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Review

Ferroptosis-associated microRNAs: Systematic review

Maria del Carmen Candia-Plata[1#], Juan Manuel Martínez-Soto[1#], Jeanette Guadalupe Arredondo-Damián[2], Astrid Nallely Ramírez-Romero[2], Lucía Guadalupe Villegas-Coronado[3], Jesús Adriana Soto-Guzmán[1], Luis Fernando López-Soto[1], Ana Lourdes Mata-Pineda[1], Gerardo Álvarez-Hernández[1], José Manuel Galván-Moroyoqui[1*]

[1] Department of Medicine and Health Sciences, University of Sonora, Hermosillo, 83000, México
[2] Ph.D. Program (Doctorate in Biological and Health Chemistry), University of Sonora, Hermosillo, 83000, Mexico
[3] National Social Service Program in Health Research, General Directorate of Quality and Education in Health (DGCES) of the Ministry of Health, México

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Abstract

Ferroptosis, an iron-dependent form of regulated cell death characterized by lipid peroxidation, has emerged as a critical process in various diseases. MicroRNAs (miRNAs), small non-coding RNAs that regulate gene expression, are increasingly recognized as key modulators of ferroptosis pathways. This systematic review aims to provide a comprehensive overview of the current knowledge regarding miRNAs implicated in ferroptosis across a spectrum of diseases. We conducted a systematic search of EMBL-EBI, PubMed, Scopus, and Web of Science databases to identify relevant studies published up to October 31, 2022. Our search strategy identified 127 articles encompassing 107 distinct miRNAs that influence ferroptosis. This review synthesizes the findings of these studies, highlighting the specific miRNAs that act as either inhibitors or inducers of ferroptosis in different disease contexts, including various cancers (e.g., lung, breast, colorectal) and degenerative conditions (e.g., acute renal failure, diabetic retinopathy). We discuss the molecular mechanisms by which these miRNAs regulate ferroptosis, often by targeting key genes involved in iron metabolism, lipid peroxidation, and antioxidant defense. Furthermore, we explore the potential of these miRNAs to serve as diagnostic biomarkers and therapeutic targets in ferroptosis-related disorders, offering insights into novel strategies for disease management.

Keywords: Ferroptosis; miRNA; microRNA; Regulated cell death; Lipid peroxidation; Cancer; Iron metabolism

1. Introduction

Cell death is a fundamental attribute of organisms [1], critical for cellular homeostasis [2], and decisive perpetrator of degenerative illnesses. Cell death is frequently abnormally activated or deactivated in numerous diseases [3], and the comprehension of the mechanisms controlling cell death is necessary for achieving its role in pathophysiology and to propose treatments for several diseases, especially cancer [4]. Until now, various types of regulated cell death (RCD), counting apoptosis, necroptosis [5], pyroptosis [6], autophagy [7], and in recent years, ferroptosis have been elucidated [8], with the agreement that all RCD forms reveal distinctive mechanisms with the common outcome (cell death). In this sense, it is possible to think that due to the different RCD processes that exist, personalized treatments could be proposed based on the mechanism of specific type of RCD that is targeted in a certain disease [4].

The term ferroptosis was coined in 2012 due to previous discoveries reported by the group of Stockwell and other groups [9]. The concept of ferroptosis refers to an RCD process with iron-dependency driven by peroxidation of the lipid membrane induced by reactive oxygen species (ROS) [10], and to date, studies indicate that is completely different from other forms of RCD, including apoptosis [11]. Although apoptosis has been thought of as the principal type of RCD and main target of several diseases [12], occasionally treatments focused on apoptosis do not find desired results [13]. Therefore, non-apoptotic cell death processes have constantly been investigated, like ferroptosis [14]. Through the advance in research on ferroptosis, the revelation of mechanisms of ferroptosis has progressively been exposed and regulatory pathways are still in investigation (Figure 1) [15, 16]. Key features implicated in ferroptosis are iron metabolism regulation, redox balance, including inducers and inhibitors of ROS production, and lipid metabolism involving peroxidation reactions [8].

Ferroptosis is morphologically highlighted by loss of mitochondrial cristae, shrunken mitochondria with aug-

* Corresponding author.
E-mail address: jose.galvan@unison.mx (J. M. Galván-Moroyoqui).
# These authors contributed equally
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mented membrane density and rupture of the outside mitochondrial membrane [17]. Genetically, ferroptosis is denoted by changes in the expression of iron metabolism, lipid mediators, and pro/anti-oxidants agents, e.g. transferrin receptor protein 1 (TFRC) [18], long-chain-fatty-acid-CoA ligase 4 (ACSL4) [19], system Xc- cystine/glutamate transporter (SLC7A11) [20], ChaC glutathione specific gamma-glutamylcyclotransferase 1 (CHAC1) [21], prostaglandin-endoperoxide synthase 2 (PTGS2) [22], and glutathione peroxidase 4 (GPX4) [23], together implicated in ferroptosis beginning and progression. Biochemically, ferroptosis is catalyzed by iron-dependent accumulation of ROS and this accumulation of ROS boosts in a vicious cycle the peroxidation of lipid membrane affecting cellular permeability and integrity, leading to cell death [10]. In fact, ferroptosis is connected to pathophysiology conditions, and targeting ferroptosis would be an element of therapeutics for numerous diseases, such as diabetes [24], cancer [25], Alzheimer's [26], cardiovascular, and iron-overload-related diseases [27]. Several compounds have been reported that might be clinically pertinent in therapeutics for ferroptosis in related diseases [28]. Whereas ferroptosis inducers/sensitizers are intended to be treatment for cancer, ferroptosis inhibitors/blockers could be valuable for previously cited degenerative diseases where ferroptosis is abnormally activated [29].

An approach that has been extensively considered is non-coding RNAs (ncRNAs), and a field in current research is the regulation function that ncRNAs exert on ferroptosis [30]. NcRNAs, mainly miRNAs have been recognized to play significant functions in ferroptosis regulation [31]. The role of miRNAs is to regulate gene expression, consequently, influencing many processes including RCD ferroptosis [32]. Up to now, miRNA functions in ferroptosis are still being studied, and considerable progress has been achieved in discovering and understanding the regulatory mechanisms exerted by miRNAs on ferroptosis [33]. Nevertheless, to our knowledge, there is no systematic review concerning ferroptosis-associated miRNAs and their implication in different diseases. In this systematic review, we explore the roles of ferroptosis-related miRNAs. Furthermore, we enumerate strategies that some groups are exploring according to ferroptosis-regulation miRNAs for biomarker and therapeutic approaches. This review will serve to increase our understanding of ferroptosis-associated miRNAs and provide ideas regarding prognosis and therapeutics employing miRNAs in the ferroptosis knowledge.

2. Methods

2.1. Literature search strategies and eligibility

This systematic review summarizes recent findings on ferroptosis-associated miRNAs. Here we discussed miRNA implications on ferroptosis-associated diseases, and their potential as novel biomarkers, and therapeutic targets. The systematic assessment was conceived according to Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) [34]. The systematic search was performed on EMBL-EBI, PubMed, Scopus, and Web of Science databases to recognize eligible publications on October 31st, 2022, without period restriction. The keywords to determine article eligibility were written as follows: ('microRNA' OR 'miRNA' OR 'mir') AND ('Ferroptosis').

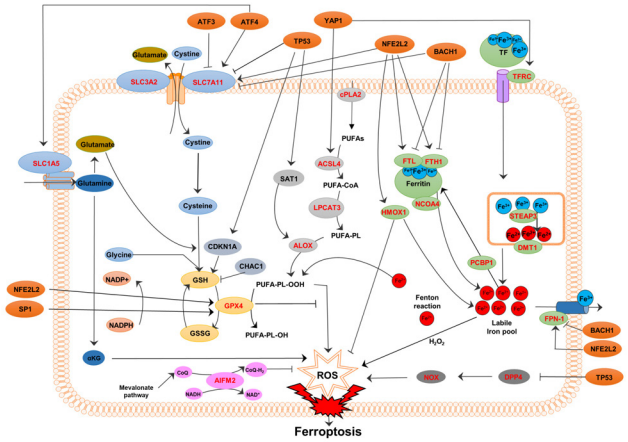

Fig. 1. Principal mechanisms of ferroptosis. Ferroptosis-related lipid metabolism: fatty acids by ACSL4 and LPCAT3 convert into PUFA-PLs, and then ALOX catalyzes PUFA-PLs-dioxygenation and produces PUFA-PLs-OOH. PUFA-PLs-OOH are regulated by GPX4. In abundance of PUFAs, there is an exacerbated generation of ROS which causes GPX4-reduced activity, facilitating the onset of ferroptosis. Ferroptosis-related iron metabolism: in circulation, oxidized iron (Fe^{3+}) is transported in TF complex, TF-Fe^{3+} complex is endocytosed among TFR1. STEAP3 produces conversion of Fe^{3+} to Fe^{2+}. Then, divalent metal transporter 1 (DMT1) transports Fe^{2+} to cytosol, where enters to the LIP for metabolic demands. If there is excess of iron, it can be secreted by FPN-1. PCBP1 activity produces iron storage in ferritin. NCOA4 can feed the LIP, by releasing Fe^{2+} from ferritin, in a process named ferritinophagy. Fe^{2+} participates in Fenton reaction to generate ROS and lipid ROS. Ferroptosis-related antioxidant metabolism: system Xc- (SLC7A11, SLC3A2) ingresses cystine, then is reduced to cysteine and utilized to produce GSH, a GPX4 cofactor for the elimination of ROS. Moreover, with the support of Mevalonate pathway, the AIFM2- coenzyme Q (CoQ) pathway inhibits lipid peroxidation defending from ferroptosis. Additionally, there are transcription factors related to ferroptosis-regulation whose function is to up or down-regulate the different components from signaling pathways involved in the induction or inhibition of ferroptosis (orange circles). ATF3 can downregulate the expression of SLC7A11. In contrast, ATF4 is related to the upregulation of the expression of SLC7A11, SLC1A5, and CHAC1. NFE2L2 (also known as NRF2), participate promoting the expression of SLC7A11, GPX4, FTL, FTH1, heme oxygenase 1 (HMOX1), and FPN-1. TP53 upregulates the expression of SAT1 and CDKN1A, and the downregulation of DPP4 and SLC7A11. YAP1 has been reported to induce TFRC and ACSL4. SP1 is related to the positive expression of GPX4. Finally, BTB domain and CNC homolog 1 (BACH1) participate inhibiting the expression of FPN-1, FTL, FTH, and SLC7A11.

2.2. Inclusion and exclusion criteria

We included experimental and observational studies published in journals meeting the following criteria: full studies written in English investigating ferroptosis-regulatory miRNAs with a specified target including studies that directly focus on miRNAs or indirectly appreciate the role of miRNAs (e.g., ferroptosis studies were ncRNAs work as miRNAs sponges) utilizing human primary cell cultures or human cell lines. Articles were also included when the ferroptosis-associated miRNAs were evaluated in human cells/tissue samples and then experimented in animal models. Articles written in other languages, reviews, brief reports, comments, erratum texts, editorials, guidelines,

letters, meeting reports, preprint manuscripts, articles warning an expression of concern and retracted articles, studies with only bioinformatic approaches, articles that only studied miRNAs into in vitro or in vivo animal models and no evaluations were done in human cells or tissue samples, and studies investigating miRNAs function however not relating to ferroptosis were excluded.

2.3. Study selection

Three investigators (Candia-Plata, M, Martínez-Soto, J and Arredondo-Damián, J) searched and reviewed articles independently. Applicable articles were detected based on titles and abstracts. Then, all sections of articles were examined, and eligible papers were collected for inclusion in the review. Articles that did not meet the eligibility criteria were excluded reporting the reasons. In case of conflict, consensus was determined by consulting a fourth author (Galván-Moroyoqui, J).

2.4. Data extraction

Three investigators (Candia-Plata, M, Martínez-Soto, J and Arredondo-Damián, J) searched and reviewed articles independently. Applicable articles were detected based on titles and abstracts. Then, all sections of articles were examined, and eligible papers were collected for inclusion in the review. Articles that did not meet the eligibility criteria were excluded reporting the reasons. In case of conflict, consensus was determined by consulting a fourth author (Galván-Moroyoqui, J).

2.5. Construction of miRNA-mRNA network with miRNAs identified in the systematic review

MiRNet database (https://www.mirnet.ca/) was utilized to predict the potential mRNAs related to miRNAs captured in the systematic search [35]. MiRNet collected 9451 potential targets of miRNAs (Supplementary Table 1). We further visualized the network of miRNet, highlighting those miRNAs with higher degrees, including some predicted miRNAs that were not found in the systematic review.

3. Results

3.1. Search Results

Three researchers independently screened and reviewed articles. The search resulted in 1268 articles detected using the strategy proposed. The articles duplicated were removed during the process. A total of 316 articles were full-text reviewed. We excluded 9 articles with no ferroptosis relation, 68 studies with no miRNAs or with miRNAs not related to targets in ferroptosis, 63 articles only focusing on experimental animal models and 49 due to bioinformatics analysis alone. Finally, 127 articles were included in this systematic review. Details of the systematic searching process are indicated in Figure 2.

Although there was no time restriction, all articles were published from 2018 to 2022. From the 127 articles included, 107 different miRNAs were obtained. Thirteen miRNAs were repeated two times: miR-378a-3p [36, 37], miR-137 [38, 39], miR-874-3p [40, 41], miR-214-3p [42, 43], miR-515-5p [44, 45], miR-497-5p [46, 47], miR-142-3p [48, 49], miR-1287-5p [50, 51], miR-520a-5p [52], miR-494-3p [53], miR-124 [54, 55], miR-125b-5p [56, 57], and miR-143-3p [58, 59]. The miR-375 [45, 60, 61] and the miR-324-3p [62-64], were repeated three times, and the miR-7-5p [65-68], and the miR-27a-3p [69-72], were reported in four occasions. All articles identified and discussed ferroptosis-related miRNAs, genes target of miRNAs, effects on ferroptosis mechanisms, and possible clinical implications on different diseases. Diseases addressed included different types of cancer (lung, breast, prostate, liver, colorectal, gastric, etc.); as well as degenerative diseases (e.g., acute renal failure, diabetic retinopathy, and pulmonary fibrosis) and finally, ischemia-related diseases including acute ischemic stroke, hemorrhagic stroke, renal ischemia-reperfusion, and acute cerebral infarction.

The miRNAs, target gene, associated disease or condition, effect in ferroptosis-mechanisms and references are listed, for ferroptosis-inhibitors/suppressors in Supplementary Table 2 and for ferroptosis-inducers/sensitizers in Supplementary Table 3.

3.2. MiRNAs identified for ferroptosis inhibition in cancer-related diseases

We found articles researching cancer and ferroptosis-related miRNAs cataloged as inhibitors/suppressors of ferroptosis cell death as follows (Supplementary Table 2): acute myeloid leukemia, miR-let-7b-5p [73], cervical cancer, miR-7-5p [67] and miR-4291 [74], colorectal cancer, miR-545 [75] and miR-19a [76], esophageal cancer, miR-372-3p [77] and miR-27a-3p [72], gastric cancer, miR-522 [19], glioblastoma, miR-670-3p [78] and miR-18a [79], head and neck cancer, miR-200 [80], hepatocellular carcinoma, miR-362-3p [30] and miR-23a-3p [81], lung cancer including carcinomas, miR-4443 [82], miR-19b-3p [83], miR-27a-3p [70], miR-6077 [84], miR-17-5p [85] and miR-367-3p [86], melanoma, miR-137 [38], miR-130b-3p [87], and miR-9 [88], oral squamous cell carcinoma, miR-7-5p [67], and ovarian cancer, miR-424-5p [89]. In the enumerated cancer diseases, miRNAs could be found upregulated or downregulated depending on the aggres-

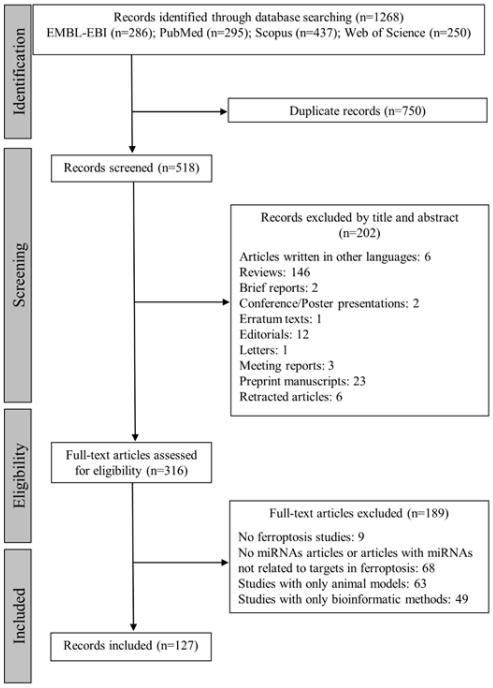

Fig. 2. Flow chart describing the selection process of studies included in this systematic review.

sive phenotypes of malignant cells [89, 90].

3.3. MiRNAs identified for ferroptosis inhibition in metabolic, cardiovascular, and oxidative stress-related diseases

In addition, we achieved the subsequent non-cancer but cardiovascular, ischemic and degenerative diseases also classifying miRNAs as inhibitors/suppressors of ferroptosis: acute cerebral infarction, miR-3098-3p [91], acute ischemic stroke, miR-214 [92], acute liver injury, miR-15a [93], cardiovascular remodeling, miR-124 [55], congenital heart disease, miR-193a-3p [94], diabetic retinopathy, miR-200b-3p and miR-7-5p [65], doxorubicin-induced cardiac injury, miR-7-5p [68], exposure to benzene, miR-142-5p [95], ferroptosis in endothelial cells, miR-30e-5p [96], hemorrhagic stroke, miR-137 [39], hypoxia, miR-6862-5p [97], intracerebral hemorrhage, miR-106b-5p [98], intervertebral disc degeneration, miR-10a-5p [99] and miR-874-3p [40], ischemia diseases, miR-17-92 [100], liver fibrosis, miR-222 [101], Parkinson's disease, miR-150-5p [102], periodontitis, miR-370 [103], preeclampsia [104], and pulmonary fibrosis, miR-150-5p [105]. In contrast to cancer diseases, ischemic and cardiovascular disorders, and in some degenerative conditions, ferroptosis mechanisms have been observed as overactivated. In this vision, the above ferroptosis-inhibitors miRNAs are usually found downregulated, adding to the physiopathology of the listed diseases [92].

3.4. Classifying miRNAs into lipid metabolism-inhibiting miRNAs and miRNAs regulating iron metabolism-propagators of ferroptosis irrespective of the type of disease

MiRNAs display functions by binding to the 3′-untranslated regions of target mRNAs, dealing with downregulation of their expression [106]. Studies have demonstrated that miRNAs can regulate ferroptosis [107]. According to the results of this systematic review, ferroptosis-inhibiting miRNAs can be categorized as the two main mechanisms that promote ferroptosis [108]: lipid metabolism-inhibiting miRNAs and regulators of the expression of genes and molecules related to iron metabolism-propagators of ferroptosis (Figure 3).

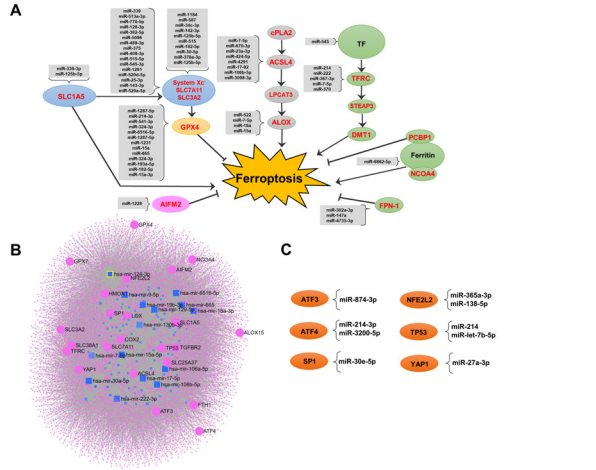

Fig. 3. Targets of miRNAs in ferroptosis mechanism. (A) miRNAs targeting components of the ferroptosis mechanisms. (B) MiRNA-mRNA network established with miRNAs identified in the systematic review. (C) miRNAs targeting transcription factors related to ferroptosis mechanisms.

In relation to miRNAs that inhibit lipid metabolism of ferroptosis, miR-424-5p [89], miR-670-3p [78], miR-23a-3p [81], miR-4291 [74], miR-17-92 [100], miR-106b-5p [98], miR-7-5p [65] and miR-3098-3p [91] regulates ACSL4 expression, thus inhibiting ferroptosis (Figure 3). ACSL4 is an important enzyme for polyunsaturated fatty acids (PUFAs) metabolism, such as arachidonic acid and eicosapentaenoic acid. ACSL4 can join PUFA-PLs to lipid peroxidation pathway, hence in conditions were ACSL4 is increased, the ferroptosis process is overactivated and vice versa [10]. Moreover, polyunsaturated fatty acid lipoxygenases (ALOXs) are a group of lipoxygenases that initiate the formation of lipid hydroperoxides that are substrates for the Fenton reaction, generating conditions for ferroptosis. In this case, we found that miR-522 [19], miR-7-5p [67], miR-18a [79], and miR-15a [93] were reported as ALOXs regulators.

With respect to iron metabolism, an important iron transport is the transferrin-ferric iron complex, and transferrin (TF) promotes iron uptake to intracellular compartments [109]. There are studies asserting that transferrin could impulse ferroptosis mechanism by feeding iron to cells [110]. MiR-545 was found to inhibit TF, promoting colorectal cancer, confirming that miR-545 [75] may play an oncogenic role in the disease. The transferrin receptor 1 (TFR1), whose protein function is to internalize iron from TF-iron complex has been shown to be a marker of ferroptosis [110]. Further, miR-214 [92], miR-7-5p [68], miR-222 [101], miR-367-3p [86] and miR-370 [103] are TFR1 gene expression-regulators, all of them, inhibiting ferroptosis mechanism. Additionally, the miR-6862-5p [97] targets nuclear receptor coactivator 4 (NCOA4), a protein recently recognized because of its role in ferritinophagy. NCOA4 binds to ferritin and leads to ferritin-lysosome degradation [97].

Finally, there are other inhibitory miRNAs regulating gene expression that are implicated in alternate routes of the primary proposed mechanisms of ferroptosis (Supplementary Table 2).

3.5. MiRNAs identified for ferroptosis induction in cancer-related diseases

In accordance to studies of cancer diseases and miRNAs categorized as inducers/sensitizers of ferroptosis mechanisms, there is plenty of literature and includes (Supplementary Table 3): acute lymphoblastic leukemia, miR-494-3p [53], bladder cancer, miR-129-5p [111], breast cancer, miR-106a-5p [112], miR-382-5p [113], miR-5096 [114], miR-324-3p [63], miR-410-3p [115], and miR-1228 [116], cervical cancer, miR-375 [45], miR-409-3p [45], miR-515-5p [45], miR-193a-5p [117], and miR-506-3p [118],colon cancer, miR-28-5p [119], and miR-423-5p [120], colorectal cancer, miR-874-3p [41], miR-539 [121], and miR-15a-3p [122], esophageal cancer, miR-30a-5p [123] and miR-513a-3p [124], gastric cancer, miR-375 [61], miR-489-3p [125] and miR-375 [60], gastrointestinal cancer, miR-4715-3p [126], glioblastoma, miR-27a-3p [69] and miR-147a [127], glioma, miR-761 [128], miR-3938 [129], and miR-29b [130], hemangioma, miR-497-5p [47], hepatocellular carcinoma, miR-541-3p [131], miR-1261 [132], miR-3200-5p [133], and miR-142-3p [48], liver cancer, miR-214-3p [42], and miR-142-3p [49], lung adenocarcinoma, miR-324-3p [62], miR-101-3p [134], miR-1184 [135], miR-520a-5p [52], and

miR-339 [136], lung cancer, miR-6852 [137], miR-365a-3p [138], miR-302a-3p [139], miR-101-3 [140], miR-1287-5p [50], miR-299-3p [141] and miR-520a-5p [52], melanoma, miR-21-3p [142], meningioma, miR-127-5p [143], oral squamous cell carcinoma, miR-520d-5p [144], and miR-34c-3p [145], osteosarcoma, miR-1287-5p [51], and miR-515-5p [44], ovarian cancer, miR-382-5p [113], and miR-587 [146], papillary thyroid cancer, miR-1231 [147], and miR-497-5p [46], prostate cancer, miR-128-3p [148], miR-15a [149], and miR-25-3p [150], rectal cancer, miR-326 [151], renal cell carcinoma, miR-4735-3p [152], miR-143-3p [59], miR-324-3p [64], and miR-27a-3p [71], thyroid cancer, miR-545-3p [153], and tongue squamous cell carcinoma, miR-125b-5p [56].

Considering that cancers are diseases where the cells involved evade the mechanisms of cell death [154, 155], in the present review we found significantly lower levels of miRNAs that promote ferroptosis in patients with cancer compared to controls, concluding that both ferroptosis-inhibiting and inducing miRNAs, influence on the development and progression of cancerous diseases [149].

3.6. MiRNAs identified for ferroptosis induction in metabolic, cardiovascular, and oxidative stress-related diseases

Between inducers/sensitizers miRNAs of ferroptosis mechanisms in non-cancer disorders involving ischemic and degenerative diseases we compiled the following: acute renal failure, miR-182-5p [36], and miR-378a-3p [37], diabetic nephropathy, miR-770-5p [156], diabetic retinopathy, miR-338-3p [157], endometriosis, miR-145-5p [158] and miR-6516-5p [159], high glucose-induced ferroptosis, miR-138-5p [160], intervertebral disc degeneration, miR-665 [161], intracerebral hemorrhage, miR-124 [54], myocardial ischemia-reperfusion injury, miR-143-3p [58], nerve injury caused by lead exposure, miR-378a-3p [37], polycystic ovary syndrome, miR-515 [162], preeclampsia, miR-30-5p [163], renal ischemia-reperfusion, miR-3587 [164], and sepsis-associated acute renal injury, miR-124-3p.1 [165]. Agreeing to reports, in pro-inflammatory and oxidative stress conditions, there is a disturb in numerous cell mechanisms, including cell death programming [166], in this case includes a dysregulation of miRNAs that could promote ferroptosis mechanisms, as these miRNAs are found to increase in expression in patients suffering pro-inflammatory and oxidative stress-cell conditions diseases [54, 158].

3.7. Classifying miRNAs into antioxidant metabolism-inhibiting miRNAs and miRNAs regulating iron metabolism-inhibitors of ferroptosis irrespective of the type of disease

The ferroptosis-inducing miRNAs can be categorized as miRNAs that inhibit the antioxidant metabolism and related-molecules, and miRNAs that target genes and molecules related to iron metabolism-inhibitors of ferroptosis (Figure 3). According to these last, miR-302a-3p [139] and miR-4735-3p [152] regulate ferroportin (FPN-1) expression, whose function is to deliver iron into the circulation, as a result, they inhibit ferroptosis.

Moreover, some miRNAs control the expression of genes related to antioxidant metabolism and such as communicated pathways like system Xc-. Actually, miR-128-3p [148], miR-382-5p [113], miR-5096 [114], miR-489-3p [125], miR-375 [45, 60], miR-409-3p [45], miR-515-5p [44], miR-545-3p [153], miR-1261 [132], miR-520a-5p [52], miR-520d-5p [144], miR-25-3p [150], miR-143-3p [59], miR-1184 [135], miR-587 [146], miR-34c-3p [145], miR-142-3p [48, 49], miR-515 [162], miR-182-5p [36], miR-30-5p [163], miR-770-5p [156], miR-513a-3p [124], miR-339 [136], miR-143-3p [58] and miR-378a-3p [37] are associated with the regulation of the system Xc-. SLC7A11 and system Xc- cystine/glutamate transporter (SLC3A2) are subunits of the system Xc-, and their key role is the internalization of cysteine, which can be transformed in glutathione (GSH) molecule, important for stabilization of hydroperoxides from PUFA-PLs [167].

Another crucial biomolecule that retards ferroptosis cell death is GPX4, having a central role in the prevention of lethal lipid oxidation [167]. GPX4 uses GSH as a cofactor to reduce PUFAs lipid peroxides to lipid alcohols. GPX4 was found to be regulated by miR-1287-5p [51], miR-214-3p [42], miR-541-3p [131], miR-324-3p [63, 64], miR-1287-5p [51], miR-1231 [147], miR-15a [122], miR-193a-5p [117], miR-182-5p [36], miR-665 [161], miR-6516-5p [159], and miR-15a-3p [122].

Lastly, there are more miRNAs reported to have inducing property of ferroptosis involving other pathways, as shown in Supplementary Table 3, and as a last result of this systematic review, a relevant mention goes to miR-125b-5p that binds and inhibits the expression of the solute carrier family 1 member 5 (SLC1A5) in gastric cancer, however, the consequence of the miR-125b-5p and SLC1A5-interaction in ferroptosis in gastric cancer stills largely unknown and should be investigated in the future [57].

3.8. Ferroptosis-related transcription factors can be regulated by miRNAs

Several transcription factors are involved in the regulation of various types of RCD. Also, some transcription factors have an important role in the regulation of ferroptosis, as it has been widely described in the literature [16]. In the present review, it was found that some miRNAs can influence the function of some transcription factors and affect the resolution of ferroptosis. The nuclear factor erythroid-derived 2-like 2 [(NFE2L2, also known as nuclear factor erythroid 2-related factor (NRF2)] is one of the most described transcription factors involved in oxidative stress conditions [15]. NFE2L2 promotes the expression of many iron metabolism-related proteins: FPN-1, ferritin light chain (FTL) and ferritin heavy chain (FTH1); and antioxidant metabolism (SLC7A11 and GPX4) during ferroptosis [168]. In the present review, it was found that miR-138-5p [160] and miR-365a-3p [138] can induce ferroptosis via NFE2L2 in cells with high glucose-induced ferroptosis and lung cancer cell models, respectively.

The tumor protein p53 (TP53) is a transcription factor very well described for cancer occurrence, with influencing qualities on the mechanisms of ferroptosis [169]. There are reports demonstrating that TP53 can induce ferroptosis through the inhibition of SLC7A11. On the other hand, it was indicated that TP53 could also inhibit ferroptosis by promoting the expression of cyclin-dependent kinase inhibitor 1A (CDKN1A), whose role is involved in the generation of GSH, an important molecule with potent antioxidant effect. In addition, TP53 can also downregulate dipeptidyl peptidase-4 (DPP4), an enzyme related to

the generation of lipid ROS [16, 169]. This review, recognized the miR-214 [92] and the miR-let-7b-5p [73] for regulating TP53, having a suppressing effect on ferroptosis.

Activating transcription factor 4 (ATF4) is another transcription factor studied within the subject of ferroptosis since it was observed that induces SLC1A5 and CHAC1, thus generating ferroptosis [15, 170]. In contrast, ATF4 can also upregulate SLC7A11, which implies the inhibition of ferroptosis [15]. Among the miRNAs affecting ATF4 are miR-214-3p [43] and miR-3200-5p [133], both inducers of ferroptosis through ATF4 in liver cancer cells.

Finally, more miRNAs regulate transcription factors related to ferroptosis listed in Figure 3 and more described in Supplementary Table 2 and Supplementary Table 3.

3.9. MiRNA-mRNA network stablished with miRNAs identified in the systematic review

We used the miRNet tool to predict targets of the systematic review-miRNAs. We obtained 9451 targets of miRNAs (Supplementary Table 1). According to results, miRNet established a network of mRNAs and miRNAs containing 9557 nodes (9451 genes, and 106 miRNAs), and 28586 edges (Figure 3B). Some genes found in the systematic review regulated by miRNAs predicted by miRNet were SLC7A11, TP53, SLC3A2, solute carrier family 38 member 1 (SLC38A1), ACSL4, solute carrier family 25 member 37 (SLC25A37), SLC1A5, NFE2L2, LOX, specificity protein 1 (SP1), Yes-associated protein 1 (YAP1), transforming growth factor beta receptor 2 (TGFBR2), activating transcription factor 3 (ATF3), FTH1, ATF4, apoptosis inducing factor mitochondria associated 2 (AIFM2), NCOA4, GPX7 and GPX4 (Figure 3B). Further, miRNet also predicted potential miRNAs that are not found in the present systematic approach and might target genes related to ferroptosis that could be valuable initiatives to study in future experimental-focused investigations. For this propose, miRNet predicted: miR-124-3p, miR-15a-5p, miR-222-3p, miR-9-5p, and miR-18a-3p.

4. Discussion

The regulation of cell death is vital for the equilibrium in cellular processes such as proliferation, differentiation, and development of multi-cellular systems [171]. Also, RCD confers a balance between health and the countering and progressing of diseases. Therefore, it is involved in numerous processes under physiological and pathological circumstances [2, 171]. Ferroptosis is a newly discovered form of RCD coined in 2012 [9] and differs morphologically, genetically, and biochemically from apoptosis, necroptosis, pyroptosis, parthanatos, and autophagy [11].

Ferroptosis is a non-apoptotic iron-dependent RCD characterized by a perpetual oxidative intracellular environment that drives to irrevocable damage of lipid membranes interrupting cell viability [8]. The manifestation of ferroptosis depends on the exposition of massive concentrations of ferrous iron (Fe^{2+}) and ROS, mainly from lipids which subsequently affect homeostasis of cellular processes, thus resulting in cell death [10]. Generally, the process initiates when excessive iron and reactive oxygen species interact through Fenton reactions with molecules from lipid metabolism, driving a pernicious increase of lipid peroxidation with an overwhelmed antioxidant metabolism that is unable to neutralize the oxidative intracellular atmosphere ending with the destruction of cell membrane [170].

Since ferroptosis is associated with several biological contexts, increasing interest has emerged in studying ferroptosis-implication in diseases. In fact, many ferroptosis investigations have turned into research on biomarkers and treatments of cancer as this systematic approach revealed [172]. On the other hand, there are also documents studying ferroptosis association to diseases where the redox balance is presumably disrupted including traumatic, cardiovascular, ischemic, and neurodegenerative diseases [173]. Ferroptosis has been uncovered as a great opportunity to fight against cancers and oxidative stress-related diseases according to literature [166]. Treatments that depend on ferroptosis mechanisms have arisen to be applied in clinical trials, as it has been shown by several molecules that can regulate pathways that induce ferroptosis [11], making different cancers vulnerable to ferroptosis-induced cell death, and secondly, it has been observed that ferroptosis-inhibiting molecules could mitigate detriment effects mediated by this type of cell death on oxidative stress-related diseases [174].

By studying the mechanisms associated with the regulation of ferroptosis, the link between ferroptosis and the development and progression of diseases will enhance the appreciation of pathophysiology behind diseases and thus will allow to propose of better biomarkers and therapeutics [171]. A genetic view of the regulation of ferroptosis has been established regarding regulatory miRNAs, molecules that control the expression of genes [175]. MiRNAs have been distinguished as the most studied ncRNAs in terms of regulation of ferroptosis [108]. MiRNAs are small single-stranded non-coding RNA molecules (containing 20-24 nucleotides), first identified in 1993 by the group of Ambros [176]. MiRNAs participate in post-transcriptional regulation of gene expression and translational suppression and their function is through base-pairing binding with 3′-untranslated region (3′-UTRs) complementary sequence within mRNA molecules [109, 177], and they are implicated in cellular processes, including cell proliferation, differentiation, bioenergetics, and was recently found that also contribute to regulation of ferroptosis mechanisms [175].

Primary mechanisms of ferroptosis could be classified as lipid, iron, and antioxidant metabolism [108]. Concerning studies of cancer and ferroptosis-inhibiting miRNAs, MA and colleagues reported that in ovarian cancer, miR-424-5p [89] could be found downregulated, and has a negative correlation with ACSL4, hence they provided a potential therapeutic vision in which ovarian cancer cells with decreased miR-424-5p expression could be especially vulnerable to ferroptosis. Lu and collaborators reported that in hepatocellular carcinoma, there is an aberrant upregulation of miR-23a-3p which targets ACSL4 and proposed that inhibition of miR-23a-3p [81] could significantly improve the responsiveness to treatments of hepatocellular carcinoma.

In attention to non-cancer ischemic diseases, Mao and Liu reported that ACSL4 was increased in acute cerebral infarction (ACI) model of cells promoting ferroptosis and worsening the dysfunction of ACI model cells. They also confirmed that ACSL4 is a downstream target gene of miR-3098-3p [91]. Therefore, they proposed that miR-3098-3p/ACSL4 axis in conjunction with other related-

ncRNAs, specifically circular RNA Carm1, could be a promising therapeutic strategy. ACSL4, a member of the Acyl-CoA synthetase long-chain family, is an important enzyme responsible for fatty acid metabolism [167]. Accumulating evidence has demonstrated that targeting ACSL4 could be a key therapeutic approach for cancer and other diseases [11]. Interestingly, ACSL4 has also been identified as a biomarker, and evidence suggests that induction of ferroptosis targeting ACSL4 may be potential therapeutic strategy. Further, ALOXs are a group of lipoxygenases that initiate the formation of lipid hydroperoxides connecting them to the ferroptosis propagation [2]. Zhang and colleagues provided clinical evidence of ALOX15 closely related to lipid ROS in gastric cancer and demonstrated that miR-522-exosomes [19] inhibit ALOX15 leading to decreased lipid ROS accumulation in cancer cells, revealing a valuable therapeutic approach.

In notion of iron metabolism regulation, there are also examples of candidates for ferroptosis regulation: miR-545 promotes colorectal cancer by inhibiting transferrin, thus blocking miR-545 increases ROS, MDA, and Fe^{2+} [75]. In addition, the receptor of transferrin, TFR, mediates the transfer of iron from the extracellular to the intracellular and is target of miR-214 [92], miR-7-5p [68], and miR-222 [101]. In the first case, Lu found that miR-214 is downregulated in brain ischemia/reperfusion patients and concluded that overexpression of miR-214 [92] could significantly reduce ferroptosis and associated comorbidities of the disease. Zhuang et al. observed that the lack of miR-7-5p [68] expression led to increased levels of transferrin receptor, promoting the uptake of iron and production of ROS, and suggested that inhibiting ferroptosis mediated by ncRNAs that regulate miR-7-5p function could provide a therapeutic possibility to control cardiac injury. Lastly, miR-6862-5p can induce NCOA4 mRNA degradation, leading to diminution of ferritinophagy, hence less iron available to react in Fenton reactions [97]. Together, the aforementioned reports display latest advances in the mechanisms of miRNAs controlling ferroptosis, including the molecules that induce ferroptosis, increasing our knowledge of the mechanisms that could undergo treatment related to ferroptosis for diseases caused by malignant cells and other high comorbidity diseases mentioned.

Oppositely, in accordance with studies reporting miRNAs categorized as inducers/sensitizers of ferroptosis mechanisms, a special mention goes to the abundant literature trying to clarify the molecular pathways implicated in the antioxidant metabolism that counteracts ferroptosis, and it is precisely this pathway that could be used as a therapeutic target in many diseases including cancer, as numerous publications assert. For example, in clinical ovarian and breast cancer samples, Sun and colleagues found downregulation of miR-382-5p but SLC7A11 (involved in cystine entry to cell) expression was upregulated [113]. They proposed a treatment (lidocaine) where repression of tumor growth was accompanied by miR-382-5p upregulation while SLC7A11 expression was decreased. Wu et al. confirmed that SLC7A11 is target of miR-375, miR-409-3P and miR-515-5p in cervical cancer cells. Nonetheless, also revealed the impact of circular RNAs on cell ferroptosis (specifically, circEPSTI1). CircEPSTI1 sponges miR-375, miR-409-3p and miR-515-5p to upregulate SLC7A11 expression attenuating the mechanism of ferroptosis in cervical cancer cells. These results indicated that circEPSTI1, via miR-375/409-3P/515-5p-SLC7A11 axis, may be a treatment target or biomarker in cervical cancer [45].

Concerning cell death as a pathogenesis feature of ischemic disorders, Ding et al. described that miR-182-5p and miR-378a-3p regulated the expression of GPX4 and SLC7A11 negatively and identified that miR-182-5p and miR-378a-3p were upregulated in ferroptosis and ischemia/reperfusion kidney injury [36]. Ferroptosis is characterized by a programmed cell death which can initiate after the inactivation of GPX4 and the system Xc- (Which consists of SLC3A2 and SLC7A11) and following iron-dependent lipid peroxidation [20, 178]. Xu et al. ensured that GPX4 was a target of miR-541-3p in hepatocellular carcinoma cells, but also found that Circ-interleukin-4 receptor (CircIL4R) could directly sponge miR-541-3p, regulating its target GPX4, thus probably inhibiting ferroptosis in hepatocellular carcinoma cells. In fact, CircIL4R was upregulated in hepatocellular carcinoma tissues of patients. They concluded that CircIL4R might be a good target for improving the therapy of this cancer by regulating ferroptosis [131]. Finally, Bazhabayi and colleagues stated that CircGFRA1 promotes the progression of HER-2-positive breast cancer via acting as a sponge of miR-1228 and enhancing AIFM2 expression, a protein like GPX4, involved in the retardation of ferroptotic cell death. They observed that AIFM2 is upregulated by the attenuation of miR-1228 expression caused by CircGFRA1, molecule increased in HER-2-positive breast cancer cells and tissues from patients [116].

Considering cancer as an entity in which malignant cells evade mechanisms of death cell and some cardiovascular diseases as disorders were cell death is overactivated [179], the induction or inhibition of ferroptosis via targeting the system Xc-, GPX4, and more recently exposed, AIFM2, is subject of research and future studies will assess the clinical value of these strategies to improve therapeutics in cancer where ferroptosis is commonly suppressed and diseases were ferroptosis is overactivated [8, 167, 179].

So far, we have discussed the role of miRNAs in different components related to the mechanisms of ferroptosis, however, the growing study of ferroptosis in cancer and other diseases requires a great overview of transcription factors that also play an important role in ferroptosis [15, 16]. Transcription factors function as regulators of gene expression, many of which are linked to ferroptosis [180, 181]. To understand the effect that transcription factors have on ferroptosis, we need to know the genes that control and how they join the signaling pathways of ferroptosis.

Of the significant and increasingly growing list of transcription factors that function as regulators of ferroptosis, NFE2L2 is the most described [181]. The main objective of NFE2L2 is to protect in oxidative stress-conditions, thus, it is observed that NFE2L2 acts on molecules such as SLC7A11 and GPX4 to promote antioxidant products to be able to counteract pro-ferroptotic agents [182]. In addition, NFE2L2 positively regulates proteins related to the metabolism of iron: FPN-1, which supports an iron-efflux, as well as FTL and FTH1, ferritin subunits that induce iron storage [16]. Consequently, NFE2L2 has mainly been related to activities of ferroptosis-inhibition. For this review, we found that miR-138-5p [160] and miR-365a-

3p [138] can induce ferroptosis via NFE2L2. Tang et al. indicated that miR-138-5p [160] is overexpressed under high glucose conditions with consequent downregulation of NFE2L2 accompanied by downregulation of GPX4, inducing ferroptosis in retinal pigment epithelial cells, a model of diabetic retinopathy. Furthermore, Gai et al. studied non-small cell lung cancer and revealed a miR-365a-3p-NFE2L2 interaction resulting in decreased cellular GSH levels and increased lipid ROS, inducing ferroptosis. More studies are needed to understand the promising application of NFE2L2-targeting since NFE2L2 is related to many components of ferroptosis [138].

On the other hand, TP53 has a double role in the regulation of ferroptosis. TP53 can prevent the generation of ROS from the axis NADPH oxidase (NOX)/DPP4, and can promote the expression of CDKN1A, thus increasing GSH levels [16, 169]. Though, TP53 also has a ferroptosis-inducing function by the negative regulation of SLC7A11, and, through the spermidine/spermine N1-acetyltransferase 1 (SAT1)/ALOX axis, the generation of lipid ROS [16, 169]. This becomes a challenge to study the TP53 since TP53 is related to other types of RCD, it also induces and inhibits ferroptosis. More studies are required to assess the conditions that provoke the induction or inhibition of ferroptosis by TP53 activation. Here, we cite that miR-214 [94] and miR-let-7b-5p [73] regulate TP53. Lu et al. reported that miR-214 levels were downregulated in the plasma of patients with acute ischemic stroke and that miR-214 overexpression significantly reduced infarct size and suppressed ferroptosis in the in vivo model of cerebral ischemia/reperfusion [92]. In addition, Dong et al. found miR-let-7b-5p expression-upregulated in patients with acute myeloid leukemia. Moreover, miR-let-7b-5p influences TP53, downregulating its expression and thus, inhibiting ferroptosis [73]. In both cases, miRNAs-TP53 interaction inhibited ferroptosis, however, more studies are needed to evaluate the impact of these findings.

Along with the boost of studies of ferroptosis in cancer, more transcription factors have been recognized as key contributors to ferroptosis [16, 169, 180, 181]. ATF4 is another studied transcription factor that is being given relevance in ferroptosis studies. Like TP53, ATF4 has been shown to have both inducing and inhibitory properties in ferroptosis mechanisms [16]. ATF4 induces SLC1A5 and CHAC1, thus promoting ferroptosis. SLC1A5 is a cell importer of L-glutamine that triggers the generation of a-ketoglutarate that contributes to the accumulation of ROS [15, 16]. Another promoter of ferroptosis is the enzyme CHAC1. CHAC1 participates in the γ-glutamyl cycle and can degrade glutathione [16, 183]. ATF4 is known to increase expression of CHAC1, which can lead to glutathione depletion creating a cellular reduction-oxidation imbalance, thus inducing ferroptosis [183]. Conversely, ATF4 can also upregulate SLC7A11, resulting in inhibition of ferroptosis [16]. the miR-214-3p and the miR-3200-5p, induce ferroptosis through ATF4 in liver cancer cells. Bai et al. recognized that miR-214-3p elevated the ferroptosis-promoting effects of erastin and decreased ATF4 expression in hepatoma cells, and proposed ATF4 as a potential target for hepatoma therapy [43]. Next, Guan et al. found that the promotion of miR-3200-5p inhibits the expression of ATF4. According to them, miR-3200-5p inhibits tumor progression and enhances ferroptosis in hepatocellular carcinoma cells through ATF4 [133]. Future studies will probably reveal advantages of ATF4 as therapeutic target of miRNAs regarding ferroptosis induction in cancer diseases.

To evaluate miRNAs found in this systematic review via informatic analysis, we screened the miRNAs in miRNet. Based on the miRNAs obtained in our systematic review, miRNet established the mRNA-miRNA network, predicting some miRNAs that we did not find in literature according to our methods, and that could be good candidates to be further investigated concerning the regulation of ferroptosis mechanisms. For this occurrence, miR-124-3p, miR-15a-5p, miR-222-3p, miR-9-5p, and miR-18a-3p were proposed. In this context, Wu and colleagues informed that miR-124-3p inhibits ferroptosis to attenuate ischemia-reperfusion injury [184]. They established a model of rat liver transplantation with a severe steatotic donor liver and a model of hypoxia and reoxygenation of steatotic hepatocytes, and they realized that miR-124-3p contained in exosomes inhibit hepatocyte ferroptosis by targeting metalloreductase STEAP3, implying iron metabolism for the ferroptosis inhibition. Additionally, a study using bioinformatics analyses described that miR-124-3p and few more miRNAs could regulate most hub genes related to ferroptosis in preeclampsia [185]. Furthermore, Fan et al. detected that miR-15a-5p was up-regulated in acute myocardial infarction of an animal model and determined that knockdown of miR-15a-5p (which targets GPX4) reduced ferroptosis in myocardial cells in hypoxic conditions [186]. Additionally, Wei et al. demonstrated that increased miR-9-5p alleviates ferroptosis in neurons in sepsis conditions of the proposed in vivo animal model, by suppressing the expression of TFRC and GOT1, providing evidence for the understanding of sepsis-associated encephalopathy [187]. Agreeing with the previously mentioned reports and miRNet results, this information provides us insights of miRNAs that could be suitable aspirants to be further investigated for the understanding of ferroptosis regulation through miRNAs.

5. Conclusions

Ferroptosis has been studied for the past ten years, and it seems to be a promising approach to employ its mechanisms to promote or inhibit cell death depending on the necessity, suggesting that it will be beneficial in new therapeutics. Yet, applications for inhibition or induction of non-apoptotic cell death ferroptosis are still at the beginning of their investigation. MiRNAs and other ncRNAs regulate gene expression and their functions could be applied in ferroptosis. In recent years, abundant information has been generated in miRNAs related to ferroptosis. Here, we summarized the information regarding miRNAs associated with the primary mechanisms regulating ferroptosis and gave concise explanations of the extensive literature published, though more studies are needed to evaluate miRNAs-function in ferroptosis. In conclusion, miRNAs might convert into promising biomarkers for prognosis of ferroptosis-related disorders and probably will have an important role in therapeutics of ferroptosis-associated diseases.

Conflict of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Data Availability Statement

The original contributions presented in the study are included in the Article/Supplementary Material, further inquiries can be directed to the corresponding authors.

Author Contributions

MdCC-P, JMM-S, and JGA-D reviewed articles, collected, and analyzed data, and wrote the manuscript. ANR-R, LGV-C and ALM-P created figures, and tables, and performed the informatic analysis. JAS-G, LFL-S and ALM-P critically analyzed and validated methods and data. GA-H, MdCC-P and JMG-M proposed, and planned the work, and critically reviewed the intellectual content of the manuscript. All authors reviewed the manuscript and approved it for publication.

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