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Review

Autoimmunity in celiac disease: Extra-intestinal manifestations

Lerner Aaron[a,b,*], Matthias Torsten[a], Wusterhausen Patricia[a]

[a] AESKU.KIPP Institute, Wendelsheim, Germany
[b] B. Rappaport School of Medicine, Technion-Israel Institute of Technology, Haifa, Israel

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ABSTRACT

Celiac disease is an autoimmune condition of the small intestine caused by prolamins in genetically susceptible individuals evoked by multiple environmental factors. The pathological luminal intricate eco-events produce multiple signals that irradiate the entire body, resulting in a plethora of extra-intestinal manifestations. Nutrients, dysbiosis, dysbiotic components and their mobilome, post-translational modification of naive proteins, inter-enterocyte's tight junction dysfunction resulting in a leaky gut, microbial lateral genetic transfer of virulent genes, the sensing network of the enteric nervous systems and the ensuing pro-inflammatory messengers are mutually orchestrating the autoimmune interplay. Genetic-environmental-luminal events-mucosal changes are driving centrifugally the remote organs autoimmunity, establishing extra-intestinal multi organ injury. Exploring the underlying intestinal eco-events, the sensing and the delivery pathways and mechanisms that induce the peripheral tissues' damages might unravel new therapeutical strategies to prevent and help the gluten affected patients.

1. Introduction

The target organ of celiac disease (CD) is the human proximal small bowel and in the past, symptomatology encompassed mainly small bowel presenting symptoms. Being a constantly changing disease, in the last decades and nowadays, novel features are continuously being unraveled. A lot of new observations and scientific knowledge on its genetic markers, epidemiology, clinical presentations, mode of diagnosis, therapeutic evolvement and high risk conditions were accumulated. Before embarking on its extra-intestinal manifestation (EIM), a background on CD and its shared aspects with other autoimmune diseases (ADs) is presented.

1.1. Celiac disease

Celiac disease is a life-long autoimmune condition [1] of the enteric tract, targeting mainly the small intestine and systemically multiple extra-intestinal sites, in genetically susceptible individuals. It affects 1–2% of Western populations and its incidence is continuously increasing [2,3]. Gluten is the storage protein of wheat and its alcohol soluble gliadins are the offending toxic molecules of the disease together with structurally related components found in barley, rye and less in oat [4]. Tissue transglutaminase (tTG) is the auto antigen [5,6] and two main auto antibodies: IgA-anti endomysium and IgA-anti tTG are the most frequently used serological markers to screen and diagnose the disease [7,8]. Lately, a new serological marker immerged, targeting neoepitope complexes formed when gliadin docks the tTG enzyme [9]. It appears that compared to the traditional IgA-tTG, the neoepitope tTG out performs and is considered as a reliable diagnostic marker and reflector of the intestinal pathology [10,11]. Interestingly, the microbial transglutaminase (mTG), a heavily used industrial food additive, that imitates functionally the tTG, was recently shown to induce specific antibodies in CD patients [12]. Potentially, it might represent a new environmental player in driving CD autoimmunogenesis [13–15].

The genetic repertoire of CD is expanding, containing more than 50 non-HLA genes but only two of them, HLA-DQ2 and HLA-DQ8 molecules are the most important, predisposing genetic factors [16].

The pathogenesis of the disease is dominated by the intestinal innate and humoral immune systems activation, resulting in enteric inflammation and destruction. In fact, each pathogenetic step: the ingested toxic environmental gluten, the luminal enzyme resistant gluten peptides, their increased intestinal uptake, the increased IL-15 and IFNγ production, tTG gluten deamidation and transamidation (cross linking), $TCD4^+$ cell proliferation and macrophage activation, are crucial events that form the basis for development of future potential therapeutic modalities [17,18].

Abbreviations: CD, celiac disease; EIM, extra-intestinal manifestations; Ads, autoimmune diseases; tTg, tissue transglutaminase; mTg, microbial transglutaminase

* Corresponding author at: AESKU.KIPP Institute, Mikroforum Ring 2, Wendelsheim 55234, Germany.
E-mail address: aaronlerner1948@gmail.com (L. Aaron).

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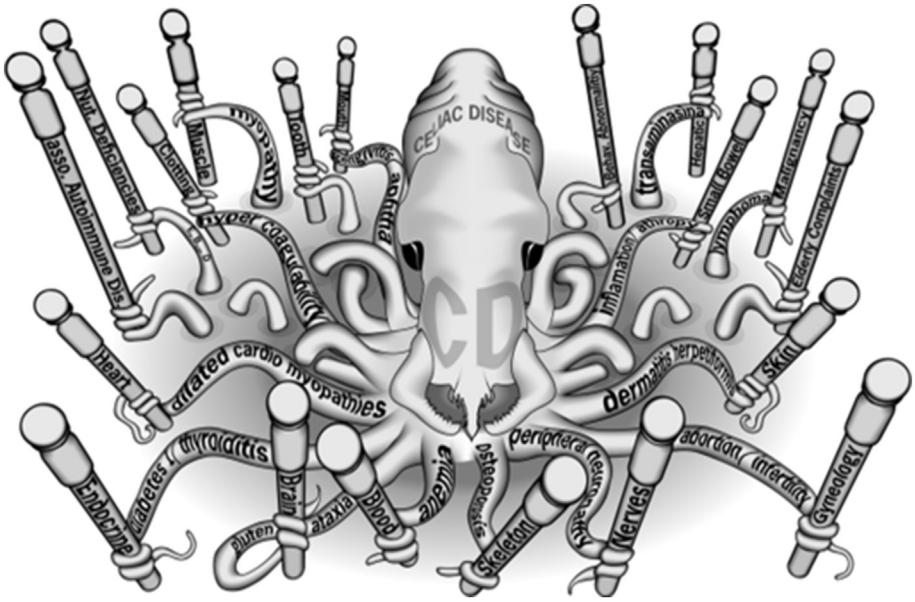

Fig. 1. The octopus of CD: A schematic presentations of the CD enteric arms extending to remote tissues and organs.

1.2. Celiac disease shares genes, environmental factors and non-target organ manifestations with other autoimmune diseases

Since genome-wide association studies became available and performed on various ADs, it appears that there exists an overlap of around 50% of genetic risk factors between those diseases [19]. Some of the shared genes are part of the human leukocyte antigens family that are routinely part of the diagnostic work-up in various ADs [20].

Interesting, regulatory genes, in the intronic, non-coding part of the genome, contain most of those genetic factors. Coming back to CD, the condition is associated with numerous ADs, including rheumatologic (S.L.E, rheumatoid arthritis, juvenile rheumatic/idiopathic, Sjogren's syndrome and connective tissue disease), endocrinal (Type 1 diabetes, Ashimoto thyroiditis, Addison's disease), dermatologic (dermatitis herpetiformis, psoriasis), neurologic, cardiologic, hepatic, pancreatic, gynecologic, gastrointestinal and immunological conditions [21–23]. In recent surveys, Hashimoto thyroiditis, type 1 diabetes, psoriasis, Sjogren's syndrome, autoimmune hepatitis, IBD and biliary ADs were the most frequently associated conditions with CD [24,25]. While the effect of gluten free diet is controversial in non-celiac ADs, the duration of the disease is considered a risk factor for polyautoimmunity [25]. It can be argued that shared genetics and environment are at the basis of the polyautoimmunity in CD patients or their family members [26]. More so, multiple screenings identified common genes shared between various ADs, supporting the autoimmune trait as part of the autoimmune tautology [23–27]. In a recent study, the following risk factors were identified for polyautoimmunity in CD patients: female gender, CD associated serology, family history of ADs, insufficient vitamin D levels, having high antinuclear antibody titer, and associate musculoskeletal conditions [28].

Conversely to the old notions upgrading genetics as the most influential, the impact of environmental exposure on autoimmune risk development, is paramount [29]. Multiple environmental factors are similarly shared between ADs. The recently coined term “autoimmune ecology” is the cross relation between us and the surrounding environment, that induce the breach of immune tolerance resulting in one or multiple ADs in an individual [29,30]. Chemicals, organic solvents, physical factors, surgery, nutrients, processed food additives, drugs and sex hormones, heavy metals, infectious agents, dysbiota, vitamins' deficiencies, smoking, alcohol, coffee, life style and stress, socioeconomic status and vaccines are some of them [13,23,29,30]. Notably, CD share some of them. Virus like enterovirus, EBV, CMV, HBV, HCV, rotavirus, reovirus, Microbes like tuberculosis, *Bacteroides* species, *Campylobacter jejuni*, *pneumococcus*, *Helicobacter pylori*, microbiotic composition and diversity, microbial transglutaminase, first year feeding pattern and antibiotic consumption, mode of delivery, amount and timing of gluten consumption, processed food additives and physical or emotional stress [4,13,14,23,31] were suggested as environmental components that influence CD induction, development or behavior. However, association and not causality was shown, except for gluten consumption in CD.

The title: “Our environment shapes us” [32], set the stage for the additional evolving topic, positioned in-between genetics and environment, meaning epigenetics. In fact, growing evidences are constantly accumulating for the pivotal role of epigenetics in driving autoimmunity. It is not only a loss of tolerance [33], since abnormal epigenetic modifications can present biomarker for ADs and be involved in multiple ADs pathogenic progression [34], CD not excluded [35,36]. Interestingly, most recently the microbiota memory was suggested to govern diseases by epigenetic regulation [37].

After mentioning the shared genes, clustering of ADs in the patients, the shared epigenetic events and environmental factors, the autoimmune trait resulting in familial coaggregation of ADs, the stage is set for extra-intestinal features of CD, shared by numerous ADs.

2. Extra-intestinal manifestations (EIM) of celiac disease

The scientific and medical literature is rich in comprehensive reviews describing EIM in CD populations. As can be expected, the list is expanding rapidly since the 90th [38] to the present [39–41]. Fig. 1 describes the multiple faces of the disease. The octopus intend to show that the CD arms can reach and affect any tissue/organ in the human body and many of the contemporary presenting symptoms of the disease are included. It goes without saying that patients' complains and symptoms, originated from the EIM are multiple and diverse and are organ systems presented in Table 1. In order to wrap up the topic of the EIM in CD, Table 2 summarizes the autoimmune condition that are associated with CD. One can appreciate the magnitude of CD associated ADs.

Table 1
Presenting symptoms and signs in CD, organized by non-intestinal organ systems (adapted from references 38–42).

Non-enteral extra-intestinal symptoms and signs in celiac disease					
Organs	Signs	Symptoms	Organs	Signs	Symptoms
Skin	atopic dermatitis	pruritus	**Endocrine**	Short stature	Stunted growth, dwarfism
	psoriasis	redness		Diabetes1	
	urticaria	swelling		obesity	
	dermatitis herpetiformis	warm	**Gynecology**	Infertility, abortion, prematurity	
				amenorrhea	
	alopecia		**Neurology**	neuropathy	fatigue
Musculoskeletal joints	myositis	aches		ataxia	Walk and coordination disturbance, imbalance
	arthritis	myalgia		epilepsy	convulsion
	Osteoporosis/penia	arthralgia		dementia	Lost memory
	fractures	pain		Cognitive impairment	confusion
Psychiatric	depression	Behavioral changes	**Lungs**	COLD asthma	Respiratory difficulties
	anxiety		**Heart**	Failure, dilated cardiomyopathy, arrhythmia	fatigue
	suicidal risk		**Oro-dental**	Aphthous stomatitis	Feeding difficulties
				Enamel dysplasia	
Blood	Anemia (Fe, B12, folate deficiencies)	fatigue, pallor	**Malignancy**	Lymphoma, adenocarcinoma	Weight loss anorexia
	Thrombocytosis/penia, leukopenia, hypercoagulability	clots, emboli			
Spleen	atrophy/megaly				

3. Enteric eco events that might drive systemic autoimmunity in celiac disease

3.1. Nutrition

The pivotal place played by nutrients, shaping human physiology and pathology, not just only in the intestinal compartment, is increasingly appreciated. In fact, the nutritional effects are irradiated peripherally to remote organs [69,70] and even to the brain [71]. Some of their effects are channeled by the microbiome, some affect intestinal permeability and many are direct by their digested and absorbed metabolites. Two aspects, related to CD, that might drive systemic autoimmunogenesis, are interesting and were summarized recently: Gluten side effects and additives used in industrial food processing. It appears that gluten has multiple side effects as shown on human originated cell lines and animal models [4]. It is pro-inflammatory, oxidative, increased pro-apoptotic, decreases cell viability and delays differentiation, is immunogenic, impacts epigenetics, changes microbiome/dysbiome balance and increases intestinal permeability. Focusing on the last effect, numerous nutrients and their metabolites, in addition to gluten or gliadin peptides can affect tight junction performance, and potentially impact peripheral organs [71]. In fact, after being absorbed, gluten sequences or gliadin metabolites are detected in urine or stools and were suggested as a way to monitor CD patient's food compliance [72]. The systemic distribution of gluten/gliadin sequences can carry those detrimental messages to any part of the human body, thus, contributing to the EIM of ADs, CD included.

Food additives contain multiple undesirable side effects [13,14,73–75]. By changing composition and diversity of the microbiome and increasing gut permeability they allow increased entry of noxious compounds to the blood or the lymph network, thus boosting EIM.

3.2. The macrobiome-dysbiome-mobilome interplay

Microbiota/dysbiota ratio changes and dysbiotic compositions and diversities are relayed to specific ADs, in an associative relation [76]. A disequilibrium created by a change in a specific microbial species or family or the entire commensal community can impact the outcome of an ADs, due to the resulting imbalance of detrimental/protective enteric or systemic immune response [77]. Much more important are the metabolites or bacterial compositions delivered to epithelial barrier, representing the so called mobilome [71,72,78]. Those are the ultimate messengers of the gut lumen able to induce EIM. To our knowledge,

Table 2
A summary of the autoimmune conditions that are associated with CD.

Autoimmune conditions associated with celiac disease					
System	Disease	Reference	System	Disease	Reference
Gastrointestinal	IBD	[43]	**Endocrine**	Diabetes type 1	[54]
	autoimmune hepatitis	[26]		Autoimmune thyroid diseases	[55,56]
	primary biliary cirrhosis	[44]		Addison's disease	[57]
	Primary sclerosing cholangitis	[45]	**Cardiac**	Autoimmune pericarditis	[58]
	Autoimmune pancreatitis	[46]		Dilated cardiomyopathy	[59]
Dermatological	Dermatitis herpetiformis	[47]	**Neurologic**	Epilepsy	[60]
	Alopecia areata	[48]		Peripheral neuropathy	[61,62]
	dermatomyositis	[49]		Gluten ataxia	[63]
	vitiligo	[48]		neuromyelitis optica	[64]
	psoriasis	[50]		Autoimmune encephalitis	[65]
Rheumatological	Rheumatoid arthritis	[23,51]	**Pulmonary**	sarcoidosis	[66]
	Juvenile rheumatoid/ idiopathic arthritis	[23,51]	**Nephrologic**	IgA nephropathy	[67]
	SLE	[52]		Glumerulonephritis	[68]
	Sjogren's syndrome	[53]			

until now, no specific mobilome is discovered able to induce CD or cause its EIM.

3.3. Tolerance break by posttranslational modification of proteins (PTMP)

The repertoire of enzymes that exist in the enteric lumen is huge and their capacity for PTMP is far from being revealed. The tTG gluten modifying ability, turning naive gluten to immunogenic and toxic gliadin peptides is well described and the modifying capacity of mTG is currently explored [12–15]. Furthermore, one can envision a joint cross talk between the intestinal mobilome and the enzymatic PTMP, resulting in autoimmune network activation, ending up with EIM in gluten dependent conditions [4].

3.4. Prokaryotic horizontal gene transfer in the human gut

It is estimated that, single-celled microorganisms appeared on earth more than 3 billions of years before the arrival of the Eukaryotic organisms. They had much more evolutionary time to adapt and survived the extreme ecological changes by acquiring very efficient genetic mechanisms to share survival genes between them. Horizontal gene transfer (HGT) is a lateral or horizontal transmission of genetic material between unicellular organisms. The most studied one is the virulent genes of antibiotic resistance that are transferred by microbes, pathobionts, probiotics and other prokaryotes [79]. Most recently the potential effects of HGT in the human gut were summarized, including the transfer of virulent genes that may induce gut originated systemic autoimmunity [80]. This might be a powerful mechanism that might operate in CD and spread the notorious factors to extra-intestinal organs. The novel mTg secreted by Streptococcus suis that possess antiphagocitic activity is an example of a virulent gene operating against the human immune protecting systems [15,80–82].

3.5. The leaky gut

The leaky gut implies a dysfunctional tight junction, allowing immunogenic and toxic molecules to pass the epithelial barrier, resulting in the development of inflammatory, allergic, cancerous and autoimmune conditions. Intestinal tight junction breach seems to be a major defect in CD and gluten peptides are one of the offender of this evolutionary well preserved apparatus [83,84]. By unregulated trans-passing of those non-self-molecules, through a dysfunctional tight junction, the autoimmune cascade is activated and affects extra intestinal tissues and organ functions, inducing EIM in CD [40,69,71].

3.6. The enteric nervous systems

In addition to the myenteric (Auerbach's) and sub-mucosal (Meissner's) plexuses the gut mucosa contains the microglial Network. Located at an extremely strategic crossroad, they modulate the epithelial barrier function, integrate local mucosal signals and coordinate the afferent information toward the brain [85]. Integrating the various enteric luminal eco events, the glial cell's homeostasis is regulated by the gut microbiota [86]. Thus, a new concept of a “nutritional-microbial-epithelial-neuronal” akin to environmental-luminal-mucosal-neuronal-brain integrated network can be created [71]. Coming back to CD, gastrointestinal motility disturbances [87], visceral hypersensitivity [88], neurological manifestations [61,62], anti-neuronal/brain antibodies [89,90] and enteric glial-derived biomarkers playing a role in nitric oxide production [91] were described in CD patients. It seems that the enteric nervous system plays a role in CD EIM initiation and progression.

3.7. The spread of the enteric pro-inflammatory messengers to extra-intestinal organs

The mucosal compartment is very rich in immune cells, blood vessels and lymphatics in close proximity to the luminal content, epithelial layer, entero-neuronal-endocrine networks and the *endo*-mesodermal interphase. Thus, an exceptional idea cross talks, inter-connections and relationships are created to deliver the ensuing messages, centrifugally to remote organs. The apostles that convey the enteric information are the numerous nutritional, microbial mobilome, enteric hormones, circulating committed immune cells, post-translated modified peptides, pro-inflammatory cytokines and lymphokines, neurotransmitters and other still unraveled factors [23,26,31,40,69,71]. This pathological orchestrated biological “harmony” join forces to spread the inflammatory/ autoimmune content to the periphery.

4. Conclusion

Multiple non-intestinal organs and tissues are affected in CD and present an end-organ disease, associated with the enteric one [21,39,41,92]. The gut originated autoimmune inflammatory network spreads peripherally and contributes to the EIM in CD population. Nutrients, bugs, chemical modifications, gut leakage, intestinal wall components like the immune, neuronal, endocrine, *endo*-mesodermal, hematological and vascular systems, gather together, in a very coordinated way, to initiate and maintain the EIM of the disease. The celiac patient's gut can be regarded as the Trojan horse [69] or the octopus (Fig. 1) that spread the damage to the periphery. Understanding the complexity of the enteric eco-events, their sensing machinery and delivery factors and mechanisms that induce the remote organ damage might bring novel therapeutical strategies to help the gluten affected populations.

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