

TRANSGLUTAMINASES : A MEETING POINT FOR WHEAT ALLERGY, CELIAC DISEASE, AND FOOD SAFETY

H. Malandain (1)

SUMMARY: Wheat is the staple cereal in many countries and its uses in manufactured foods are ever growing due to the technological qualities of gluten proteins. Transglutaminases (TG) are ubiquitous enzymes with many functions. They are able to transform proteins by deamidation and/or transamidation. This last reaction can cross-link proteins together. Intestinal tissue TG has been shown to play an important role in two kinds of immune reactions to wheat: celiac disease and wheat-dependent exercise-induced anaphylaxis. In addition, new epitopes have been suspected in cases of anaphylaxis to wheat isolates, a food ingredient consisting mainly of deamidated gluten proteins. As a microbial TG is included in many food technological processes, its safe use should be checked. This assessment must cover not only the safety of the TG itself but also that of the deamidated/cross-linked proteins generated by this enzyme. This article aims at discussing the possible consequences of using TG in food industry in the light of today knowledge about immune reactions to wheat.

Key-words: Transglutaminase - Food technology - Celiac disease - Wheat allergy - Wheat isolates.

Wheat is one of the most consumed cereal in the world (1). An ever growing list of foods contain wheat or wheat-derived products. Among wheat components, gluten is especially valuable for its physico-chemical qualities. In addition to giving bread its characteristic structure, gluten is used in many ways by food industry, as such or as transformed products (hydrolyzed, deamidated, ...).

Wheat is responsible for a wide variety of immunological reactions (2). Inhalation of wheat flour can lead to baker's asthma. Wheat allergy is rather common in infants and children, especially those suffering from atopic dermatitis. Rare but serious reactions are seen in cases of wheat-dependent exercise-induced anaphylaxis (WDEIA). In addition to these IgE-mediated reactions, wheat is also the cause of celiac disease (CD), an auto-immune state triggered in susceptible individuals by the ingestion of gluten-containing foods. Symptoms are sometimes restricted to abdominal complaints, not related to CD but to wheat allergy, even in adults.

Transglutaminases (TG) are ubiquitous enzymes with many physiological actions (3). A tissue transglutaminase (tTG), located in intestinal mucosa, has been recently shown to play a central role in WDEIA and in

CD (4, 5). Transglutaminases are able to transform protein: the resulting deamidated and/or cross-linked proteins are key components in these diseases (4, 6).

Food technologists are interested in using the properties of TG. A microbial brand of TG (mTG) is already on the marketplace for several purposes (7). For example, mTG can stick small pieces of meat or of seafood into classical servings, such as steaks or filets.

To cope with consumers' pressure, regulations have been introduced to strengthen the safety assessment of new foods and/or new ingredients. A model of this assessment is the FAO/WHO protocol designed to check the safety of genetically engineered food products (8). This protocol was recently applied to a commercial mTG (9). The authors of this work concluded that mTG entails no particular risk to consumer's health.

That mTG was itself safe does not infer that this enzyme is without any effect on wheat immunogenicity. One could suspect that mTG, once added to food, would induce new digestion-stable epitopes by transforming the proteins contained in the processed food. This paper aims at discussing the possible consequences of using mTG in food industry in the light of today knowledge about immune reactions to wheat proteins.

(1) Laboratoire de Biochimie - Centre Hospitalier Chubert - 56000 Vannes (France) - henri.malandain@ch-bretagne-atlantique.fr

WHEAT PROTEINS

Milling separates wheat endosperm from other components of wheat grain (embryo, bran and aleurone layer). Most food uses of wheat are based on the flour obtained from the endosperm. In addition to starch, wheat flour contains a wide array of proteins (10): soluble albumins/globulins (enzymes, defence proteins,...) and seed storage proteins. In wheat, the storage proteins correspond to gluten and are made of prolamins. Prolamins differ from storage proteins found in dicotyledones by many aspects, for example their high content in proline and glutamine residues. Prolamins are also responsible for some distinctive features of immune reactions to wheat.

Prolamins are highly diverse. Two-dimensional immunoblots reveal no less than 50 different spots. In addition to this diversity several factors explain why published data about IgE-reactive proteins in wheat are often discrepant: a wide range of molecular weights (10-100 kDa) depending on the experimental conditions chosen (eg. analysis after cooking or not, rupture of disulfide bonds upon reduction, ..), a diversity resulting from patients' individual sensitizations (allergy with/without exercise, effect of age, mode of contact), etc.

Prolamins belong to a superfamily of proteins deriving from a common ancestor (11): some of these proteins kept a characteristic cysteine-rich motif, while other proteins acquired a proline/glutamine-rich domain (Figure 1).

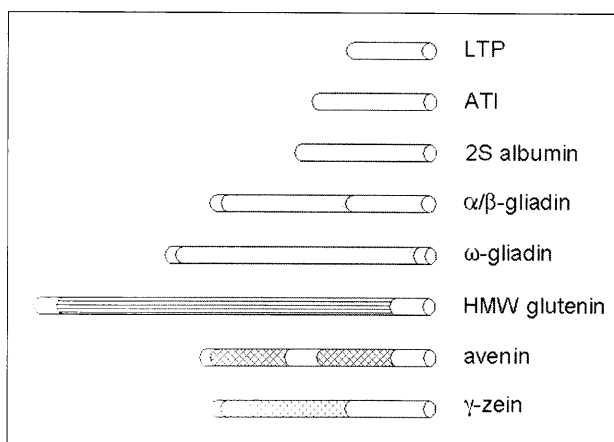


Figure 1: Schematic view of some types of proteins belonging to the prolamin superfamily.

Non-repetitive domains form the basis of the superfamily (in white). Repetitive domains contain repeated blocks of amino acids. These domains are characteristic of prolamins (gliadins, glutenins, avenins, zeins, ...). Some homology is present between gliadins, but repetitive domains of HMW glutenins, avenins and zeins are all different.

(LTP = lipid transfer proteins, ATI = amylase/trypsin inhibitors).

This last domain gives gluten its visco-elasticity, a valuable feature for numerous wheat-based food products. More or less identical sequences of amino-acids are found along this domain. These repeated motifs explain protein extensibility (1). Among wheat prolamins, HMW glutenins are central to this property: their repetitive domain is very long and their free cysteines in the nonrepetitive parts of the molecule can act as an anchor for binding other prolamins during dough processing.

Repeated sequences of amino-acids, although not strictly identical, share enough homology to give rise to cross-reactivity between wheat and similar proteins in barley or rye flours. Cross-reactivity also occurs between the non-repetitive domains of prolamins. Omega gliadins are especially poor in non-repetitive domains and rich in proline (up to 70%). This feature seems related to their particular immunogenicity.

Some repeated sequences are immunodominant: in celiac disease, for example, a PQPQxPx motif shows strong affinity for HLA-DQ2 molecules (P = proline, Q = glutamine, x = various amino-acids) (12).

Wheat proteins are diversely sensitive to digestive enzymes: whereas soluble albumins/globulins are quickly broken down upon gastric digestion, gluten proteins do not disappear before being attacked by pancreatic enzymes (13). Some parts of prolamin molecules are even completely resistant to digestion. For example, an undigested 33-mer peptide plays an important part in the immunogenicity of gluten in celiac disease (14).

Such a resistance is explained by an unusual content in proline residues.

Data obtained with wheat extracts do not reproduce the conditions of a real digestive process: some more stability to digestion is expected when the same proteins are mixed in a complex matrix like a meal (15). Furthermore, prolamins are thermally stable and cooking favours the formation of aggregates and/or adducts (eg. Maillard products). And these modified proteins are less digestible (16).

PROTEINS IN OTHER CEREALS

Prolamins in other Triticeae, such as barley and rye, are very similar to wheat prolamins (1). In rice and in oats, most storage proteins consist of 11S-globulins instead of prolamins. Furthermore, oats prolamins (avenins) have a twice lower proline content. And

repeated motifs are absent in rice prolamins. Corn, millet and sorghum are also different. In corn, main storage proteins consist of alpha-zeins, whose structure do not resemble classic prolamins.

TRANSGLUTAMINASES

Transglutaminases, or protein-glutamine gamma-glutamyl transferases (EC 2.3.2.13), are rather ubiquitous enzymes (3). They have been described in most living species. In vertebrates, tissue transglutaminases (tTG) are found in many different locations: intestines, muscles, central nervous system...

Transglutaminases (TG) take part in many physiological processes such as hemostasis (factor XIIIa), keratinocyte maturation, TGF-beta Activation... These enzymes are also involved in case of stress, cell damage, inflammation, or apoptosis.

TG enzymatic activity on proteins leads to two different kind of products:

- firstly, TG can convert a glutamine residue into a glutamic acid. This deamidation tends to enhance the water solubility of the protein. A particular sequence of amino acids around the glutamine is mandatory.
- if suitable amino groups are available in the reaction environment, TG performs a second enzymatic step: it consists in linking an amino group to a newly obtained glutamic acid. Such amino groups can be small molecules (eg. histamine, cadaverine,...) as well as epsilon-amines of lysine residues in proteins. This reaction of transamidation can thus cross-link two proteins, and eventually lead to a complex matrix of proteins bound together. The isopeptide bond resulting from this transamidation reaction is highly stable and resists to most proteases thus limiting any complete digestion of cross-linked proteins.

When substrates suitable for cross-linking are poorly available, TG end-products are mainly deamidated proteins. For example, gliadins are quite deficient in lysine and TG has been used to prepare deamidated soluble proteins from gluten (eg. wheat isolates).

Food industry is interested in TG as a technical aid. A microbial TG (mTG) is currently marketed to this end (7). This mTG is obtained from *Streptomyces mobaraensis*. And a bio-engineered TG is in the pipeline (17). Substrates for mTG are rather diverse: soybean glycinins, gluten, whey proteins, caseins, egg proteins (eg. ovomucin ...), muscle proteins (actin, myosin...).

End-products of mTG-driven reactions are more or less simple, depending on variables such as the presence or not of a heating step (TG enzymatic activity is destroyed at 70°C or higher), and the time elapsed before this heating is applied to the food. When TG is used to stick food items together or to tightly hold some components into a food, cross-linked proteins are expected to result from such a process.

Modifications of proteins in the final food will thus vary with the ingredients and the recipe, but most probably will favour the formation of new protein species and sometimes of new potential epitopes.

In addition to applications in cosmetic and textile industries and as a biomaterial cross-linker (18), a steadily growing number of technical uses of mTG is observed in food industry (19). For example, mTG is currently used in order to:

- enhance firmness by improving protein network : eg. bread, pasta, noodle, tofu, surimi... (20);
- improve texture and/or shelflife by holding water in the food product : eg. sausages, tortillas, low fat cheese...;
- incorporate ingredients to improve sensory qualities (eg. baked goods, fruit concentrates...) (21), or to recycle otherwise wasted products (eg. whey proteins entrapped into cheese) (22);
- protect proteins towards heating-induced negative effects (23);
- produce edible films or coatings (eg. from soybean, caseins, deamidated gluten) (24);
- stabilize gelified or emulsified goods : eg. yoghurt, dressings, ice cream; (25);
- restructure second-hand pieces of meat, fish or shellfish into larger and/or more attractive items (26): steaks, ham, fish filets, bigger scallops, shrimps...

Altogether, a maximum daily intake of mTG could range up to 15 mg. Dosing for restructuring is about 50-100 mg mTG for each kg of treated food.

IMMUNE REACTIONS TO WHEAT PROTEINS (2)

Inhalation of cereal flour can lead to baker's asthma. In this occupational disease, allergens are mainly water soluble proteins : amylase/trypsin inhibitors (ATI), several enzymes found in the flour itself (peroxidase, triose-P isomerase, ..) and/or in baking additives (amylases, xylanases, ..). A weak IgE-reactivity can be also found towards prolamins (13), a result which could come from some cross-reactivity between ATI and non-repetitive domains of gliadins. Most patients with baker's asthma can eat the cereal

to which they react at work. Clearly, sensitization to flour through the intestinal tract is a separate entity, this being at least partly due to the modifications that cooking and digestion induce to the structure of proteins.

Reactions to wheat as a food encompass a wide array of clinical situations. These reactions can shortly follow the ingestion of the food, a phenomenon favouring an IgE-mediated mechanism, or can be expressed after a lag time or through a chronic disease. Diagnosing cereal hypersensitivity is thus often challenging.

Studying which proteins are involved in these different diseases is even more difficult because, in addition to clinical diversity, cereal proteins are complex mixtures and because cereals are cooked in numerous different ways.

No characteristic pattern of IgE-reactivity is observed in **food allergy to wheat** (13, 27-29). In its classical expression, wheat allergy is mainly responsible for cutaneous symptoms: eg. atopic dermatitis in infants/children, urticaria in adults. Most children ultimately outgrow their wheat allergy. Sensitization to albumins/globulins is frequently found in children and tends to fade out in adulthood. And reactivity to the repeated motifs of prolamins follows an opposite evolution (30).

When patients allergic to wheat are grouped, some trend can be deduced regarding the spectrum of IgE-reactive prolamins: subjects react more frequently to alpha/beta-gliadins and to LMW glutenins (around 60%) than to gamma-gliadins (45%) or to HMW glutenins (25%). A relation between a sensitization to epitopes lying in repetitive domains and the chronicity/severity of allergy to wheat has been assumed on the grounds of the uneven reactivity to omega-gliadins: children with atopic dermatitis are less often sensitized to these gliadins than adults reacting to the combination of wheat and exercise (30).

In a sizable proportion of patients with food allergy to wheat, symptoms are limited to the gastro-intestinal tract. These local reactions might result from undigested, unabsorbed high molecular aggregates as those favoured by cooking (16). In addition, non-IgE-dependent mechanisms are suspected in some 20-30% cases of hypersensitivity to wheat.

The importance of omega-5 gliadin, also known as Tri a 19 in IUIS nomenclature (31), has been stressed by Palosuo's team (4). This particular kind of gliadin, which includes a large repetitive domain (see Fig. 1),

is a major trigger for the reactions seen in **wheat-dependent exercise-induced anaphylaxis** (WDEIA). Wheat is the most frequent culprit in reports of food-dependent exercise-induced anaphylaxis. Major epitopes in omega-5 gliadin follow a characteristic pattern of glutamines and prolines (QQxPxQQ) (30, 32). Because WDEIA patients do not react to wheat in the absence of exercise, some additional factors must complete the silent sensitization of these patients so as to induce a reaction as severe as anaphylaxis is. Exercise itself could enhance the transfer of undigested proteins/peptides through the intestinal epithelium (33). Adjuvants such as aspirin or ethanol seem capable of amplifying the effects of exercise (34, 35). But strenuous exercise is known to stimulate some stress-related mechanisms, for example an increased secretion of intestinal tTG (36). Furthermore, tTG cross-links peptides deriving from omega-5 gliadins and the resulting aggregates show strong IgE-reactivity in WDEIA patients (37).

Modifications to wheat proteins are also suspected in **anaphylaxis to wheat** isolates (38): some of the patients reacting to these isolates are also allergic to plain wheat but other ones react only to wheat isolates. This lends support to the formation of new epitopes during the manufacturing of wheat isolates. Such new epitopes could result from new protein conformations adopted by deamidated prolamins.

A similar mechanism is to be expected with isolates obtained from other ingredients (eg. soybean).

Finally, the central role of TG in some reactions to wheat is demonstrated by the recent data recorded about the molecular mechanisms involved in **celiac disease** (39). This non-IgE-dependent auto-immune disease afflicts a substantial part of population as its incidence is estimated of 0.2-1.0% in Europe (40, 41). Even if it necessitates also a genetic predisposition (HLA-DQ2, sometimes HLA-DQ8), the modification of wheat prolamins by intestinal TG appears mandatory to lead to a clinical reaction (42). Auto-antibodies show an especially high affinity for deamidated peptides (43). As the tTG enzymatic reaction includes a step during which a covalent bond is created between tTG and its substrate (eg. a gliadin), some auto-antibodies are also directed towards tTG. And these anti-tTG antibodies are acknowledged as specific markers of CD.

Whatever the initial event in gluten-induced mucosal damage in CD, tTG is overexpressed in active disease (44) and tTG seems able to polarize T cells towards a Th1 response by scavenging local histamine into prolamine-histamine cross-links (45).

The central role of tTG in celiac disease is demonstrated by the extreme rarity of reactions to oats in afflicted patients (5, 46). Indeed, oats prolamins differ from prolamins in wheat and other related species (spelt, kamut) as well as in other Triticeae cereals (barley and rye) in that their repeated sequences of amino acids are poor substrates for tTG (47). Similarly, the safety of rice and corn in CD seems related to the absence of deamidated peptides able to bind to HLA-DQ2 or -DQ8 molecules.

TRANSGLUTAMINASES AND FOOD SAFETY

Owing to the importance of tTG in CD (and maybe in WDEIA) and of deamidated repetitive domains of prolamins in CD and in anaphylaxis to wheat isolates, the

use of transglutaminases, such as mTG, in manufactured foods merits to be closely studied (48).

As shown in Fig. 2, deamidation and cross-linking of prolamins are suspected to induce different immune reactions in susceptible individuals. And adding these molecular modifications during the technological steps of food manufacturing could result into some unwanted health effects.

Such an outcome has been overlooked by studies dealing with the assessment of mTG safety (9). The FAO/WHO protocol is centred onto the molecule susceptible to enter the food chain but does not address the question of potential effects this molecule could have on the foods (8). Efforts should aim at developing methods to study mTG end-products in food-

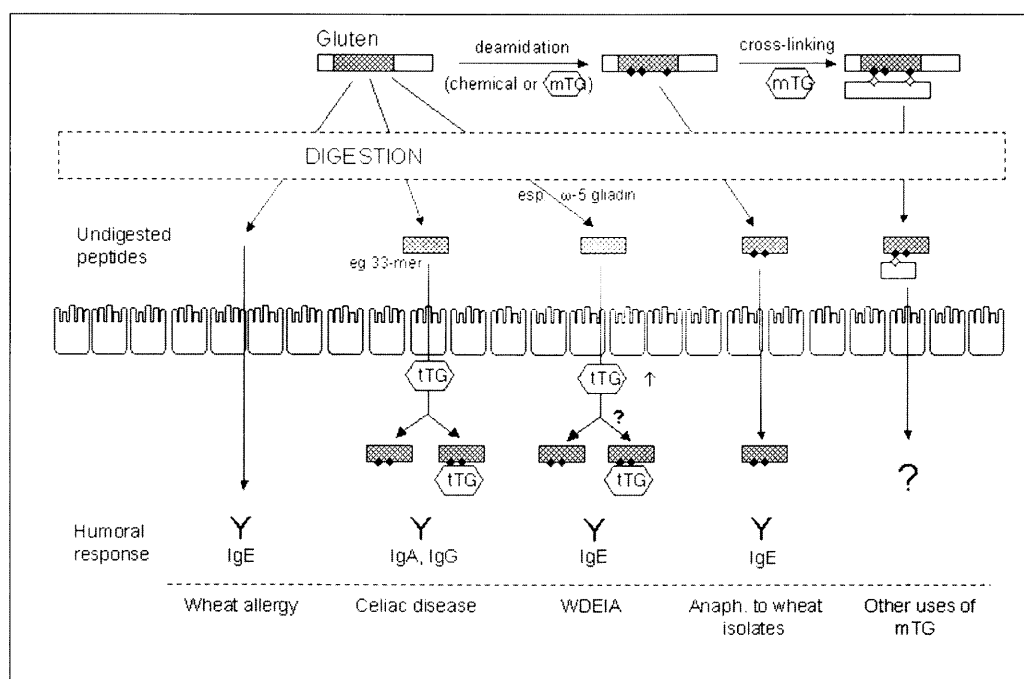


Figure 2: Transglutaminases and immune reactions to wheat.

The figure shows how modifications of wheat proteins by transglutaminases (TG) can induce and/or favour some reactions to wheat flour and/or to wheat-derived products.

Microbial TG (mTG) as well as intestinal tissue TG (tTG) can convert some glutamine residues into glutamic acids. This deamidation step can be followed by a transamidation step which is the cross-linking of the deamidated protein/peptide with another protein/peptide.

Digestion of gluten is not fully complete: some parts of the repetitive domains can resist due to their proline content, even to brush border enzymes (eg. 33-mer peptide).

If undigested peptides cross the epithelial layer, they can reach immuno-competent cells and induce an immune reaction. In classical wheat allergy, antibodies are directed towards a wide array of wheat proteins, including other proteins than gluten (not shown). In celiac disease and in wheat-dependent exercise-induced anaphylaxis (WDEIA), tTG is activated and gives rise to modified peptides which are especially potent immunogens.

In anaphylaxis to wheat isolates, new epitopes appear during the manufacturing process: these modified proteins are thus already in the food before eating it. Depending on the availability of other substrates, cross-linked proteins can also be formed. The isopeptide bond generated by this cross-linking cannot be split by digestion: one can thus assume that some undigestible gluten peptides cross-linked to other undigested peptides could behave as new allergens. To what extent these cross-linked species are present in the diet is largely unknown. As well as whether these mTG modified proteins could have any significant impact on the incidence of immune reactions to wheat.

stuffs. Although other TG-treated ingredients such as soybean or milk proteins could merit a similar scrutiny, wheat is especially important to study because this cereal is the basis of a considerable number of different uses in manufactured foods. In many cases, the presence of wheat-derived products is hardly detectable by consumers as exemplified by the recalls of marketed items (49) or by accidents due to hidden components (50).

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Conformément à la Loi informatique et libertés n°27 du 6/01/78, vous disposez d'un droit d'accès et de rectification aux données vous concernant.