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Toward an Etiology of Celiac Disease

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Abstract The review proposes a model of the etiology of celiac disease. It describes how an enteroviral attack by a lytic virus leads to hyper-extracellular Transglutaminase 2, Tg2, evident at all stages of the disease by the presence of anti-tTG. The demand for Tg2 is supplied by both the cell and the lytic virus. The demand leads to excess Tg2 passing through the cell wall, excess ingress of Ca^{2+}, the destruction of the mitochondria by Ca^{2+}, and pyroptosis of the cell. The increase in extracellular Tg2 during the cell's life and following pyroptosis has two effects. First, it binds a C1r inhibitor to the vascular wall, preventing C1r-LP from converting prehaptoglobin (zonulin) into haptoglobin, causing the weakening of the tight junctions among the epithelial cells and allowing the entry of extraneous luminal materials and particularly the access of Tg2 arterial and luminal, as it is now open directly to the lumen and the mesenchyme structure. It is this Tg2 that damages the villus structure as the Tg2 binds fibronectin into the mesenchyme, causing scarring, shrinkage, and turning the villi into the rigid scarred structures characteristic of CD. The model suggests why CD is a chronic lifelong disease reactivated upon the resumption of gluten consumption. A discussion of Non-Celiac Gluten Sensitivity and Refractory CD follows. The paper explains how extracellular transglutaminase causes zonulin and damages the extracellular membrane. Thus, zonulin is a symptom, not a cause. Notably, the paper demonstrates that the basic tenet of autoimmune diseases, that the cells destroy themselves, is incorrect, at least for CD. Applying this etiology to other conditions may be relevant because of the almost universal glutaminolysis in cells and the substantial amount of Gluten in modern diets.

Keywords: *Celiac, Non-Celiac Gluten Sensitivity, NCGS, Refractory, Coxsackie virus, Transglutaminase, Gluten, Villus, Apoptosis, Pyroptosis*

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1. Introduction

The paper proposes a model of celiac disease (CD). It incorporates new research into the viral instigation of the condition, the consequent excess generation of transglutaminase 2, followed by cell destruction, and explains all subsequent stages of the disease.

CD is a lifelong chronic condition. Thirty per cent of the Caucasian population has the HLA DQ2 or DQ8 (HLA DQ2/8) genes. It affects approximately one in thirty of these [1]. Thus, approximately 1 in 100 develops the disease. The diseases that are triggered in the susceptible population by an enterovirus, now confirmed as Coxsackie (CxSV) virus [2]. Twenty-nine out of thirty people with the genes do not have the disease, demonstrating that genetic susceptibility is not the sole cause. Marked evidence of anti-transglutaminase (ATg) or, specifically in the intestine, anti-Tg2 staining is present at all stages of the disease [3]. The viral intracellular requirements for additional Tg2 are the cause. The cell discharges Tg2 while progressing up the villi and on cell destruction by pyroptosis. The remaining seventy per cent of the population is also susceptible to the viral infection, though they lack the DQ2 and DQ8 genes and consequently cannot develop full CD. Nonetheless, they can experience discomfort from the effect of the viral attack and raised Tg2, causing the symptoms of Non-Celiac Gluten Sensitivity (NCGS). The infection is likely at the same rate as the one in thirty of CD, which would mean that 2.33 people in a hundred would contract NCGS. This is discussed further in the section on NCGS.

Serum and luminal Tg2 instigate three further stages of CD. First, luminal Tg2 deaminates luminal Gluten, forming gliadin fragments that are strongly attracted by HLA DQ2/8 binding grooves. Second, it binds a C1r inhibitor to the vascular wall, preventing C1r-LP from converting prehaptoglobin (zonulin) into haptoglobin. Weakening of the tight junctions among the epithelial cells follows, allowing the entry of extraneous luminal materials, particularly the access of Tg2 arterial and luminal, as it is now open directly to the lumen and the mesenchyme structure. Third, Tg2 damages the villus structure as Tg2 binds fibronectin in the mesenchymal structure, which causes scarring and shrinkage and turns the villi into rigid scarred structures characteristic of CD. Thus, the villi lose the ability to absorb nutrients. Fatty stools occur.

The withdrawal of dietary Gluten leads to remission, not a cure. The model proposed confirms that a return to gluten consumption reinstates the disease. Several positive

feedback loops exacerbate the condition. Non-Celiac Gluten Sensitivity and Refractory Celiac Disease are considered. Appendix 1 summarizes the experiments suggested throughout the text. The paper offers a thorough etiology of CD based on a viral origin and consequent Tg2, unavailable elsewhere.

2. Viral initiation of Celiac Disease

A member of the enterovirus family triggers CD. One family member, CxSV virus B1, has been considered (2]. Significantly, CD can occur in those diagnosed with type 1 diabetes and vice versa, both of which conserve HLA-DQ2/8 genes [4,5]. The CxSV virus CVB4 is implicated in causing type 1 diabetes. The comorbidity has a mean of 8% [6], which supports this finding. There may be a different serotype of CxSV virus B (1 to 6), which induces CD, or B1 or B4 may do so. The experiments described in (2] of the report tried CxSV B1 and advised further experimentation (Appendix 1.1). Rotavirus has also been considered [7]. Studies that preceded this on a viral cause of CD are [8,9].

CxSV virus-B (CVB) is a nonenveloped cytoplasmic double-stranded RNA enterovirus and a member of the picornavirus family. It has been detected in the blood and pancreas of type 1 diabetes patients [10]. CVB viruses are lytic [11], as are rotaviruses. Lytic viruses implant their DNA in a separate capsule floating inside the cytoplasm and replicate virions using the cell machinery, particularly the mitochondria. In contrast, lysogenic viruses implant their genetic material in the host's genome. Lytic viruses can alternate between phases of latency and lytic activity [12]. High stress induces lytic phases. MicroRNAs (miRNAs), which suppress viral activity, are reduced when the cell is stressed. Examples of stress are starvation, amino acid depletion, endoplasmic reticulum (ER) stress (ER is a capacious sink for Ca^{2+}), oxidative stress, and detection of intra/extracellular pathogen-associated molecular patterns (PAMPs) [12,13]. miRNAs control the balance between the lytic and latent phases in conjunction with the increase or withdrawal of these stressors. Viral RNA can still be found in vivo long after eradicating the infectious virus. Retro-implantation of the viral genome into the host genome may achieve this [14,15]. The double-stranded RNA structure may help stabilize the viral genome. This structure may contribute to persistent infection [12] However, upon wounding, the production of virions can be resumed even after the infection has been eradicated [11]. Since proposing this, it has been confirmed experimentally that the CxSV B1 virus causes CD [16]

Serum anti-Tg2 (ATg) increases in CD [3,17]. The HLA DQ2/8 genes have a superior ability to bind gliadin peptides and consequently increase glutamine absorption. Viral infection requires increased availability of Tg2. Tg2 production increases the concentration of intracellular Ca^{2+}. Increased Ca^{2+} stresses the mitochondria, initiating the lytic stage of CxSV, and the remission of the latent stage ceases. Conversely, after removing gliadin peptides, miRNAs regain control, and the cell returns to the latency phase or remission. Feedback from Paneth cells returning to the crypt through WNT signaling can report stresses occurring in cells distant from the crypt [18]. The model developed here is that the stress arises from mitochondrial breakdown due to excessive Ca^{2+} concentration in the cell from increasing the Tg2 supply. Experimental verification is required, Appendix 1.2. Since proposing this, it has been confirmed experimentally that following CxSV B1 infection, there is a high expression of intracellular Tg2 [16]. However, it still needs to be confirmed that this results in mitochondrial breakdown.

Lytic DNA coupled with host DNA increases the whole-cell production of Tg2. For example, in enterovirus 71, sixteen hours post inoculation, glutaminase increased by 20%, glutamate dehydrogenase increased by 50%, and CAD metabolism increased by 115% [19] (measured from graph printouts of Figure 6 B). Such increases are essential to viral reproduction. Tg2 is produced directly from the TGM2 gene in the cell nucleus [20]. Viral infection could initiate the additional replication of TG2 from the TGM2 gene [21]. Experiment Appendix 1.3. This has been confirmed experimentally that following CxSV B1 infection, causing CD, there is a high expression of intracellular Tg2 [16]. Lytic autophagy virions in microvesicles leave the cell. Their departure controls the virion content of the cell, avoiding the emission of stress signals from the stem cell, which would lead to its destruction by killer T cells. The emission of cellular caspase does not occur, preventing the induction of apoptosis. Thus, the cell has additional longevity even though it is infected. At the same time, the extracellular virions can infect other cells. This infection process travels down the intestine.

MicroRNAs (miRNAs) can silence the activity of intracellular viruses. Paneth cells can provide information about how stressed enterocytes (ECs), among others, are by WNT signaling upon their return to the crypt and in proximity to columnar base stem cells (CBCs,see Figure 1). WNT signaling regulates Paneth cell function and enterocyte (EC) differentiation [18]. High stress, for instance, from Ca^{2+}-stressed ER, increases replication and silences miRNA activity [13]. Therefore, EC cells undergoing pyroptosis will lead to the silencing of miRNAs and increased stem cell activity.

When the stem cell undergoes mitosis, the lytic virus forms virions in parallel. Under cytokinesis, not only do the genes of the parent cell move to the nucleus of the daughter cell, but separately, virions stay in the endoplasm of the parent cell and move to the daughter cell's endoplasm. Thus, the ECs carry the virions with them, enabling them to produce excess Tg2 and increase the cell's glutamine metabolism. Experimental verification is required, Appendix 1.4.

The withdrawal of gliadin from Gluten reduces glutamine. The EC cells become less stressed, and the Paneth cells signal this to the CBCs. MiRNA release is encouraged, which reduces and eventually stops the lytic behavior, making the virus quiescent and putting the celiac patient into remission. However, the question of how the virus can remain quiescent for many years but restart the lytic phase upon resuming gluten consumption is unanswered. The proposal here is that the label-retaining cells (LRCs,see Figure 1, zone A) remain lytic but quiescent due to miRNA, as they are seldom required to produce daughter cells [22] unless there is dramatic

damage to the CBCs [23].

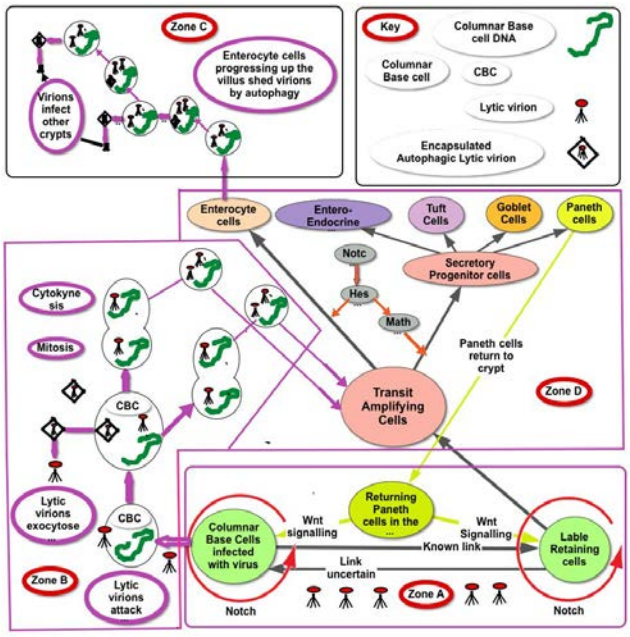
Lytic viruses can become active after very long periods. It explains why CD returns in celiac patients if they return to a gluten diet. The introns and exons of genes contain miRNAs [24]. CxSV viruses can assume a latent form and reactivate under certain stimuli [12,14]. CxSV-B3 ribosomes bind directly to the Internal ribosome entry site, permitting cap-independent translational initiation and polyprotein synthesis. miRNAs encode some cellular proteins synthesized during mitosis, which contain an Internal ribosome entry site. This initiation appears to be dependent on the phase in the cell cycle, as it does not occur in all cells. When a quiescent cell is wounded, as it would be on restarting a gluten diet by overloading the endoplasmic reticulum, it will recommence lytic viral production and reinfect cells [11]. Experiment Appendix 1.5.

Stem cells in the villus pit produce endothelial cells

The crypts between the villi contain stem cells that produce the five types of endothelial cells (Figure 1). Their function depends on Notch processes. [25,26,27]. A virus must insert itself into the cell at the root of the hierarchy of stem cells, producing ECs. The ECs on the villi have a turnover time of 2 – 3 days [27]. Therefore, stem cells have rapid turnover. There are two stem cells at the base of the crypt: rapidly cycling CBCs (Figure 1, Zone A and Zone B) and slowly cycling LRCs (Figure 1, Zone A). The CBCs affect the LRCs, although it is uncertain whether there is a complementary effect from the LRCs to the CBCs. LRCs only act when there is significant damage to the CBC cell production. The communication between CBCs and LRCs may infect LRCs with the virus. Together, they produce the Transit Amplifying cells (TACs), Figure 1 Zone D. These activate notch processes on the daughter cells of the TACs. Hes, Hey, and Math1 act and hence propagate specific endothelial cells. Hes 1 alone produces ECs, while Hes 1 and Math1 produce secretory progenitor cells (SPCs). Notch inhibition increases the secretory cell pathway under CxSV virus B, Echovirus 11, and EV71. At the same time, it depletes the formation of ECs [28]. The behavior of Notch, HES1, and Math1 activities in TA cells forming absorptive and secretory cells was confirmed. The raised glutamine level apparent from the view of the HLA DQ2/8 binding groove could imply Experiment Appendix 1.6.

Together, the cells move up the villus within the crypt and give rise to two cell types: absorptive cells, ECs, and SPCs. The secretory cells are hormone-producing, enteroendocrine, tuft, goblet, and cells with a particular function, Paneth cells, which have a feedback role to the CBCs and LRCs. The absorptive ECs are the most numerous and absorb gliadin. Their study is essential here. The Paneth cells move back down to the base of the crypt, where they communicate with the CBCs using WNT communication and control their differentiation [22]. Notably, Paneth cells are pyroptotic in Crohn's disease [29].

The process ensures a genetic refreshment cascade of the epithelial cells containing the virions (Figure 1 Zone B). It depends on the rapid stem cell (ISC) production of ECs [26]. The ECs are where the first phase of damage occurs in CD, as evidenced by the anti-transglutaminase behavior described above in [3]. The effect of a lytic virus on the CBCs, the TACs, and the LRCs is to affect the ECs, Figure 1, Zone C. They are the absorptive cells that process dietary gliadin and are dependent on the effect of HLA DQ2/8 and Tg2 deamidating gliadin in the lumen of the intestine.



Zone A, B, C: The viral infection of the CBC is reproduced in the ECs, causing pyroptosis. The Ecs shed virions among the villi, causing viral infection to spread through the small intestine. Zone D details the role of Notch in the SPCs, which does not affect the Ecs.

Figure 1. The route of viral infection from CBC stem cells increases Tg2 in enterocytes (adapted from [22]

3. Stem cells in the Villus Pit

Two features are essential to ensure the longevity of viral propagation: the shutting down of cell communication to alert the immune system to viral attack and the availability of ribosomes to enclose stress hormones to prevent signaling, which would invite killer T-cell attention. LRCs have, among them, a very low concentration of Ki67-positive cells, a marker of ribosomal transcription (5.3 +/- 0.9%). In contrast, the CBC and TA cell populations, 43.3+/-3.7%, were Ki67 positive for ribosomal transcription. The implication is that ribosomes are mainly present in TA and CBC cells but not in LRCs [23]. The CBC and the TA cells are better targets for viral reproduction than the LRCs and, therefore, more vulnerable to enduring viral attacks. CBC cells also express Lgr5, a ligand-receptor [30], indicating that they are rapidly cycling stem cells [23]. This ligand may enable a rapid increase in viral propagation.

Long tails of telomerase are essential for the longevity of stem cell life. Each time RNA is copied from the DNA to make a protein, the telomerase tail shortens. The longer the tail, the more copies can be made by the stem cell. The genetic cascade system used by the stem cells of the crypt ensures greater longevity of the genetic information than might otherwise be the case and helps preserve the rapidly recycling ECs. Mouse telomerase reverse transcriptase (mTert) has been shown to produce long cycles of villus cell population production [23]. In the population of LRCs, the $mTert^{+}$ cells give rise to both absorptive and secretory

cell lines but are slowly cycling and contribute minimally to normal cell production, but over the whole life of the organism, they contribute to the maintenance of cell homeostasis of the crypt and villus cellular organization. Following injury, with low-dose radiation, mTert^{+} LRCs are activated eight- to tenfold to re-establish the crypt and villus cell structure. Under high-dose radiation, LRC mTert cells increased twelve- to fifteenfold to re-establish the cell structure. LRCs express Bmi-1, which is activated to prevent genetic damage and plays a role in antisenescence, as reported in LRCs [31,23]. If the lytic virus modifying the production rate of Tg2 integrates into the LRCs, possibly through CBC to LRC communication, it will ensure continued production of excessive Tg2 in the ECs.

Specific peptide sequences in gliadins in Gluten, which are known to have high proportions of glutamine (32% to 53%) and proline (11% to 29%) [32], are strongly attracted to the HLA DQ2/8 binding sites and are known to stimulate a T-cell response in celiac patients which destroys the epithelial cells of the villi [33]. Table 1 lists the primary amino acids in twenty gliadin chains that precipitate gluten-specific monoclonal antibodies in celiac patients [34] and the lead amino acids. Notably, glutamine is the most common protein by percentage. Proline is the next most common. The pH of all the lead amino acids and the others are alkali equal to or more so than glutamine. In short, these are chains of highly concentrated glutamine.

Table 1. Data from twenty gliadin protein fragments precipitated by gluten-specific monoclonal antibodies in celiac patients [33]

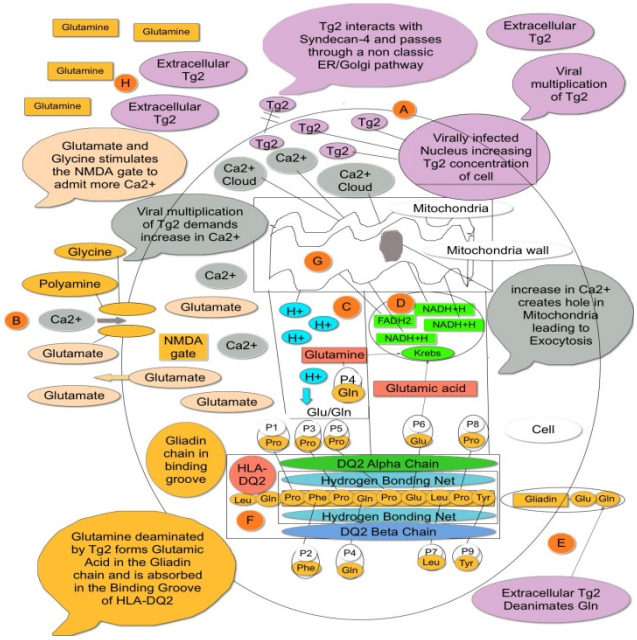
Amino Acid	Mean percentage in 20 Gliadin chains	Percentage of Lead Protein in 20 Gliadin Chains	Ph
Glutamine	38.31	10%	9.1
Proline	27.89	45%	10.96
Serine	6.76	20%	9.15
Arginine	1.41	15%	13.8
Tyrosine	5.35	5%	10.5
Valine	1.41	5%	9.62

Glutamine transporters SLC 38A3 and SLC 38A5 are N transporters associated with H^{+} flux. As the H^{+} ions travel down the transporter, glutamine travels up. Transporters also have a significant impact on intracellular pH. Their activity is increased by an alkali extracellular medium [35]. Glutamine is a charge-neutral, polar amino acid. It has an acidity of 9.1 (Amino) [34]. The properties of these peptide sequences make them prime glutamine sources for the SLC 38A3 and SLC 38A5 transporters.

Tg2 deaminates glutamine to glutamic acid in the lumen of the intestine. X-ray crystallography investigations of the binding groove of HLA DQ2 show that the lining of the binding groove is an extensive hydrogen bonding network that strongly attracts some gliadin peptides [36]. There are nine binding pockets. It accommodates negatively charged residues at positions 4, 6, and 7. Hence, DQ2 has a superior ability to bind gluten peptides, exposing people with this gene to becoming potential celiac patients. Proline can be accommodated at position one, which explains why it accounts for the lead protein for approximately 45% of the gliadin chains, activating a T-cell reaction. Proline residues may be in other positions if they do not interfere with the hydrogen bond backbone. Thus, proline is the most frequently occurring amino acid after glutamine. However, increasing proline reduces the number of binding sites available for glutamine. HLA-DQ8 differs from HLA-DQ2, as there is a noticeable difference in the H^{+} binding structure [36]. The charge configuration in HLA-DQ2/8 is probably a critical contributor to the susceptibility of CD with either gene. The connection between H^{+} in the glutamine transport system and the hydrogen lattice in the binding groove of HLA-DQ2 needs to be investigated in experiment Appendix 1.7, as the H^{+} flow may recharge the HLA-DQ2 hydrogen lattice, something that nonceliacs do not have. A positive feedback loop may exist, increasing the demand for Tg2 in the Krebs cycle.

Intra- and extracellular events leading to pyroptosis of ECs

Six phases contribute to the pyroptosis of ECs in CD.



Zone A: The viral infection of the ECs increases TG2, which requires an increase in intracellular Ca^{2+}. Excess TG2 interacts with Syndecan-4 and leaves the cell. The TG2 acts on serum glutamine to increase glutamate concentration in Zone H. In conjunction with glycine and polyamines, this furthers the Ca^{2+} flow through the NMDA gates, generating a positive feedback loop. The gliadin, deamidated from dietary gluten Zone E, is strongly attracted to the HLA DQ2 binding groove, Zone F. The glutamine transporter increases its activity, which is also facilitated by the increased $H^{=}$ ions from the additional mitochondrial activity, creating positive feedback. The increased Ca^{2+} leads to damage of the mitochondria and pyroptosis of the cell.

Figure 2. The dynamics of an EC cell and its immediate environment lead to pyroptosis

1. Hydrogen flow. The more energy the cell requires as ATP from ADP (spent ATP), the greater the amount of H^{+} given off by the mitochondria (Figure 2C). The rise in H^{+} increases the glutamine transport (Figure 2E, F). Hence, the peptide sequences referred to above [33] are ideal sources to increase ATP in the cell. ADP in the cytosol is transported across the mitochondrial membrane [37] where $FADH^{2}$ and $NADH + H^{+}$ from the Krebs cycle (Figure 2D) provide the energy to convert

ADP to ATP by the flow of hydrogen ions out of the inner mitochondrial membrane (Figure 2C). These ions, in turn, drive glutamine transporters. Experiment Appendix 1.7.

2. Increased Tg2 production, driven by the viral and the cell's own Tg2 requirements, requires increased intracellular Ca^{2+} [38]. Ca^{2+} enters through NMDA gates (Figure 2B). Excess Tg2 interacts with Syndecan-4, passing through the cell wall in a nonclassic ER/Golgi pathway [39] (Figure 2A). Extracellular Tg2 synthesizes more glutamate from serum glutamine (32% to 36% of high molecular weight gliadins [32], see Figure 2H), raising the serum glutamate concentration found in celiac patients 29% higher than that in controls [40]. Glutamate is the first of three keys to the NMDA gates. Polyamines can form from the abundant proline (11% to 13% of high molecular weight gliadins [32] and another amino acids, giving the second key to the NMDA gates (Figure 2B). The third key is glycine (18% to 20% of high molecular weight gliadins) [32]. Thus, increasing Tg2 exacerbates the problem of Ca^{2+} cellular overload of cells by increasing NMDA activity. Experiment Appendix 1.8. Although the ER is a capacious sink for Ca^{2+}, its capacity is limited, and when stressed, Paneth cells sense this, providing feedback through Wnt signaling to the CBCs to increase cellular activity.
3. Demand for Glutamine. Increased Tg2 increases glutaminolysis, which increases H^{+} from the mitochondria. H^{+} increases glutamine transport (Figure 2C), driving an increased demand for additional extracellular glutamine from gliadin released from Gluten by luminal Tg2 (Figure 2E), which increases the demand for additional Tg2.
4. Hydrogen lattice. The superior ability of HLA-DQ2/8 to bind to gliadin peptides and the consequently increased absorption of glutamine (Figure 2F), combined with increased Tg2, increases hydrogen-driven absorption of glutamine by the glutamine transporter (Figure 2C) to the Krebs cycle (Figure 2D). The hydrogen pump flowing to the HLA DQ2 gate may refresh the hydrogen lattice bed of the HLA DQ2 gate (Figure 2F). If so, this could be the fundamental cause of the strong affinity of HLA DQ2 to glutamine (Experiment Appendix 1.9).
5. Mitochondrial Ca^{2+} plays a part in the opening and closing of mitochondrial aspartate/glutamate carriers (Figure 2G). The N-type transporters open in the presence of calcium [41]. Low Ca^{2+} induces aspartate/glutamate exchangers, whereas strong Ca^{2+} signals induce short Ca^{2+}-regulated mitochondrial transporters. Therefore, high cytosolic Ca^{2+} and Tg2 produce high ATP output [42].
6. Pyroptosis. Ca^{2+} destruction of mitochondria occurs due to pore formation in the mitochondria (Figure 2G) under high intracellular Ca^{2+} concentrations, which destroys the mitochondria [43]. Under viral attack, Erp57 interacts with cytoplasmic p53 to inhibit p53-induced apoptosis via permeabilization of the mitochondrial outer membrane [44,45]. The inhibition of p53 prevents apoptosis by suppressing caspase formation, distinguishing apoptosis from pyroptosis. The result is pyroptosis. Proinflammatory molecules are released, which leads to small holes in the cell wall. If not rapidly repaired, killer T cells destroy the cells [46]. Thus, increased Ca^{2+} induces pyroptosis [47,46]. Neighboring cell pyroptosis increases the serum and luminal concentrations of Tg2, Ca^{2+}, and glutamate. Pyroptosis spills out the entire cell contents. It differs from apoptosis induced by internal caspase release, which packages the cell contents for phagocyte absorption. In EC pyroptosis, the contents are spilled into the serum and lumen. The concentration of serum Tg2, glutamate, and Ca^{2+} increases, Experiment Appendix 1.10, 1.11, 1.12, 13.

Distressed ECs release IL-1β and IL-18 cytokines, which activate cytotoxic/killer T cells. These extend CD95L ligands into the inflamed cell, which leads to pyroptosis, and the contents of the cell spill out into the extracellular space. Genetic material spills out, as shown by the positive TUNEL tests in [3]. Lymphocytes specifically recognize the protein sequences in the gliadin strands [34].

Over time, lymphocyte learning recognizes the gliadin strands [34] and activates killer T cells. In apoptosis, which is controlled cell death, there is no T-cell activity, as it is instigated and controlled by an intracellular caspase sequence, which packages the cell contents for reuse in blebs, fragments the nucleus, and phagocytes absorb the resulting cellular components. The literature frequently states that CD cell death is apoptotic, for example, in [3]. The above discussion shows that this is incorrect. The TUNEL test establishes whether there is a breakdown of genetic material. A positive result does not mean that only apoptosis is taking place. It can also be positive where pyroptosis occurs, and

if killer T cells cause collateral damage to healthy cells [48]. Collateral damage may occur when pyroptosis commences, with T cells signaling CD95L ligands to the excitototic cell. Some of these ligands may go astray and cause pyroptosis in otherwise healthy cells, causing collateral pyroptosis. Experiment Appendix 1.14. Around a pyroptotic cell, stray CD95L ligands could destroy an umbra of cells. However, the induction of T-cell activity and hence the CD95L ligands from killer T cells still comes from cell pyroptosis, not apoptosis, arising in the first place. Only then could there be any T-cell activation.

Only people with the HLA DQ2/8 genes are susceptible to this process outcome. The gliadin protein fragment sequences are very attracted to the HLA-DQ2 binding groove. People without this gene do not have this binding groove or the genetic means to produce it. The same enterovirus may infect them, but this alone appears insufficient to ensure CD. For celiac patients, the withdrawal of dietary Gluten effectively inactivates the impact of HLA-DQ2/8's strong affinity for gliadin peptides.

At this point, NCGS cannot proceed further down this route. It has imported too little glutamine for the full effect experienced by the celiac with the HLA DQ2/8 genes. The EC will not have emitted much, if any, glutamate or Tg2, so it will not have softened the vascular walls. The EC will not be destroyed before it leaves the tip of the villus.

So, the further progress of CD will not take place, and the villus will remain intact.

In CD, following the Tg2 binding of the C1r inhibitor to the vascular wall, the concentration of prehaptoglobin/ zonulin increases, and the wall softens. EC cells undergo pyroptosis. Then, peptides, gliadins, toxins, bacteria, and other materials from the lumen can enter the gap under epithelial cells into the lamina propria. The order of these events is essential. Some peptides will fail to be deamidated in the lumen and will penetrate through the new holes in the epithelium. They can be deamidated by extracellular Tg2 and bind to HLA grooves in dendritic cells. The lymph nodes drain these cells and activate CD4 T cells, which migrate back to the lamina propria. $CD4^+$ cells produce IFNγ and participate in a chronic inflammatory process [46]. Investigating the binding properties of human leukocyte antigens to several gluten peptides has not shown any direct association with CD [46,49].

CD patients have several increased cytotoxic mechanisms. Intraepithelial lymphocytes in the lamina propria are cytotoxic CD8+ T lymphocytes, γ/δ T cells, and large and granular lymphocytes. These can generate IL-15, IL-21, and type I and II interferons (46,et seq references). While these cause considerable damage, it is the result of the ravages of Tg2 in destroying the EC in conjunction with HLA-DQ2/8 in the first place, followed by Tg2 binding C1 inhibitor to the vascular wall, causing prehaptoglobin/zonulin, see below, which are the leading causes of wall softening. Many papers assume the effect of zonulin but make no connection to its cause through extracellular Tg2, as discussed below.

Extracellular tG2 and prehaptoglobin/zonulin.

Celiac and gluten-sensitive patients have remarkably high serum zonulin levels [50]. Those with irritable bowel syndrome have elevated levels, but less than half the levels of celiac or gluten-sensitive individuals [51]. Healthy volunteers have negligible blood levels of zonulin [52]. Prehaptoglobin is also known as zonulin, an immature preprotein of haptoglobin [53]. Haptoglobin is cleaved from the endoplasmic reticulum in hepatic cells and enters the serum as prehaptoglobin. C1r-LP prehaptoglobin convertase is co-released in the liver [54] [55]. It converts prehaptoglobin into haptoglobin in the serum. A C1 inhibitor controls this process [56].

The release of Tg2 into the extracellular space has two crucial effects. First, it binds the C1 inhibitor to the perivascular region [57,58]. The inhibition of C1r arising in that region prevents it from complementing prehaptoglobin. Second, it softens the tight junctions locally in the cell wall of the blood vessel by forming a complex with vascular endothelial growth factor 2 (VEGFR-2), which contributes to angiogenesis [59]. Second, prehaptoglobin/zonulin transactivates VEGFR via proteinase-activated receptor-2 PAR-2, which increases intestinal permeability in vivo [57]. The increase in permeability allows enzymes such as Tg2 to cross the vascular wall into the mesenchyme. In interpreting the importance of the roles of Tg2 against those of prehaptoglobin, Tg2 takes the lead action by binding the C1 inhibitor to the vascular wall, hence causing prehaptoglobin to remain as such and enabling it to act as a promoter of angiogenesis. Zonulin/prehaptoglobin presence is a symptom, not the cause, Experiment Appendix 1.15. In addition, gliadins, toxins, bacteria, and other items in the lumen of the intestine can enter under the epithelial cells as described above.

The incremental effect on Claudins in the small intestine

Softening the vascular walls plays an integral role in CD. It increases its permeability. It appears to modify the claudins, forming tight junctions between the epithelial cells. CD disrupts the claudins. In celiac children, Claudins 2 and 3 were significantly increased in both mild and severe forms of CD in the proximal region and, in severe CD, in the distal region. Claudin 4 showed no significant difference between celiac patients and controls [60].

Anti-Tg2, and hence Tg2, penetrates beyond the complete covering of the affected epithelial cells [3]. In severely damaged celiac intestines, the crypts between the villi are full of epithelial cells. The crypt of the villus is where stem cells generate ECs [22,61]. Thus, the source of the epithelial cells is undiminished.

The Effect of TG2 on the Extracellular Membrane

The net of epithelial cells covering the villus has gaps between cells in healthy people and celiac patients. Tight junction materials form a net that extends under an apoptotic cell, leaving the epithelium. The net forms a seal preventing the influx of other materials under the epithelium [62], and examining the net in the presence of a C1 inhibitor in a coeliac model could nullify its presence. However, while this may prevent direct access of gliadin to the mesenchyme in healthy individuals, it does not answer the question of how the structure of the villus is damaged when pyroptosis destroys a cell. Experiment Appendix 1.16

Scarring and malformation of the extracellular membrane (ECM) are characteristics of the villi in CD. The modification of claudins is evidence of damage and changes to the tight junctions between ECs. In particular, Claudins 2 and 3 were significantly increased along the length of the small intestine as the severity of the disease increased. Excessive TG2 can percolate into the extracellular matrix ECM layer. Myofibroblasts support the structure of this layer [63]. They require fibronectin for their differentiation [61]. TG2 anchors fibronectin in the extracellular matrix [64,65]. Syndecan-4 facilitates TG2 leaving the cell [39]. Free Tg2 crosslinks with fibronectin, a high-affinity binding partner, in matrix remodeling [66]. Increased TG2 leads to increased fibronectin deposition in the ECM directly through crosslinking or activation of matrix-bound TGFβ1 via the crosslinking of the latent TGFβ binding protein [39,67]. In CD, scarred villi result from this excessive deposition of fibronectin.

Fibroblasts are part of the structure of the stroma. Their long-term survival depends on stem cells. The productivity of stem cells depends on the level of Notch activity. Loss of Notch leads to depletion of cell production [68,69]. Notch activity ceases in Jurkat cells in high glutamine concentrations [70,71]. Stromal stem cells form connective tissue in the vi llus. There are also stem cells for the smooth muscles of the lamina propria, which together support the villus. If reduced notch activity prevents the proper function of stem cells, the villus will be deformed [61]. The shape of a healthy villus is

instrumental in supporting healthy epithelial transport through the even shedding of cells [72]. Hence, the misshapen villi of CD damage the even shedding of cells.

Villi require a certain elasticity, as they act as a muscular pump of longitudinal smooth muscle to operate the lymph ducts they surround, which act as a channel for dietary fat from the intestine [61]. The scarred tissue introduces rigidity and prevents the villi from acting correctly. Experiment Appendix 1.17. If so, this could be an additional reason to the loss of ECs for weight loss in CD and fatty stools, classic symptoms of CD.

Cellular metabolism changes along the crypt-villus axis

The lumen of the intestine and the mesenteric artery are adjacent to the villi. The epithelial cells migrate from the crypt to the tip of the villus in approximately three days. The proportions of glutaminolysis and glycolysis vary along the crypt-villus axis [73]. The miRNA associated with glycolysis increases to the top of the villi from a low level in the crypt. The primary metabolism in the crypt is glutaminolysis, reducing toward the tip. Together, the metabolism steadily increases toward the tip. Experiment Appendix 1.18. ECs have more than two days of glutaminolysis and Tg2 to initiate pyroptosis. Put another way. The cells have time for pyroptosis to occur before reaching the tip rather than after. If glutaminolysis were low in the crypt and increased toward the tip, the cells would not undergo pyroptosis before they left the tip. They die "because of it, not with it." In healthy cells, the gap caused by the apoptotic departure of the ECs results in a tight junction referred to as a zipper theory [62]. Caspase is part of the process, thus demonstrating true apoptosis in healthy ECs [74,75].

Possible medication to reduce the effect of the H^+-driven SLC 38A3 and SLC 38A5 transporters

Celiacs miss the elasticity of Gluten in flour. An enzyme breaks the disulfide bond of Tg2 to activate it. The enzyme Erp57 restores the disulfide bond, making TG2 inactive outside the cell. Thus, TG2 can be controlled by an on/off switch [76]. However, the ectopic expression of Erp57 partially restores the ribosome entry site, increasing potential viral activity. While extracellular Erp57 could reduce extracellular Tg2 activity, upregulating external Erp57 increases the viral internal ribosome entry site, potentially increasing the viral activity of CxSV and other viruses [77]. It does not overcome the pyroptosis of the cell itself.

One way to counter the Lytic effect of the virus is through an antilytic viral treatment, which would target CxSV. This would enable the one per cent of people with Celiac disease to rejoin the 29 per cent of people with the same genes who are not CD.

Another way might be a reduction in the glutamine pump action of the H^+ to the HLA DQ2/8 grooves. Developing a medication that turns the H^+ stream into water and reduces the effect of the glutamine pump.

Non-Celiac Gluten Sensitivity

Here, it is proposed that NCGS is caused by CXSV B1 in the 70% of patients without the HLADQ2/8 gene. This means that the initial access of glutamine to the cell is substantially reduced. However, the cell is still infected by the virus. It can still follow through the processes described above, albeit at a much reduced rate and level, up to, but not including, binding of the C1r inhibitor to the vascular wall. The EC cells will have been discharged at the tip of the villus before they die, so the subsequent stages of vascular wall softness, etc., which take place in CD, will not happen to an NCGS patient. And there will be no visible evidence of modification of the villi. Only by starving the cell of glutamine in the form of gliadin can the viral activity be reduced to negligible, and the patient be in remission, and hence the physical experience of the NCGS patient be restored to normal. The cause of viral infection in those without the HLA Dq2/8 genes requires experimental investigation Appendix 1.22. The presence of raised serum glutamate or Tg2 would need to be included in the investigation. If found, the advantage of this addition to the causes of NCGS is that testing for the viral infection would be a positive confirmation of the condition with a definitive diagnosis.

NCGS may be a disease with multiple causes, but it shares common symptoms, which is why it may be a number of diseases given one name. Several chemicals in wheat flour could cause similar symptoms. One set is Fermentable Oligosaccharides, Disaccharides, Monosaccharides, and Polyols, known as FODMAPS [78]. There are other possible factors [79].

Another consideration is the frequency of NCGS arising from viral infection in the 70 % non-celiac population. Here, assuming the same rate of viral infection as in celiacs, the expected rate is 2.33 in 70 of the non-celiac population or 3.33 in the total population. 13% of the UK adult population are reported to have adopted a gluten-free diet. Of them, 7% were found to be celiac [80]. This equates to about one person. So 12 people in 100 have largely self-diagnosed as NCGS. However, an Australian study found that only 1 in 4 self-diagnosed NCGS patients fulfilled the strict criteria for NCGS [81]. If this were the case in the UK, it would mean that of the 12 UK patients in 100 people, only three would meet the strict diagnosis of NCGS. The argument presented here for a viral origin of NCGS in individuals without the HLADQ2/8 gene, which accounts for 3.33% of the UK population being NCGS patients, and the findings from NCGS population studies in the UK and Australia at 3% are numerically consistent with each other. Only experimental evidence can confirm this.

4. Refractory CD

People who still suffer from the symptoms of CD, even though they have been on a gluten-free diet for a long time, have refractory CD. The likelihood of this increases in those who have inherited HLA DQ2/8 genes from both parents [82]. The above suggests that there are four possible explanations.

- Patients may have an increased number of HLA DQ2/8 gates. Increasing access to glutamine ensures continued demand for excessive Tg2. Other food sources supply dietary glutamine, which may have to be additionally removed [83] even though gliadin is no longer part of their diet. Most likely, the only way of reducing this is to reduce the glutamine pump action of H^+ to the HLA DQ2/8

grooves. The medication that collects H^+ and removes it from the cell, possibly as water, could be the answer; see above.

- The HLA DQ2/8 gates may attract glutamine from other sources, such as meat, eggs, white rice, Tofu (soy), and corn [83]. If this is the case, an accurate food diary reporting on excluding and reintroducing specific glutamine sources might provide some dietary guidance.
- Mouse telomerase reverse transcriptase (mTert) has been shown to produce long cycles of villus cell population production [23]. Human telomerase reverse transcriptase (hTert) may be the vehicle to rebuild the villus cell population. Every time the departure of RNA to produce new proteins reduces the telomere tails. Eventually, this makes RNA production impossible. Human LRCs could be destroyed or worn out through such damage and overuse, and hence, the shortening of the CBC and LRC telomere gene tails could mean cell death due to the inability to reproduce. Refractory CD may be due to the inability of the cell population to rebuild. If so, the only cure would be the induction of hTert with long recharged telomeres into the CBCs and LRCs in the crypts of the villi. The suitability of this approach could be assessed by studying telomere tails of villi stem cells in people with refractory CD to assess whether they are significantly shorter—experiment Appendix 1.19, 20.
- MicroRNAs (miRNAs) can silence the activity of intracellular viruses. The introns and exons of genes contain miRNAs [24]. The destruction of CBCs may have happened many times in long-term CD. The LRCs repeatedly reset the CBCs. The LRCs may have become lytic rather than quiescent in such cases if they have lost the miRNA gene fragments required to maintain viral quiescence. Losing the miRNA gene could lead to the same fate as the CBCs and might be an explanation for refractory CD. Similarly, they may be people who did not have sufficient miRNA in the first place to induce quiescence or remission of CD. If this is the case, some form of seeding of cells with miRNA would be required to achieve remission. Experiment Appendix 1.21.

It is now possible to design a new gene to overcome these problems. The answer could be an implant of the gene in a virus, followed by implanting the viral vector in the crypts of a refractory patient. Adeno-associated viruses in retina and cochlea therapy is an example of this approach [84,85].

5. Conclusion

CD only happens to people with the HLA DQ2/8 genes, but it only happens to one in thirty. This fact and viral infection by a lytic virus are the starting point for this paper. Many papers on CD examine metabolic changes. They are essentially audits, vertical slices through the etiology timeline of the established condition. They do not document the horizontal time axis of the etiology. Here, a CD etiology model is proposed based on experimental evidence of excessive Tg2 in celiac patients at all stages of the disease. Glutamine's contribution to the energy production of ATP through the Krebs cycle is almost universal for cells. The paper splits Celiac disease into distinct phases. Each suggests a template based on a specific property of Tgs. Each template may be applied separately or in combination with other conditions to help elucidate their etiology. Where subjects have increased serum glutamate against the control levels, free serum Tgs may be present and relevant to the etiology of their condition. The cause of tight junction weakening is frequently ascribed to zonulin. Digging deeper into the physiology of zonulin/prehaptoglobin maturation into haptoglobin suggests that zonulin is a symptom, not a cause, of tight junction breakdown.

Apoptosis occurs when the cell releases caspase without T-cell involvement. Many papers cite apoptosis as the cause of cell death in CD. Gliadin chains elicit T-cell reactions in celiac patients, so apoptosis cannot occur; instead, viral infection results in pyroptosis following an increased requirement for Tg2, creating hyper-Tg2, which causes Ca^{2+} overload and destroys mitochondria. Proinflammatory molecules are released, which leads to small holes in the cell wall. If not rapidly repaired, killer T cells destroy the cells [46]. Hence, the cells are not destroying themselves as in apoptotic cell death, but dying from the effect of lytic viral infection and the resulting hyper Tg2. Autoimmune diseases may need to be reassessed in this light.

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Competing interests

SHW is celiac

Abbreviations

Atg: Ante Transglutaminase; CBCs: Columnar Base Cells; CD: Celiac Disease; CxSV: Coxsackie Virus; EC: Enterocyte cell (absorptive); ER: Endoplasmic Reticulum; HLA (DQ2/8): Haplotype DQ2 or DQ8; hTert: Human telomerase reverse transcriptase; IL: interleukin; ISC: Intestinal stem cell; LRCs: Label Retaining cells; miRNA: Mouse telomerase reverse transcriptase; SPCs: Secretory Progenitor Cells; TACs: Transit Amplifying cells; Tg2: Transglutaminase 2; Tgs: Transglutaminase; VEGFR-2: Vascular Endothelial Growth Factor 2.

Declarations

Ethics approval and consent to participate Not Applicable

Consent for publication Not Applicable

Availability of data and materials Not Applicable

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Appendix 1

Suggested experiments from the text

The following is a list of experiments that may help elucidate CD and other conditions. The relevant part of the paper gives the numbered reference.

1. Continue experiments with Coxsackie, Rotavirus, and other viruses to establish a precise viral cause of CD, ATG, furthering the work of [2] and [8,9]. CxsB1has now been confirmed as the cause of CD [16].
2. Measure Tg2 in virally modified cells relative to control cells. Then, compare mitochondrial breakdown in both infected and control cells. CxsB1 triggers a high expression of Tg2 intracellularly [16], but mitochondrial breakdown has not been investigated experimentally.
3. Measure the increase or otherwise of key enzymes: Tg2, glutamate dehydrogenase, and CAD metabolism. See [19]. CxsB1 triggers a high expression of Tg2 intracellularly [16].
4. An experiment to determine whether parent stem cell virions transfer into daughter cells with the parent cell DNA.
5. Assess whether the viral RNA can be retro-transposed into cellular DNA for epithelial stem cells: columnar base cells, label-retaining cells, and transit-amplifying cells.
6. In connection with Notch activity and NMDA activity, repeat the experiments described in [86] and [71] with villus stem cells, columnar base cells, label-retaining cells, and transit-amplifying cells. In particular, determining whether this affected the production of enterocytes, entero-endocrine cells, tuft cells, goblet cells, and Paneth cells would have value in understanding other intestinal illnesses, such as Crohn's disease and IBS. The rationale for this is that when Jurkat cells, a type of immortalized cancer cell, were grown in a glucose-free medium with added glutamine. There was a reduction in cleaved Notch1 expression, downregulating Notch1 activity. Further experiments showed significant crosstalk between the Notch signaling pathway and glutamine consumption by the cells, like a switch whereby high glutamine implied low or nonexistent Notch activity, and high glucose and low glutamine implied high Notch activity and low or nonexistent NMDA activity [86]. If high glutamine implies low-notch activity in the stem cells, this would reduce SC reproduction by the SPCs in a high-glutamine diet. Therefore, the patient would suffer a double blow to the ECs.
7. Study any changes to the glutamine transport system, particularly with raised H^+ production by the mitochondria in ECs containing HLA-DQ2 and HLA-DQ8. See how the H^+ bed of HLA-DQ2 is affected by the mitochondrion-stimulated H^+-driven glutamine pump.
8. Assess whether there are significant changes in NMDA activity with virally modified TG2 cells.
9. The hydrogen pump, driving the glutamine transporter to flow to the HLA DQ2 gate, may refresh the hydrogen lattice bed in the binding groove of the HLA DQ2 gate. If so, this could be the fundamental cause of the affinity of HLA DQ2 to glutamine. CD could be fundamentally affected by H^+ refreshing the lattice. This refreshment question requires experimental work for verification.
10. When a virus infects a cell, does increasing Erp57 increase viral activity, particularly members of the Coxsackie virus family?
11. Examine the longevity of virally modified enterocyte cells compared to unmodified cells.
12. Examine the effect on the immune system of the young and old, virally modified and unmodified ECs.
13. Assess whether pyroptosis or apoptosis takes place in older virally modified ECs.
14. Examine the possibility of collateral damage to cells when killer T cells attack a single cell. Can an umbra of healthy pyroptotic cells result when T cells attack one cell? If so, the phenomena are relevant to enterocytes and diabetes mellitus, strokes, and other conditions.
15. Tg2 binds the C1r inhibitor to the vascular wall, which causes prehaptoglobin/zonulin to remain immature. Tg2 has binding properties in cell structures. If they are used to bind the C1r, are they less available to bind cells? If this were the case, the weakening of the tight structure of the vascular wall might happen without the presence of prehaptoglobin/zonulin. Therefore, in CD, their presence would be as accessories, not the cause of the weakening of the vascular wall. Clarification is needed.
16. Examine tight junction materials in healthy apoptotic cells when a C1r inhibitor is in the vascular wall.
17. Examine the scarring of the stroma by Tg2-imported fibronectin, creating a rigid structure, and its effect on the muscular activity of the lymph ducts and fat absorption.
18. Glutamate accounts for over a third of the metabolism in the Krebs cycle in piglets after the enterocyte has left the crypt and started its migration up the villus [73]. To what extent does glutamate sustain the Krebs cycle after enterocytes have left the crypt? What are the proportions of glutamine and glutamate inputs to the Krebs cycle as the enterocyte progresses up the villus? What are the overall proportions, including glucose?
19. Study the Telomerase gene tails of villi stem cells to assess whether there is a significant shortening of the tails in refractive CD. In connection with this, examine whether it is possible to reseed the villus crypts with young stem cells to replace refractory stem cells.

20. Experiment on the lengthening of telomeres in villus crypt stem cells using human telomerase reverse transcriptase (hTert) [23]. The length of the telomeres in the modified stem cells could produce normal ECs.
21. Investigate miRNA in patients with refractory celiac disease.

Added later: Examine whether patients with NCGS are infected with CXSV B1 or another virus and whether their Tg2 and glutamate serum concentrations vary from those of controls.

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