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Review

The multifaceted roles of Zinc in Cancers

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Simple Summary: Zinc is one of the most abundant trace elements in our body. It is very important since it plays a role as a signaling molecule in cell homeostasis and immune system. These functions are essential in cancer. This is the reason why dysregulation of zinc causes a plethora of issues and in particular participates in tumor development. In this review, zinc homeostasis in healthy and cancer cells is described. We also describe zinc-related diagnostic and prognostic markers for cancer. Moreover, therapeutic strategies linked to zinc as a target for cancer are given.

Abstract: Zinc (Zn) is a trace element crucial for oxidative stress, apoptosis, the immune response, and more globally for various processes involved in cellular homeostasis. In some cancers, Zn homeostasis is dysregulated. In this review, the role of Zn in cancer and all the components associated to Zn, the use of Zn and Zn-related proteins as biomarkers and Zn-based strategies for the treatment of tumors will be described. ZIP and ZnT are proteins related to Zn metabolism in normal conditions. In cancer, the level of expression of Zn related proteins is abnormal. These Zn proteins may act as prognostic or diagnostic biomarkers, and may be helpful for detecting early-stage cancers or monitoring the course of the disease. Additionally, Zn and its pathways may also be targeted to treat cancers. Indeed, the use of metals for binding Zn cations allows to regulate the biodistribution of Zn within cells, and will control several downstream signaling pathways. Zinc may also be directly used as a therapeutic substance to improve the prognosis of cancer patients, especially with the supplementation of zinc or the use of Zn oxide nanoparticles.

Keywords: Zinc homeostasis; cancer; therapy; prognostic; diagnostic; nanoparticles; biomarkers

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1. Introduction

Zinc (Zn) is one of the most important trace elements in the same way as iron (Fe) and copper (Cu). Zinc plays a role as a central signaling molecule for cell homeostasis[1,2]. The dysregulation in Zn homeostasis leads to structural abnormalities, or to the loss of essential physiological functions, enabling the development of a variety of diseases, including cardiovascular diseases, cancer, or diabetes[3–7]. It has been clearly demonstrated that Zn homeostasis is disturbed in many cancers[1,7,8]. Moreover, numerous studies showed that the disturbance of trace element homeostasis might be, at the same time, the cause and the consequence of carcinogenesis. Some studies have also revealed that these dysregulations could be of clinical interest as prognostic and/or predictive biomarkers of response to treatments[9–11]. Accordingly, several therapeutic strategies targeting or using trace elements have been designed. Among the immense literature in the field, we present the most significant studies on cell mechanisms relating to Zn homeostasis dysregulation and cancer. This review is also an opportunity to present discordant results obtained in this field. Finally, in this work, we will also review the main therapeutic strategies targeting Zn or using Zn as a central player for cancer treatment.

2. Zinc metabolism in normal conditions

Zinc is an essential and the second-most abundant trace element in humans. In cells, Zn appears in two forms: protein-bound Zn and mobilizable-Zn (not free but bound by unknown non-protein-ligands) **[12]**. The activity of about 300 enzymes and the maintenance of structural integrity of approximately 2,000 transcription factors are Zn-dependent. These transcription factors contain zinc finger domains that coordinate Zn cations to stabilize their structure and folding **[13]**. Thereby, Zn plays a crucial role in a wide range of cellular processes such as oxidative stress, apoptosis, the immune response, etc.…**[14]**. Moreover, Zn is clearly associated with pathophysiological conditions such as growth retardation, hypogonadism, neurosensory and cognitive disorders, cardiovascular disease, diabetes mellitus and cancer **[1,15]**. Among the 2 g of Zn contained in our human body, 99.9% is present inside the cells, while the remaining is found in blood plasma **[16]**. Zinc is present in our organism as a divalent cation that can form tetrahedral complexes. Unlike Cu and Fe **[17,18]**, its absorption does not require oxidation or reduction **[19]**.

2.1 Zinc homeostasis

Zinc homeostasis is definitely based on two Zn transporter families that function in opposite direction to tightly maintain Zn homeostasis. The first family of Zn transporter is composed of 10 members named ZnTs or SLC30, and the second family of Zn transporters is composed of 14 members named Zrt- and Irt-like proteins, also known as ZIPs or SLC39. ZnTs allow the exportation of Zn from cytosol to the extracellular medium or into intracellular compartments whereas the cytosolic Zn concentration is increased by ZIPs (Table 1). ZIP family is divided into 4 subfamilies. Among the 14 human members of ZIP family, nine of them belong to the LIV-1 subfamily **[20]**.

Table 1. The different Zn-binding proteins in human. Inspired from Zhao et al. and Bafaro et al. [1,14].

Protein	Function	Major Tissue distribution	Subcellular localization
ZnT1	Plasma Zn exporter	Ubiquitous	Plasma membrane
ZnT2	Plasma Zn exporter, transport Zn into mammary gland vesicles	Mammary gland, pancreas, prostate, retina, intestine, kidney	Endosome, lysosome, secretory vesicles, plasma membrane
ZnT3	Transport Zn into synaptic vesicles	Brain, pancreas, testis	Synaptic vesicles
ZnT4	Plasma Zn exporter, transport Zn into mammary gland vesicles	Mammary gland, placenta, prostate, kidney, brain	Endosome, secretory vesicle, plasma membrane
ZnT5	Plasma Zn exporter, transport Zn into Golgi	Heart, placenta, prostate, ovary, testis, intestine, thymus, bone	Golgi, vesicles, plasma membrane
ZnT6	Transport Zn into Golgi	Brain, lung, intestine	Golgi, vesicles
ZnT7	Transport Zn into Golgi	Intestine, stomach, pancreas, prostate, placenta, testis, retina, muscle	Golgi, vesicles
ZnT8	Transport Zn into insulin granules	Pancreatic islet, adrenal gland, thyroid, testis	Secretory granules
ZnT9	Plasma Zn exporter, transcriptional regulation in nucleus	Brain, muscle, kidney	Endoplasmic reticulum, nucleus
ZnT10	Cation transporter	Brain, retina, liver	Golgi, plasma membrane
ZIP1	Plasma Zn importer, Zn release from vesicles	Prostate, small intestine, kidney, liver, pancreatic α cells	Plasma membrane, endoplasmic reticulum
ZIP2	Plasma Zn importer	Prostate, uterine, epithelial cells, ovary, liver, skin	Plasma membrane
ZIP3	Plasma Zn importer, Zn release from lysosomes	Testes, pancreatic cells	Plasma membrane, lysosomes
ZIP4	Plasma Zn importer	Small intestine, stomach, colon, cecum, kidney, pancreatic β cells	Plasma membrane
ZIP5	Plasma Zn importer	Liver, kidney, spleen colon, pancreas	Plasma membrane
ZIP6	Plasma Zn importer	Testis, pancreatic β cells	Plasma membrane
ZIP7	Zn release from Golgi and the Nucleus	Brain, liver, pancreatic β cells	Golgi, endoplasmic reticulum, nucleus
ZIP8	Plasma Zn importer at the onset of inflammation	Pancreas, placenta, lung, liver, testis, thymus, red blood cells	Plasma membrane, lysosomes, endosomes
ZIP9	Zn release from Golgi	Prostate	Golgi
ZIP10	Plasma Zn importer	Testis, kidney, breast, pancreatic α cells, red blood cells	Plasma membrane
ZIP11	Cation transport	Mammary gland, testis, stomach, ileum and cecum	Golgi
ZIP12	Cation transport	Neurons, endothelial, smooth muscle and interstitial cells	N.D.
ZIP13	Zn release from Golgi and vesicles	Retinal pigment, epithelial cell line, Osteoblasts	Endoplasmic reticulum, Golgi
ZIP14	Plasma Zn importer	Smooth muscle, pancreas islet, liver, lung, brain, heart, intestine	Plasma membrane, mitochondria, endosome, lysosomes

1. *N.D.: Not determined*

About intracellular Zn sensing, the metal regulatory transcription factor 1 (MTF-1) is zinc dependent. Indeed, that factor needs Zn to regulate expression of its target **[1]**. MTF-1 has 6 Cys_2-His_2 Zn fingers as DNA-binding domains **[21]**. In response to Zn, MTF-1 allows the transcription of several genes and particularly genes encoding for ZnT1 and ZnT2, and metallothioneins **[1,22]**.

Metallothioneins (MTs) have a high affinity for Zn (and for other metals such as Cu, Cd,…) and thus are the major intracellular Zn -binding proteins **[23]**. These small, cysteine-rich proteins can control the storage and release of intracellular Zn **[24]**. Among the total Zn, less than 1% is located in the serum, of which about 80% is bound to serum albumin and 20% to α2-macroglobulin **[25]** (Figure 1).

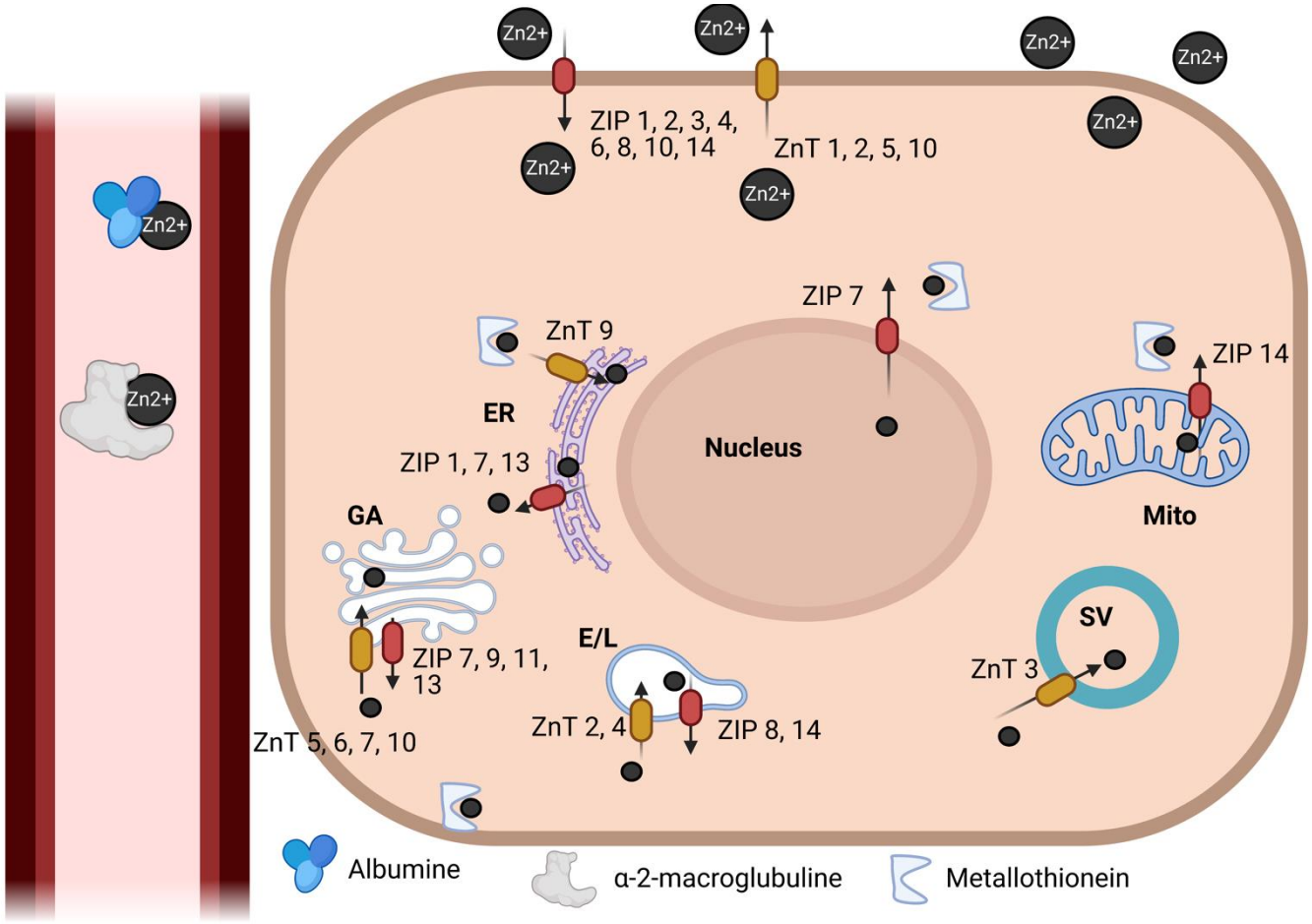

Figure 1: General overview of zinc metabolism. *In the bloodstream, Zn is mainly bound to albumin and α-2-macroglubulin while inside the cell, metallothioneins are the major zinc-binding proteins. The internalisation of Zn inside cells is carried out by ZIPs (in red) and the externalisation of Zn outside compartments is carried out by ZnTs (in orange). Zn^{2+} = Zn ion; ER = Endoplasmic reticulum; GA = Golgi apparatus; Mito = Mitochondria; E/L = Endosome/Lysosome; SV = Synaptic vesicles. Created with Biorender.com*

2.2 Zinc signaling

Zn is a key chemical element for cell signaling, acting both as an extracellular (neurotransmitter) and intracellular (second messenger) signaling molecule [26]. Zinc stimulates serine/threonine protein kinases (MAPK) that

are implicated in cell proliferation, differentiation, and apoptosis. Among MAPK, the extracellular signal-related kinase (ERK) and the c-Jun N-terminal kinase (JNK) are two targets of Zn signaling [1]. Moreover, Zn promotes T-cell proliferation through the MAPK pathway, inhibiting the dephosphorylation of MEK and ERK [27]. Thus, Zn clearly acts as a second messenger, since it is involved in intracellular signaling events [28]. Another signaling pathway instigated by Zn is the STAT pathway, which will promote the expression of genes associated with differentiation, survival, cell proliferation and apoptosis [29].

In lymphocyte T cells, PKC is activated and is bound to the membrane and cytoskeleton upon Zn treatment [30]. However, the chelation of Zn inhibits these mechanisms [31]. Zinc is present in synaptic vesicles and has a role in postsynaptic cells by their activation. Indeed, Zn is released from vesicles *via* exocytosis to bind ligand ion channels [32].

The dysregulation of Zn homeostasis and its consequences are known to promote of series of pathologies, including cancers, which will be discussed in the following part.

3. Altered Zinc metabolism in cancer, and Zinc proteins as cancer biomarkers

There is a general agreement suggesting that Zn may prevent cancer. Indeed in cancers, an important cause of chromosome instability is the attrition of telomere, but high Zn levels reduces the telomere attrition [33]. Moreover, a high level of Zn is correlated with a decrease of micronucleus frequency [34]. Micronuclei are fragment from chromosomes, generally used as biomarkers for chromosome instability [35]. Hence, Zn plays a protective role for DNA integrity and may prevent cancer evolution. Depending on the type and stage of cancers, Zn related proteins are differentially regulated (Table 2).

3.1. Pancreatic cancer

The analysis of the mRNA levels of ZIP and ZnT proteins shows that all ZIP proteins are downregulated in human pancreatic adenocarcinoma compared to normal tissues, with the exception of ZIP4, which is upregulated [36]. ZIP4 has been proven to increase cell proliferation. Through CREB, ZIP4 overexpression causes an increase in the activity of mi-373 promoter. That process leads to the silencing of mi-373 target genes and thus to a subsequent increase in cell proliferation and tumor progression [37]. The tumor progression is also promoted by ZIP4 *via* decreasing the expression of tight junction protein ZO-1 and claudin-1 [38]. Concerning ZnT transporters, gene expression levels are lower or similar in the pancreatic cancer compared to normal tissues [36]. After Zn supplementation, ZnT1 up-regulation is linked with the induction of cytotoxicity in pancreatic cancer cells [39]. This cytotoxicity is defined by ubiquitination of proteins, which is an important mechanism for cell death [40], independent from apoptosis. In pancreatic cancer, ZIP4 is upregulated. Exosomal ZIP4 may be used as diagnostic biomarker. Exosomes are small molecules secreted by cells [41]. This secretion is carried out by normal and pathological cells, including cancer cells. Thereby, exosomal proteins have a huge potential as biomarkers for diagnostic [42]. For exosomal ZIP4 level, a significative difference has been established between samples from patients with malignant pancreatic cancer and patient normal control [43]. Moreover, with the decreased of ZIP3, there is a considerable loss of Zn level in pre-cancerous pancreatic tissues [8].

3.2. Prostate cancer

The human prostate contains the highest level of Zn in our body. In normal prostate, cells are accumulating Zn [44]. The role of Zn in this organ is to block citrate oxidation. The inhibition of this process allows the production of citrate, a constituent of the prostatic fluid [45]. Depending on the study, contradictory results concerning the effect of Zn in prostate cancer can be observed. In fact, the supplementation of Zn seems to increase the risk of advanced prostate cancer [46]. The level of Zn seems to be decreased in prostate cancer, since prostate cancer cells lose their ability to accumulate Zn. Moreover, the inhibition of malignant cells is associated with Zn effects [47]. Zinc has the capacity to induce the arrest of the cell cycle and to trigger the apoptosis [48].

In normal prostate cells, the expression of ZIP1 is notable. In contrast in prostate cancer, Zn is decreased and ZIP1 is downregulated [44,49,50]. Thereby, the cause of low amounts of Zn in cancers seems to induce ZIP1 downregulation. In prostate carcinoma, despite its unknown role, ZIP4 expression is decreased. ZIP4 and ZIP1 may actually behave as tumor suppressors. Before, the evidence about the decrease of ZIP1 and ZIP4 in prostate cancer were showed. The measurement of the ZIP1 and ZIP4 level of expression may serve as biomarkers in early steps in the development of prostate cancer [51,52]. In addition, compared to healthy prostate cells, prostate cancer cells display a diminution of Zn concentration and this decrease continue during the progression of the cancer [53]. Thereby, a monitoring of Zn status in association with PSA screening can be a relevant and more specific approach to diagnostic prostate cancer [54].

MT, the major intracellular Zn-binding protein, is used as marker for tumor in prostate cancer. Indeed, the level of MT in serum from prostate cancer-diagnosed patient is systematically increased [55]. Additionally, MT are markers for head tumors, melanoma and to differentiate malignant and benign tumors [56].

3.3. Breast cancer

Tamoxifen is a treatment for estrogen-receptor (ER) positive breast cancers [57]. With time, a resistance against this drug (TamR) can appear giving rise to cancer cells able to proliferate and metastasize in presence of tamoxifen [58]. Studies have shown that in TamR cells, the level of Zn is higher than in tamoxifen sensitive cells [59,60]. Zinc also induced the inhibition of PTP1B, which is a protein tyrosine phosphatase [61]. PTP1B has a plethora of substrates, including EGFR, insulin receptor, or Src. Thereby, the inhibition of PTP1B through Zn has a significant effect on these signalling pathways, blocking dephosphorylation and thus preventing their inactivation. So, Zn has an effect on cell growth by induction of gene expression [60]. The increase of intracellular Zn is correlated to the increased expression of ZIP7. Indeed, when ZIP-7 is silenced by siRNAs in TamR cells, different signalling pathway such as EGFR and Src are inactivated and cell migration is significantly reduced [59].

LIV-1 is a protein belonging to a subfamily of ZIP Zn transporters named LZT (LIV-1 subfamily of ZIP Zn transporters)[62]. LIV-1 is also involved in breast cancer since it has been reported that LIV-1 is associated with ER positive breast cancer [63]. LIV-1 is also linked with metastatic breast cancer [60]. Thereby, LIV-1 is used as a reliable marker. Indeed, an increase of LIV-1 is described in oestrogen-receptor positive cancers [64]. LIV-1 is correlated with metastatic breast cancer. Thereby, it is a valuable indicator of these types of cancer [65]. As mentioned above ZIP7 is increased in oestrogen-receptor positive breast cancer and participates to the resistance of tamoxifen. ZIP7 is activated by phosphorylation on two serine residues [51]. This activation leads to pathways involved in cancer progression [8]. Therefore, phosphorylated ZIP7 may be a reliable biomarker for this particular cancer.

3.4 Lung cancer

In lung cancer, the role of Zn remains unclear, with variable expression levels of ZIPs and ZnTs in lung cancer cell lines, or in tumors. ZnTs are downregulated while ZIPs are upregulated [66]. In lung tumor tissue, several genes are overexpressed and Zn may prevent lung cancer [67]. Zinc deficiency induced DNA damage and increased APE expression [68], which is an endonuclease playing a crucial role in base-excision repair. Besides causing DNA damage, low intracellular Zn concentrations prevented the DNA binding activity of p53, which is a Zn-binding tumor suppressor [69].

3.5 Hepatocarcinoma

Zinc finger proteins (ZNF) play a role in DNA transcription and replication. One of them, ZN191 has the potential to promote hepatocellular carcinoma proliferation [70]. In hepatocellular cancer, ZIP14 is decreased at the early stage of cancer and persists at late stage [71]. Hence, the quantification of ZIP14 in liver tissues may be a potential indication for the development of this cancer.

Table 2. The role and the location of zinc associated proteins in cancers.

Cancer	Altered player	Regulation	Sample	Prognostic	Ref.
Pancreatic adenocarcinoma	ZIP4	+	Pancreatic tissue		[36–38]
Pancreatic adenocarcinoma	ZIP3	-	Pancreatic tissue		[8,72]
Prostate cancer	ZIP1	-	Prostate		[44,49,50]
Prostate cancer	ZIP2	-	Prostate		[73]
Prostate cancer	ZIP3	-	Prostate	Early event	[8,73]
Prostate cancer	ZIP4	-	Prostate	Early event	[74]
Prostate cancer	MT	+	Prostate		[55]
Oestrogen-receptor positive breast cancer	LIV-1	+	Breast	Poor	[60,64]
Oestrogen-receptor positive breast cancer	ZIP7	+	Breast	Increased growth and invasion	[8,59,63,75]
Breast cancer	ZnT1	-	Rat breast		[76]
Breast cancer	ZIP6	+	Lymph-node metastasis		[77]
Breast cancer	ZIP10	+	Lymph-node metastasis		[78]
Renal cell carcinoma	ZIP10	+	Kidney	Late event, aggressive	[79]
Colon cancer	ZIP10	+	Colon		[8]
Liver cancer	ZIP4	+	Liver		[80]
Liver cancer	ZIP14	-	Liver	Early event	[71]

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4. Zinc as a target for cancer treatment

4.1 Targeting Zinc with metal-binding compounds

The role of metals in cancer has been acknowledged [17,18,81]. Nowadays, metal-binding compounds are explored as potential anticancer agents [82].

Depending on its effect, a metal-binding compound can be classified as a "metal chelator" or a "metal ionophore". The former reduces the availability of a metal by chelating it, while the latter locates in membrane bilayer and enables the diffusion of the metal between both sides of the membrane leading to equilibration of the concentration of the free metal ion. Ionophores are thus transmembrane metal ion transporters [83]. This is possible since the binding between an ionophore and a molecule is reversible. On the contrary, the binding of a metal with a chelator is almost irreversible [84].

Clioquinol (5-chloro-7-iodo-8-hydroxyquinoline) is a Zn^{2+} chelator that acts as an anticancer molecule in prostate cancer. Indeed, ZIP1-deficient malignant cells need Zn to apply its tumor suppressor effect in prostate cancer. Clioquinol is the Zn delivery agent that allows the internalization of Zn inside these cells, therefore also acting as an ionophore. The complex Zn-Clioquinol overcomes the absence of ZIP1 by increasing the cellular level of Zn [85]. Clioquinol inhibits tumor growth in animals [86]. A phase-I clinical trial using clioquinol as a treatment for different hematological malignancies such as leukaemia, lymphoma and myeloma was completed in 2012 and indicated a minimal inhibition of the proteasome [87,88].

Dithiocarbamates are metal-chelating compounds. Disulfiram (DSF), a dithiocarbamate, is used as a treatment of melanoma and hepatic cancer. This treatment is enhanced by Zn supplementation [89] and the activity of the complex DSF-Zn could be explained by the inhibition of the proteasome [82], a key player for the degradation of unfolded or ubiquitinated proteins [90]. The proteasome activity is increased in several cancers [91] suggesting that cancer cells use more the ubiquitin proteasome-pathway than normal cells. Indeed, proteasome inhibition is able to prevent the elimination of pro-apoptotic factors [92]. DSF, in association with copper, is currently tested for multiple myeloma [93].

The N,N,N,N-Tetrakis(2-pyridylmethyl)-ethylenediamine (TPEN) is a Zn chelator and more specifically a membrane permeable Zn chelator [94,95]. It is known to induce apoptosis in several cancer cells [96]. TPEN triggered apoptosis of pancreatic cancer cells [97]. The apoptosis induced by TPEN was associated with the activation of caspase 3 and 8. Additionally, the anti-proliferative effect of TPEN in pancreatic adenocarcinoma cells is time and dose-dependent [98].

4.2 Targeting zinc metabolism proteins

Depending on the type of cancer, up-regulation or down-regulation of selected Zn transporter proteins leads to carcinogenesis or, conversely, slows the progression of tumor cells.

In pancreatic adenocarcinomas, Zn supplementation led to an increase of cytotoxicity and the up-regulation of ZnT1 [39]. ZIP4 is upregulated in pancreatic cancer. The use of RNA interference against ZIP4 induced the inhibition of cell proliferation, migration and invasion in ZIP4-overexpressed pancreatic carcinoma [99].

ZIP1 is decreased in prostate cancer. Transfection of ZIP1 in prostatic cancer cells results in a recovery of Zn uptake and an inhibition of cell growth [47,100]. Moreover, in contrast to pancreatic cancer, the silencing of ZIP4 increased cell proliferation in prostate cancer cells while overexpression of ZIP4 inhibited invasiveness and proliferation [74] .

Since the activation of ZIP7 in estrogen-receptor positive breast cancer is phosphorylation-dependant, targeting that activation may be an interesting therapeutic approach. In addition, protein CK2 induces the activation of ZIP7 [8]. This suggests that CK2 inhibitors may prevent the phosphorylation of ZIP7 and ultimately act as anti-cancer agents.

4.3 Other strategies

The supplementation of Zn may also represent a valuable strategy in some cancer treatment. In pancreatic cancer cells, the addition of Zn (0.01–0.5 mM) increased cytotoxicity in human adenocarcinoma cell lines. Importantly, normal human β-cells were not impacted by the supplementation of Zn [39]. Treatments of human prostate cancer cells with supplementation of Zn led to the decreased expression of intercellular adhesion molecule 1 leading to the reduction of tumor cell adhesion and invasiveness [101]. An oral supplementation of 70 mg of Zn, every day during 16 weeks prevented fatigue and enhanced quality of life for patients treated by chemotherapy with colorectal cancer [102]. Patients undergoing cancer chemotherapy have a poorer quality of life and oral mucositis is a classical complication of cancer chemotherapy [103]. Oral supplementation of Zn was used for patients with oral mucositis. The study showed that Zn reduced both the frequency and the severity of oral mucositis [104]. In rats with early stage breast cancer, the supplementation of Zn nanoparticles inhibited tumor growth [105]. The mechanism of action still needs to be elucidated.

The use of nanoparticles (NPs) is a different therapeutic strategy, emerging as valuable treatments for cancer. Zn oxide nanoparticles (ZnO NPs) are approved by the Food and Drug Administration as safe substances [106]. ZnO NPs are one of the most attractive metal oxide nanoparticles, because of their low toxicity, their cheapness and their good biocompatibility [107]. Therefore, they are used in a wide range of fields including antibacterial, antidiabetic and anticancer treatments [108]. The cytotoxicity of ZnO NPs has been successfully assessed in different cancers such as cervix carcinoma, tongue squamous cell carcinoma, non-small cell lung cancer and urothelial carcinoma, glioblastoma, cervical carcinoma cells [109–112]. In all these cancer cell lines, ZnO NPs triggered cell death, notably apoptosis, while normal fibroblasts were unaffected [112]. In liver cancer, ZnO NPs increased p53 expression [113]. In ovarian cancer, ZnO NPs treatment induced both oxidative and proteotoxic stresses, and finally apoptosis [114].

5. Conclusions

Zinc is a chemical element that plays a crucial role in cancer. Its activity as a second messenger is important in a plethora of cellular pathways, such as cell proliferation, differentiation, and migration. Small disruption in Zn homeostasis may result in the development/aggressiveness of cancers. Despite a few contradictory results, there is a clear association of the dysregulated levels of ZIPs and ZnTs in several cancers. The exact signaling process by which these transporters are involved in oncogenetic processes remain to be elucidated, for each cancer type or even probably at the individual cancer patient level, since there may exist a strong interindividual heterogeneity among Zn protein expression levels. The status of Zn and its associated proteins can serve as biomarkers for the detection and the diagnosis of cancer at early stages or to evaluate the outcomes of a cancer (prognostic marker). Moreover, specific alterations of Zn metabolism in cancer may represent valuable targets for therapy. Effectively, the down-regulation or the overexpression of Zn-associated proteins have already been used as rationales for developing innovative therapeutic strategies. Some compounds with high affinity with Zn are potential treatments for some cancer but for now, little clinical trials have been conducted. Zinc is also used as another way to

treat cancers. Indeed, the field of therapeutic nanoparticles is emerging and lots of studies using ZnO NPs are currently being released. ZnO NPs are efficient and show a selective toxicity against cancer cells. In the future, Zn and its metabolism will undoubtedly continue to play an important role both for cancer diagnosis and therapeutic strategies.

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