, including WNT, PI3K/Akt, and PPAR, as has been proposed by other authors under different circumstances [5].

As we previously cited, Tsvetkov et al., (2022) reported that Cu is bound to the lipid-acylated components of the Tricarboxylic Acid (TCA) cycle, causing lipid-acylated protein aggregation and RCD.

We hypothesize that LncRNAs (class of RNA molecules) are involved in the pathogenesis of NCC, as we will comment below, despite the scanty publications on the function of LncRNAs in Cp and their role in tumorigenesis [46].

Brief comments on cuproptosis in NCC

Beyond classical Ap, several forms of Regulated Cell Death (RCD) have been identified, such as Fp, Np, Pp, PANp and, more recently, FEPANp [47]. Fp has been defined as an iron-dependent form of oxidative cell death (OSCD) caused by unrestricted LP [48]. The Tsvetkov et al., (2022) proposal of Cp is gaining attention in the research RCD field [10]. Cp differs from OSCD (e.g., Ap, Fp, Np, Pp, PANp and FEPANp). In contrast, Mt stress, especially the destabilization of Fe-S cluster proteins and the aggregation of lipoylated proteins, leads to proteotoxic stress and, ultimately, CD [3]. We hypothesize that Cp is a type of CD in cases presenting NCC depending on Mt respiration. Cu directly binds to lipoylated components of the TAC, as we graphically represent in Figure 4. Afterwards, aggregation of these lipoylated mitochondrial proteins, Cu-bound, and subsequent Fe-S cluster protein loss trigger proteotoxic stress and a different kind of CD.

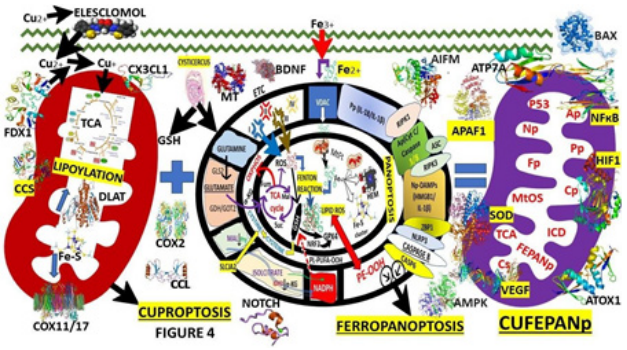

Figure 4: Graphical hypothesis on the Mt pathways engaged in

CUFEPANp combining PANoptosis, Ferroptosis, Cuproptosis, and oxidative stress. Showing a diagram of the simple mechanism of Cu. Elesclomol imports Cu^{2+} into the cell, which is reduced to Cu^{+} by FDX1. Cu^{+} binds to lipoylated components of the Mt TCA cycle, leading to lipoylated protein aggregation followed by a diminish Fe-sulfur cluster proteins, thereby inducing proteotoxic stress, promoting to CD. Abbreviations: AIFM-Apoptotic inducing factor mitochondrial; AMPK-AMP-activated protein kinase; APAF1-Apoptotic peptidase activating factor 1; ATOX1-Antioxidant 1 copper chaperone, ATP7A/B-ATPase copper transporting alpha/beta; BAX-BCL2 associated X apoptosis regulator; BDNF-Brain-derived neurotrophic factor; CCL-Chemokine (C-C motif) ligand; CCS-Copper chaperone for superoxide dismutase; CoQ10-coenzyme Q10; COX-Cytochrome c oxidase, COX2-Cyclooxygenase-2; CX3CL1-C-X3-C motif chemokine ligand 1; ES-elesclomol is a drug that triggers Ap in cancer cells; ETC-electron transport chain; DLAT-dihydrolipoyl transacetylase an enzyme component of the multienzyme pyruvate dehydrogenase complex which is responsible for the pyruvate decarboxylation step that links glycolysis to the citric acid cycle. Its involves the transformation of pyruvate from glycolysis into acetyl-CoA to be used in the citric acid cycle to carry out cellular respiration; FDX1-ferredoxin 1; FSP1-ferroptosis suppressor protein 1; Fum-fumarate; GDH-glutamate dehydrogenase; GLS2-glutaminase 2; GOT2-glutamic-oxaloacetic transaminase 2; HIF1-Hypoxia inducible factor 1; ICD-Immunogenic cell death; IDH2-isocitrate dehydrogenase 2; IMM-inner mitochondrial membrane; IMS-intermembrane space; α-KG-α-ketoglutarate; Mal-malate; MT-Metalloprotein; MtFt-mitochondrial ferritin; NF-Kb-Intranuclear protein complex factor kappa-B; Notch-Notch Receptor; NOX4-NADPH oxidase 4; OMM-outer mitochondrial membrane; Pyr-pyruvate; SOD1-2-Superoxide dismutase 1-2; Suc-succinate; TCA cycle-tricarboxylic acid cycle; VDAC-voltage-dependent anion channel; VEGF-Vascular endothelial growth factor. Note: 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

Crosstalk between elements of Cp, Fp and PANp in NCC

Fp, iron dependent PCD, is featured LP of unsaturated fatty acids *via* Fe^{2+}, leading to CD [49]. We speculate that all types of NC/GC inevitably self-destruct in response to different stimulus signals and all PCD/RCD play a vital role in tissue homeostasis, development of the cell population, and defence mechanism against unplanned cell growth as has been proposed by Bian and colleagues for regulation of tumorigenesis [50].

Based on the findings of Tsvetkov et al., (2022), we also hypothesize that in cases of NCC on treatment addressed to modulated CD mechanism including FEPANp and OS, then copper ionophore-mediated CD will not participate in this mechanism of CUFEPANp, but further investigations including unique clinical trials must be performed to find out the adequate treatment, and it will take a long time to happens [10].

Fp is the only modality of iron-dependent CD triggered by unrestricted LP on cell membranes, which strongly participate in the pathogenesis of various diseases, including neurodegeneration, malignancies, and ischemic organ injury [49].

Finally, we hypothesize that the process of Cp in NCC on top of FEPANp can be summarized as follows: The exaggerated concentration of intracellular Cu^{2+} is transported to the Mt *via* Ferredoxin 1 (FDX1) reduces Cu^{2+} to Cu^{1+}, Cu ionophores (elesclomol); Lipoic Acid Synthetase (LIAS) converts the octanoylated domains into lipoylated derivatives. On top of that, large concentrations of Cu^{1+} bind directly to lipoylated components (including DLST, GCSH, DBT, and DLAT) of the TAC (Tricarboxylic Acid Cycle), resulting in ensuing proteotoxic stress, lipoylated proteins oligomerization, Fe-S cluster proteins loss, and CD This hypothesis is supported by the postulate delivered by other authors under different pathological conditions [51].

Based on our previous reports, we hypothesize the crosstalk between the newly described metal-related RCDs, Cp and Fp. We speculate that all processes are closely related during the colloid stage of NCC from the primary success secondary to the release of glutamate followed by Mg polarization/proinflammatory cytokines/OS and induced Fp *via* suppressing intracellular Glutathione (GSH) synthesis to inhibit Glutathione Peroxidase 4 (GPX4)-mediated antioxidant reaction [24,26,27,40,47,48]. In contrast, excessively increased concentration intracellular Cu ion-dependent RCD acting as the scaffold directly binds to lipoylated components in the Tricarboxylic Acid (TCA) cycle, leading to the aggregation of lipoylation-related proteins, plus disrupting protein homeostasis triggering a Cp depending on Cu ionophores (elesclomol) expression. Other authors have postulated that Fp inducers promoted Cp in liver cancer in vivo, and they also have proven that Fp inducers promoted Cp in liver cancer cells through depleting intracellular GSH, an alternative copper chelator, and bridged the crosstalk between Fp and Cp [4].

Based on the above findings, we based our hypothesis regarding NCC patients with excessive levels of intracellular Cu and iron, which are remarkably harmful, causing Mg polarization/cytokine storm and cytotoxic oedema, while the damage caused by NC/GC and disruption of BBB cause pericystic vasogenic oedema.

The crosstalk between different Regulated Cell Death (RCD) such as Np, Pp, Fp, PANp, and Cp has been gradually reported, and we hypothesize all are involved in the NC/GC response to the presence of glutamate during the colloid stage of NCC; therefore, the best terminology to name this process is CUFEPANp. This mechanism includes disrupting the Mt homeostasis/OS due to excessive Cu ion delivered by Cu ionophore disulfiram, promoting the accumulation of intracellular iron/LP/Fp.

We speculate that in patients presenting NCC at the colloid stage, around the cystic lesion, GSH has a double function. One function act as the substrate for GPX4 to reduce LP/Fp, and the second controls the concentration of liable Cu ion pool working as an alternative chelator of Cu apart from providing lipoylated proteins aggregation using Cu ions as a core. Based on the previous postulate, we hypothesize that GSH is the most relevant element to mediate the crosstalk of Fe and Cp (Cu levels exceeding homeostasis

thresholds) inducing RCD. Because we cannot separate Fp from PANp as we documented in a previous publication, we hypothesize that both mechanisms are present in NCC; that is why we prefer the terminology of CUFEPANp, as we graphically represented.

We hypothesized that patients presenting NCC for an extended period with recurrent colloid stages can develop chronic OS caused by moderate concentration of Cu, known as cuproplasis. The role of OS was documented recently by us [48]. Based on the previous information, we postulated that increasing Cu concentration beyond the AO capacity of the NC/GC will be pushed to undergo Cp. If other associated PCD/RCD are present, then the mechanism of CUFEPANp will lead to the NC/GC permanent damage seen at the perilesional region of the colloid/nodular-fibrotic stage of NCC.

Brief comments on the role of P53 in cuproferropanoptososis/NCC

We hypothesize that in CUFEPANp, the Cu^{2+} directly associates with the Lipoylated proteins (Lpp) of the TAC, causing the disulfide-bond-dependent aggregation of these Lpp with the destabilization of the Fe-sulfur cluster proteins, leading to proteotoxic stress. We also hypothesize that some NC/GC during the colloid stage of NCC prefer glycolysis (Warburg effect) to oxidative phosphorylation for producing energy and intermediate metabolites, thereby achieving resistance to CUFEPANp as has been documented by Xiong et al., (2023) in cases presenting malignant disorders [52].

It is not specific if suppressor p53 inhibits NC/GC glycolysis and promotes oxidative phosphorylation between NCC's colloid and nodular-fibrotic stages. However, we hypothesize that p53 may control the biogenesis of Cu chelator glutathione and Fe-Sulphur cluster (relevant components of Cp pathway), playing an essential role in CUFEPANp in response to several cellular stress, being the main reason why we included p53 in the graphic illustration shown. Therefore, p53 might increase sensitization to Cp by inhibiting glycolysis because we hypothesize that damaged NC/GC at the perilesional cysticercus can utilize glycolysis instead of the TCA cycle to produce energy and intermediate metabolites (aerobic glycolysis/Warburg effect) triggering the use of other sources of energy such as glutamine/galactose which sensitizes NC/GC to CUFEPANp. On top of that, other authors have documented that p53 mutation also inhibits glucose metabolism through repression of glucose transporter expression in obesity [53].

Upon glucose restriction, the ATP level diminishes, resulting in an elevated ratio of AMP to ATP, leading to activation of the AMPK signaling, which induces p53 expression and phosphorylation. Nonetheless, p53 regulates genes involved in the biogenesis of Fe-sulfur clusters and controls the endogenous Cu chelator glutathione concentration. We also speculate that the recurrent expression of AMPK might trigger CUFEPANp by inhibiting mTOR/dysfunctional Mt and lack of glucose supply to the NC/GC. Another author has made similar postulates in cases with chronic leukemia [54].

Brief comments on the role of Cu in neuroinflammation caused by NCC

Conforti established the role of Cu in the regulation of neuroinflammation (NI) in animal models in 1983, and high concentrations of Cu in fluids/tissues in animals and humans during the inflammatory process have been proven by Milanino et al., (1981) even before [55,56]. Based on the reported shreds of evidence, we hypothesize that during the colloid stage of NCC, the mechanism of NI is modulated by Cu transported by ATP7B into CP, which is an acute phase response protein highly concentrated during the pathogenesis of NI, and it has upregulated by proinflammatory cytokines (IL-1 and IL-6) plus Hypoxia-Inducible Factor (HIF1). On the other hand, it has been proven that a high concentration of Cu leads to many types of inflammatory vascular diseases, while Cu chelators inhibit NI [57].

In a previous publication, we hypothesized the role of MAP kinase family such as Mitogen-Activated Protein Kinase (p38 MAPK), p38 Mitogen-Activated Protein Kinase (p38 MAPK), and c-Jun N-Terminal Kinase (JNK) in the generation of proinflammatory cytokines and cytokine storm in cases with NCC and COVID-19 [14-16], while inhibitory process of p38 and JNK contribute to reduce the excess of Cu. We speculate that Cu influx causes MEK1 phosphorylation of ERK1/2 and MAPK expression, triggering stimulation of other kinases and activating the transcription of proinflammatory genes based on the results reported by Qin and colleagues [58].

In the same study, we documented the function NF-κB (Nuclear Factor kappa B) as a remarkable activator of the inflammatory response to released glutamate during the colloid stage of NCC, also modulating the overall expression of interleukin-8, interleukin-1β, inducible nitric oxide synthase, and cyclooxygenase-2 in NC/GC [41]. Nonetheless, the NI process is regulated by MAPK and NF-κB while Cu-transporting ATPases (ATP7A/B) keep the normal concentration levels of Cu in NC/GC, mainly in Mg cells. On the other hand, we hypothesize that the metabolism of Cu is remarkably enhanced in the colloid stage of NCC based on the report delivered by other authors under different conditions [41].

Conclusion

We also hypothesize that many components of the oxidant defence system, like GSH, CP, Superoxide Dismutase (SOD), and metallothionein, are impaired in Cu deficiency. Furthermore, we considered that SOD, Cu/Zn and CP activity are sensitive to tissue Cu and lack of Cu cause a decrease in Cu/Zn SOD expression leading to a great OS and CD.

This review was the first study to comprehensively analyses the association between copper-induced CD and

NCC in combination with Fp and PANp, which we named CUFEPANp. Based on this comprehensive review, we delivered several hypotheses on the participation of Cp, Fp, and PANp in NCC. However, future well-designed investigations will support or deny the hypotheses proposed in the present manuscript.

Declarations

Consent for Publication

No written informed consent was necessary to obtained for our review with it has not Bioethical implications.

Declaration of anonymity

All authors certify that they did not reveal the names, initials, and other identity issues of any patient in this publication, and complete anonymity is guaranteed.

Availability of data and material

The data supporting this study's findings are available on reasonable request from the corresponding author.

Ethical Approval

The WSU/NMAH Institutional Ethical Committee did not consider this report for additional ethical approval.

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Competing Interest

The authors declare that they performed this study without any commercial, financial, or otherwise relationships able to construe a potential conflict of interest.

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Authors' Contributions

Study concept and design: MNG, HFS and LFIV. Data collection from searched literature: MNG, LdeFIV and HFS. Analysis of the obtained data: LdeFIV/HFS/MNG. Drafting of the manuscript: MNG, LFIV, HFS. Revising the manuscript: HFS, MNG and LFIV. Supervised research and manuscript writing process: HFS. All authors have approved this version for publication.

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