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Zinc as a modulator of transglutaminase activity – Laboratory and pathophysiological aspects

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ABSTRACT

For a whole century, citrate has been used as an *in vitro* anticoagulant via chelation of calcium. Later, also EDTA was introduced as an anticoagulant. An often overlooked fact is that zinc is bound to citrate and EDTA with affinities much greater than that for calcium, imposing problems in biomedical research. *In vivo*, proteins of the S100 family are released from leukocytes and known to bind calcium. Some of them, e.g., calprotectin, also chelate zinc. Thus, at an inflamed site, the ratio between Ca^{2+} and Zn^{2+} is changed. This mechanism is of importance for the modulation of the activation of a fascinating family of post-translationally acting calcium-dependent thiol enzymes, the transglutaminases, which are inhibited by zinc. This presentation illustrates the complexity of *in vitro* studies with zinc. Moreover, it exemplifies the role of Zn^{2+} in pathophysiological situations such as celiac disease and neurodegeneration.

1. Introduction

Citrate additive to blood tubes was introduced to bind calcium and thereby prevent blood coagulation [1]. The method represents a milestone in medicine history and is applied globally. However, an often overlooked effect shadows the success since citrate also binds zinc ions. After a century, this drawback still has consequences for biomedical research in enzymology. With this background, we want to highlight the complexity of *in vitro* studies with zinc but also illustrate how this trace metal physiologically modulates the activation of transglutaminases (TGs), a post-translationally acting family of thiol enzymes with multifaceted properties.

2. Zinc in the human body

After iron, zinc is the most abundant transition metal in man and is found in body fluids and in the nuclei, cytoplasm and membrane of all cells in the body. About 90% of the total 2–3 g are found in the skin, skeletal and muscles, while the highest concentrations have been reported in the prostate gland [2], retina [3], and the insulin-producing β-cells [4]. Zinc is bound to numerous proteins with varying affinities [5]. The serum concentration of zinc is normally 11–18 μmol/L [6].

The zinc homeostasis is controlled by metallothioneins and specific zinc transporters (ZIP and ZnT) [7]. The biological role of zinc can be divided into structural, catalytic and regulatory functions. The physiological significance of zinc is reflected by the symptoms of zinc deficiency. The first cases were described in the 1960s with hypogonadism and poor height growth due to one-sided low-zinc diet [8]. Simultaneous intake of other foods, especially salts of phytic acid which bind zinc in the intestine, can also reduce zinc absorption [9]. Other causes of zinc malabsorption may be damaged intestinal mucosa, e.g., in untreated celiac disease. Later, the importance of zinc for the immune system has been elucidated [10].

2.1. Biochemical aspects

The affinity of chelators such as citrate and EDTA is significantly greater for Zn^{2+} than for Ca^{2+} [11]. In practice, this means that the concentration of free Zn^{2+} never can be restored in blood that has been anticoagulated with these agents. In laboratory experiments, addition of EDTA to labile, calcium-dependent thiol enzymes is common to prevent accidental activation. Moreover, dithiothreitol (DTT) is used to protect against oxidation. Interestingly, DTT also binds Zn^{2+} with high affinity [12]. Remarkably, *in vitro* studies on zinc with these additives are still common.

The concentration of active Zn^{2+} (free or transiently protein-bound with low affinity) varies highly. The S100 family is a unique class of

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Abbreviation list

Ca	calcium
CP	calprotectin
DTT	dithiothreitol
EDTA	ethylenediaminetetraacetic acid
FXIII	factor XIII
PAD	peptidylarginine deiminase
TG	transglutaminase
TG2	transglutaminase type 2
Zn	zinc

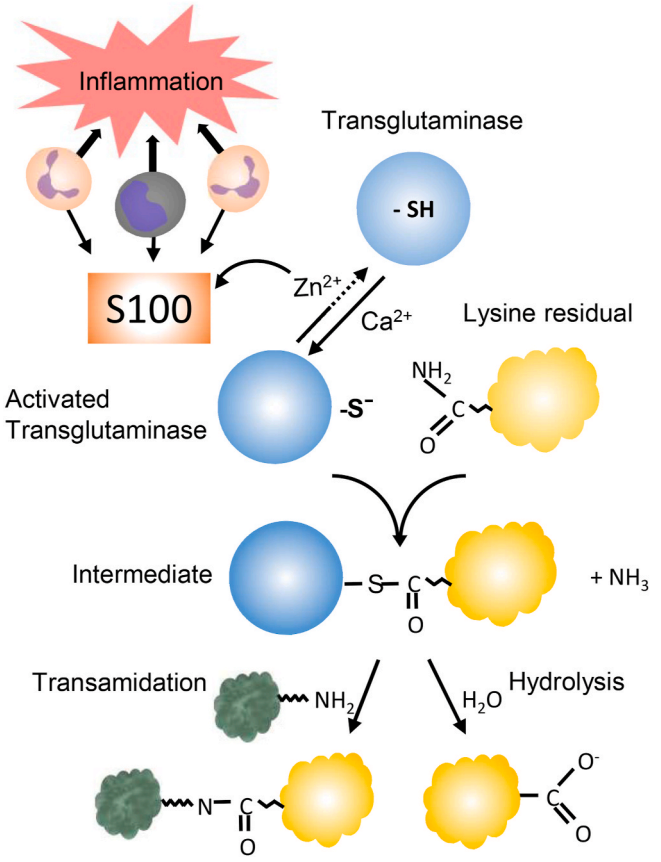

Fig. 1. Zinc-modulated activation of transglutaminase. Leukocytes at a site of inflammation release S100-proteins which sequester Zn^{2+}, thus facilitating the calcium-dependent activation of the enzyme. The intermediary thioester formed between the enzyme and a glutamine residue is then attacked by a primary amine, resulting in a transamidation. In the absence of an amine, water acts as the nucleophile, resulting in hydrolysis of the glutamine residue. In the transamidation, the formation of the thioester is rate limiting. In hydrolysis, the last step is rate limiting. Since the intermediate is essential for the reactions, both transamidation and hydrolysis (deamidation) are inhibited by zinc.

cell- and tissue-specific proteins which have been associated with calcium binding [13]. However, of the 25 human members of the S100, at least 10 also chelate zinc, with affinities that greatly exceed the binding for calcium [14]. The most well-known example is the heterodimer calprotectin (CP; S100A8/A9). CP is released from neutrophils and monocytes/macrophages [15]. Interestingly, Ca^{2+} increases the affinity between CP and Zn^{2+} [14]. Therefore, the concentration of active Zn^{2+} is reduced in inflammation. With respect to the binding of Zn^{2+}, CP may physiologically be said to correspond to the *in vitro* properties of citrate, EDTA, and DTT.

About 300 enzymes are zinc-dependent [5]. In addition, zinc can inhibit the activation of at least two fascinating families of enzymes, namely the TGs and the citrullinating peptidylarginine deiminases (PADs). These are post-translationally acting, calcium-dependent thiol enzymes considered to have pathophysiological effects in major autoimmune diseases [16]. At a site of inflammation, an altered ratio of Ca^{2+}/Zn^{2+} orchestrated by S100, can explain the modulation of enzyme activity.

2.2. Transglutaminases

The human TG family comprises eight thiol enzymes including coagulation factor XIII (FXIII) and a protein called band 4.2 [17]. The enzymes are present both intracellularly and extracellularly in the body. The eight enzymes have the same sequence of amino acids around the active center; the cysteine residue (GQCWV).

TGs catalyze the formation of proteolytically stable intermolecular ε-(γ-glutamyl)lysine pseudo-peptides between specific protein-bound lysine and glutamine residues [18,19]. The process is called transamidation and takes place in several steps. Ammonia is released upon formation of a thioester intermediate. In the absence of an amine group, water can serve as the second substrate, thereby hydrolyzing glutamine residues to glutamate (Fig. 1). In transamidation, the formation of the thioester is rate limiting [20]. In hydrolysis, on the other hand, the last step limits the rate [21].

The discovery that Zn^{2+} inhibits TGs was made in the mid-1970s with a fluorescent technique that enables continuous measurement of transamidase activity [20]. Initially, the effect of metal ions was studied on thrombin-activated plasma FXIII. When Zn^{2+} did not activate the process, Ca^{2+} was added as a control, but still without effect. The finding initiated a detailed study that showed that zinc concentrations within the physiological range reversibly and competitively inhibited the calcium activation of thrombin-activated FXIII [22]. Moreover, Zn^{2+} prevented the Ca^{2+} -dependent alkylation of the catalytically essential cysteine sulfhydryl group of the enzyme with ^{14}C-iodoacetamide [22,23]. Zinc also inhibited transamidation and deamidation, catalyzed by TG [22,24].

2.3. Factor XIII

FXIII is the only thiol enzyme among the classical coagulation factors. FXIII stabilizes the fibrin network during bleeding by catalyzing the formation of polymers between γ or α fibrin monomers [25]. The zymogen is a heterodimer, A_2B_2. The A-chain is formed in the bone marrow and the B-chain in the liver. Upon activation, thrombin cleaves a peptide in the A chain. Ca^{2+} has a dual function, partly when the A- and B-chains are separated and then when the A-chain changes in conformation, thereby exposing the active center, the cysteine residue [23]. Zn^{2+} inhibits the latter step competitively and reversibly [22].

Hereditary deficiency of FXIII is very rare and can lead to severe bleeding, defective wound healing and pregnancy complications [26]. Moreover, acquired deficiency has been reported during inflammatory conditions [27,28]. *In vitro*, citrullination of cellular FXIII (A_2) gradually reduces the transamidating activity. Interestingly, citrullinated FXIII is an antigen to serum from rheumatoid arthritis (RA) patients [29], adding FXIII to the numerous lists of potential agents involved in the pathogenesis of RA.

2.4. Transglutaminase type 2 (TG2)

Upon Ca^{2+}-induced activation of TG2 *in vitro*, the protein opens, exposing the cysteine group of the active center. Zn^{2+} inhibits this activation [22]. *In vivo* experiments on experimental animals show that TG2 is not active under normal physiological conditions despite the presence of Ca^{2+}. However, the enzyme is activated after chemical or

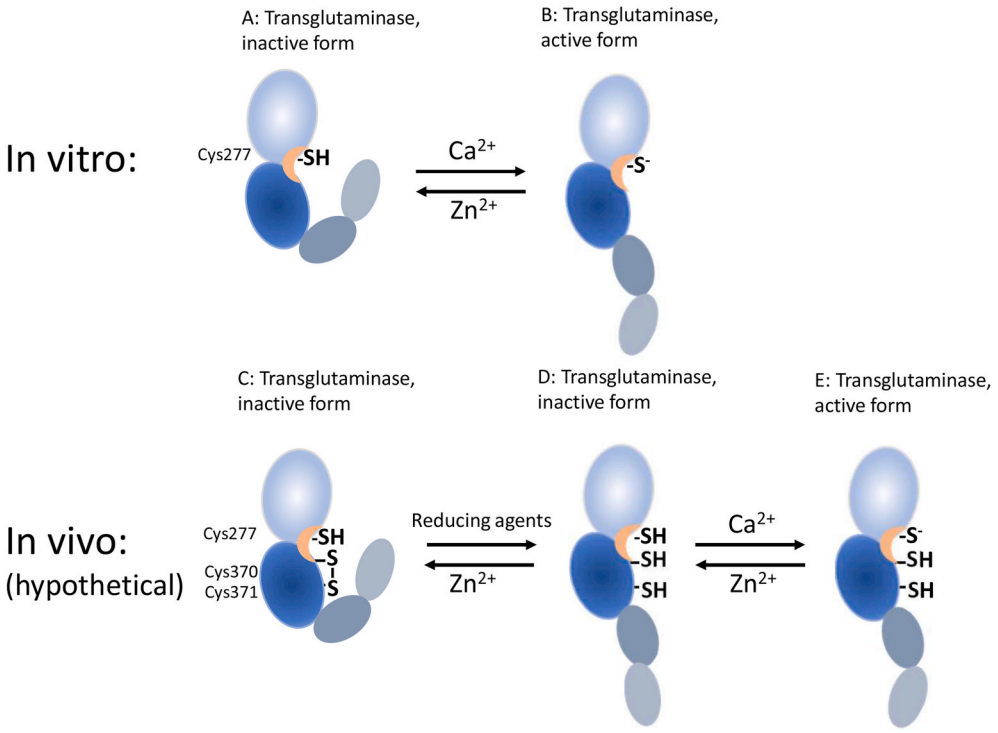

Fig. 2. The proposed involvement of zinc in the activation of TG2. In vitro, Zn^{2+} competes with the binding of Ca^{2+} and the exposition of the active site cysteine thiol is blocked. In vivo a disulfide formed between two vicinal cysteine residues might inhibit the activation. When this disulfide is reduced, the enzyme is activated. Normal levels of Zn^{2+} prevents this reaction by binding to the thiol group of the reducing agent. When the concentration of active Zn^{2+} is reduced due to the release of S100-proteins such as calprotectin, the activation of TG2 can be completed.

physical induction of tissue damage [30]. The reduction by thioredoxin and glutathione of an abrogating disulfide between two vicinal cysteine residues outside the active center may contribute to the activation of TG2 [31] (Fig. 2). Since Zn^{2+} is a stable ion, it does not participate directly in redox processes. Nevertheless, Zn^{2+} binds to thiols such as glutathione with high affinity [32].

TG2 are considered to be associated with a number of physiological functions, including apoptosis and receptor-mediated endocytosis, but has been particularly noted for its role in pathological contexts such as celiac disease and neurodegenerative diseases [17,19].

2.5. Transglutaminase type 2 and celiac disease

In celiac disease, antibodies are developed against both deamidated gluten peptides and TG2, the latter constituting the antigen to the histologically detected endomysial antibodies [33]. The affinity between TG2 and serum from subjects with celiac disease increases several folds when calcium is present [34,35], i.e., when the enzyme is activated. Zn^{2+} in low concentrations neutralizes this effect [34]. Celiac antibodies do not affect TG2 activity [34], which strengthens the hypothesis that the active center of the enzyme is masked to a thioester in the intermediate. These data have led to the hypothesis that the neoantigen consists of a Michaelis-Menten complex, in this case a thioester formed between the active thiol group of TG2 and a glutamine residue of partially deamidated gliadin (Fig. 3). This hypothesis has generated new ideas about the development of autoimmunity [34,36].

The pathogenesis of dermatitis herpetiformis (skin celiac disease) is considered to be similar to that of celiac disease. The major difference is that the isoenzyme is epidermal TG type 3 (TG3) [37].

The established treatment for celiac disease is a gluten-free diet. *In vitro*, zinc chloride and ascorbic palmitate, a dietary supplement that has some structural homology to α2-gliadin, have been shown to attenuate TG2 activity. This combination has been suggested to produce celiac-safe products [24].

2.6. Transglutaminase in neurodegenerative diseases

A common feature of several neurodegenerative diseases is the formation of stable, sparingly soluble protein aggregates. TG-catalyzed effects on proteins in the central nervous system (CNS) are therefore an exciting field of research with many perspectives on Alzheimer's, Parkinson's and Huntington's diseases and also on amyotrophic lateral sclerosis (ALS). Amyloid-β, hyperphosphorylated tau and α-synuclein are *in vitro* substrates for TGs [38]. A special case is Huntington's disease where the mutated gene leads to sequences of extra glutamine residues that may form substrates for TG [39]. Homeostasis for zinc is particularly complex in the brain [40], which may lead to a disturbed balance between Ca^{2+} and Zn^{2+}, and explain a harmful activation of TG in inflamed parts of the CNS.

3. Conclusions

In vitro, citrate is routinely used to bind calcium ions and thus prevent blood clotting. An often overlooked aspect is that citrate, like EDTA and dithiothreitol (DTT), also chelate zinc. Therefore, laboratory studies with Zn^{2+} require major consideration of good laboratory practice.

S100 is a family of proteins known to chelate calcium. Of the 25 members, 10 of them including CP, also bind zinc. During inflammation, CP is released from neutrophils and monocytes/macrophages. With respect to the binding of Zn^{2+}, CP has physiologically similar properties as citrate, EDTA, and DTT have in *vitro*. Therefore, the concentration of reactive Zn^{2+} is reduced at a site of inflammation.

Competitively, Zn^{2+} inhibits the calcium-dependent activation of TGs. Thus, the activation of TGs is facilitated during inflammation, supporting their physiological functions. Occasionally, this activation might induce pathophysiological reactions as illustrated by celiac disease and possibly also neurodegenerative illnesses.

The current presentation illustrates the complexity of *in vitro* studies with zinc, and how zinc binding additives may influence the catalytic processes of several thiol enzymes. Awareness of these processes are necessary in the evaluation of the laboratory findings concerning zinc-dependent processes.

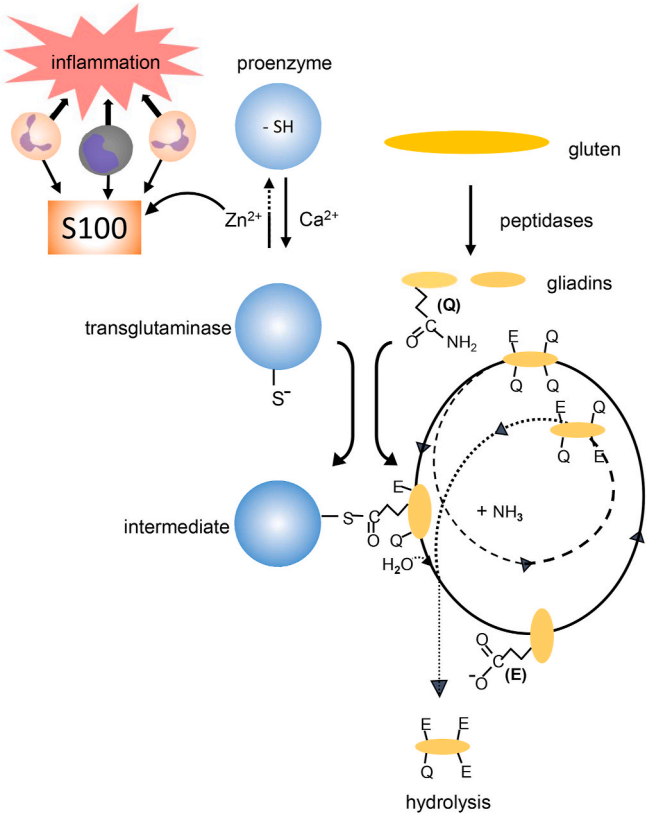

Fig. 3. Postulated initiation of celiac disease. S100-proteins released from inflammatory cells chelate Zn^{2+}, facilitating the calcium-dependent activation of transglutaminase type 2 (TG2). In a given order, specific glutamine residues (Q) in dietary gluten are deamidated (hydrolyzed) via TG2-catalysis, forming negatively charged glutamate residues (E). During the repeated process, a thioester intermediate is formed between the active site of the enzyme and a glutamine residue of a partly deamidated gliadin peptide. Since this complex is rather long-lived, it can function as an antigen resulting in the formation of antibodies against both deamidated gliadins and against TG2.

Credit author statement

Conceptualization, P.S.; Data curation, P.S.; Formal analysis, P.S.; Funding acquisition, B.O.; Investigation; P.S., Methodology, P.S.; Project administration; B.O.; Resources; not applicable; Software, not applicable; Supervision, B.O.; Validation, P.S.; Visualization, B.R.; Roles/Writing - original draft, P.S.; Writing - review & Editing, B.R., B.O. All authors revised the manuscript critically and approved the final version for submission.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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