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WHAT IS THE NEW BIOMARKER CALLED ZONULIN?

YENİ BİYOBELİRTEÇ ZONULİN NEDİR?

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Abstract
The human intestine, one of the body's largest barriers against potential external factors, performs this function through the tight junction elements between intestinal epithelial cells. Although more than 150 molecular components are known to form these tight connections, "zonulin" is the only identified endogenous molecule. Zonulin levels have been observed to increase in situations where intestinal permeability rises, as well as in conditions such as intense bacterial exposure, gluten enteropathy, various autoimmune diseases, and neurodevelopmental disorders. Zonulin, which appears to be a molecule that can be used in the diagnosis and monitoring of many such diseases, is considered a promising biomarker that may change the course of clinical practice in the follow-up of numerous disorders in the future.

Keywords: Autoimmunity, Biomarker, Tight junction, Zonulin

Öz
İnsan bağırsağı; vücudumuzun olası dış etkenlere yönelik en büyük bariyerlerinden olmakla beraber, bu görevi intestinal epitel hücreleri arasındaki "tight junction" (sıkı bağlantı) elemanlarıyla gerçekleştirmektedir. Bu sıkı bağlantıyı oluşturan 150'nin üstünde moleküler komponent bulunmakla beraber, saptanmış tek endojen molekül zonulindir. Barsak permeabilitesinin arttığı durumda arttığı görülen zonulin molekülünün; yoğun bakteri maruziyeti, gluten enteropatisi, birçok otoimmün hastalık ve nörogelişimsel bozuklukla birlikte yükseldiği görülmüştür. Bu ve benzeri birçok hastalığın tanı ve takibinde kullanılabilecek bir molekül olduğu görülen zonulinin; gelecekteki kullanımıyla, klinik pratikte birçok hastalığın takibi için rutin izlemi değiştirebilecek bir molekül olduğu düşünülmektedir.

Anahtar Kelimeler: Otoimmünite, Biyobelirteç, Sıkı bağlantı, Zonulin

1. Introduction

The length of human intestine is approximately 8–9 meters, representing the largest interface between the body and the external environment. The intestinal mucosa, composed of a single layer of tightly connected epithelial cells, serves as the primary barrier against environmental exposure. Covering an extensive surface area of roughly 200 m^2, this mucosa is continuously exposed to and interacts with external microorganisms, dietary components, metabolites, and other environmental factors (Chieppa M et al., 2006).

Tight junctions between intestinal epithelial cells are essential structures that regulate intercellular antigen trafficking (Arrieta MC et al.,2006). These junctions play a critical role in maintaining epithelial integrity under both physiological and pathological conditions (Nov, Turner JR., 2009). Initially considered static and impermeable, the understanding of tight junctions was revised following the identification of zonula occludens-1 (ZO-1) in 1993 (Itoh M et al., 1993).

Subsequent research has revealed that over 150 molecular components, including occludin (Furuse M. et al.,1993), claudins, junctional adhesion molecules (JAMs) (Martìn-Padura et al., 1998), tricellulin (Ikenouchi J et al., 2005), and angulins (Higashi T et al., 2013), contribute to the tight junction complex. Despite this extensive molecular characterization, the functional mechanisms governing intercellular tight junctions remain understoodincompletely.

Recognition of the significance of intestinal permeability in human health led to one of the

most notable discoveries in this field: zonulin, which is currently regarded as the only identified endogenous protein that physiologically modulates intestinal permeability (Fasano A et al., 2000).

2. Materials and Methods

Zonulin is a member of the protein family identified approximately 20 years ago and serves as the precursor of haptoglobin-2 (HP-2), known as prehaptoglobin-2 (Tripathi A et al., 2009; Rittirsch D et al., 2013). Haptoglobins initially evolved from proteins associated with the complement system and have been found to have additional functions over time, including the regulation of intercellular tight junctions (Fasano A et al., 2011).

Various luminal factors can trigger zonulin release. Among these, intestinal bacterial overgrowth and gluten exposure have been identified as the most potent inducers (El Asmar R et al., 2002; Drago S et al., 2006). Furthermore, intestinal infections have been shown to disrupt barrier integrity, contributing to the pathogenesis of allergic, autoimmune and inflammatory diseases (Fasano A et al., 2012).

Zonulin release has been demonstrated to be MyD88-dependent (Thomas KE et al., 2006). MyD88 is an adaptor protein that mediates innate immune responses. Upon activation, ZO-1 dissociates from the tight junction complex, resulting in increased intestinal permeability (Clemente MG et al., 2003).

Gliadin binds to CXCR3 receptors on intestinal epithelial cells and stimulates zonulin release via MyD88 signalling. This process suggests that gluten may be mistakenly perceived as a harmful protein through the zonulin pathway (Lammers KM et al., 2008).

These findings indicate that activation of the zonulin pathway may serve as a defense mechanism, facilitating the clearance of harmful microbes while modulating innate immune responses to changes in the intestinal microbiota. This response appears particularly relevant in conditions of increased bacterial colonization or dysbiosis in the small intestine (Fasano A et al., 2020).

All these observations suggest that alterations in the intestinal microbiota can influence intestinal permeability, and enhanced antigen translocation may contribute to the development of chronic inflammatory diseases in genetically susceptible individuals (Falszewska A et al., 2018).

Zonulin, as a precursor of HP-2, protects against hemoglobin-mediated oxidative tissue damage. It exists as a single-chain protein comprising alpha (α) and beta (β) subunits (Nelson, 2020). Zonulin can indirectly activate the epidermal growth factor receptor (EGFR) either directly or via proteaseactivated receptor 2 (PAR2). This activation modulates trans-epithelial electrical resistance (TEER) and regulates intestinal permeability.

Upon cleavage by proteolytic enzymes, zonulin becomes a double-chain molecule that loses its ability to bind EGFR, thereby functioning as an inflammatory biomarker (Fasano A et al., 2011). Zonulin and occludin molecules have molecular weights ranging from 45,000 to 65,000 Daltons (Da) (Vanuytsel T et al., 2013, Furuse M et al., 1993).

Molecules larger than 5,000 Da are immunogenic and can activate immune cells, which explains the rapid fluctuations in zonulin levels over minutes or hours (Sapone A et al., 2006; Yao Z et al., 2016). Once in circulation, these molecules are cleared by macrophages or Kupffer cells in the liver. The half-life of circulating zonulin ranges from 4 minutes to 4 hours (Vojdani A et al., 2017). Inpatients with sepsis in intensive care units, serum zonulin levels were reported to fluctuate 2- to 10-fold over a six-day period (Klaus DA et al., 2013).

2.1. Zonulin-Associated Diseases

Increased intestinal permeability has been implicated in the pathogenesis of numerous inflammatory and autoimmune diseases. Disruption of the intestinal barrier allows antigens to penetrate the submucosa, which, in genetically susceptible individuals, can trigger autoimmune responses through molecular mimicry. Depending on this issue, serum zonulin levels serve as an important biomarker in these conditions (Fasano A et al., 2011).

2.1.1. Celiac Disease

Celiac disease (CD) is an autoimmune enteropathy triggered by the ingestion of gluten-containing cereals in genetically susceptible individuals, and it can be reversed by dietary gluten withdrawal. Gluten peptides that are incompletely digested bind to CXCR3 receptors, inducing zonulin release. Due to the well-characterized role of zonulin in the pathogenesis of CD, this condition has been widely used as a model to study zonulin-mediated effects (Gorelick MH et al., 1997).

Although gluten stimulates zonulin release in both healthy individuals and CD patients, the magnitude and duration of zonulin secretion are significantly higher in affected patients, pointing a marked increase in intestinal permeability (Gopalakrishnan S et al.,2012).

2.1.2. Type 1 Diabetes Mellitus

Type 1 diabetes mellitus (T1DM) is a chronic autoimmune disorder resulting from the destruction of pancreatic insulin-producing β-cells. Although its pathogenesis is not fully elucidated, studies in both animal models and humans have

demonstrated that intestinal permeability increases prior to T1DM onset (Carratù R et al., 1999).

Pre-diabetic assessments have shown that approximately 50% of T1DM patients exhibit elevated serum zonulin levels. Interestingly, about 25% of first-degree healthy relatives of patients also demonstrate increased zonulin levels (Sapone A et al., 2006). These findings suggest that zonulin may serve as an early biomarker and potential contributing factor in T1DM development.

2.1.3. Inflammatory Bowel Diseases

Elevated intestinal permeability has been shown to play a key role in the pathogenesis of inflammatory bowel diseases (IBD) (Buhner S et al, 2006). Clinical studies indicate that patients with active Crohn's disease exhibit increased serum and fecal zonulin levels, whereas this elevation is less pronounced in ulcerative colitis patients (Malíčková K et al., 2017).

More recent research has reported that zonulin levels are significantly higher in both IBD subtypes compared to healthy controls, and serum zonulin concentrations negatively correlate with disease duration (Caviglia GP et al., 2019).

2.1.4. Multiple Sclerosis

Studies using the experimental autoimmune encephalomyelitis (EAE) model indicate that Zonulin mediated intestinal permeability increases during the early stages of multiple sclerosis (MS) development (Nouri M et al., 2014).

MS patients show enhanced permeability in both the blood-brain barrier (BBB) and intestinal barrier. Imaging studies demonstrate significantly elevated serum zonulin levels in MS patients with BBB disruption. Moreover, initial zonulin concentrations correlate with disease progression in progressive MS, relapsing-remitting MS, they reflect BBB integrity alterations (Camara-Lemarroy CR et al.,2020).

These data suggest that zonulin may modulate both intestinal and BBB permeability, contributing to the gut-brain axis in neuroinflammatory processes.

2.1.5. Obesity

Obesity and associated metabolic disorders-including hypercholesterolemia, type 2 diabetes (T2DM), coronary artery disease, hypertension, and stroke-are linked to chronic inflammation and often correlate with dysregulation of the zonulin pathway (Olszanecka-Glinianowicz M et al., 2011).

Multiple studies report that serum zonulin levels are significantly higher in obese individuals compared to non-obese controls (Kuzma JN et al., 2020). Correlations between zonulin concentrations and total gut bacterial load suggest that microbiotadysbiosis may drive zonulin elevation. Consequently, increased intestinal permeability to endotoxins and associated microinflammation have been implicated in obesity-related pathophysiology (Gharial J et al., 2017).

2.1.6. Irritable Bowel Syndrome

Irritable bowel syndrome (IBS) is another condition associated with increased intestinal permeability (Camilleri M et al., 2007). Specifically, patients with diarrhea-predominant IBS exhibit elevated serum zonulin levels and involvement of protease-activated receptor 2 (PAR2) in the process (Linsalata M et al., 2018, Singh P et al., 2019).

2.1.7. Cancer

Recent evidence suggests that enhanced antigen translocation may contribute to the initiation of certain cancers. Zonulin, as a biomarker of epithelial and endothelial permeability, has been associated with multiple tumor types.

Notably, gliomas and hepatocellular carcinomas have been linked with elevated zonulin levels, which are often considered alongside increased permeability in these malignancies (Díaz-Coránguez M et al., 2013, Wang X et al., 2019).

2.1.8. Neuroinflammatory Disorders

Compromised intestinal barrier function can be assessed via immune responses (IgG, IgA, IgM) against proteins such as occludin and zonulin. Barrier disruption increases the systemic circulation of microbiota-derived molecules, triggering immune activation and cytokine production.

This phenomenon has been reported in various neuroimmune disorders, including chronic fatigue syndrome, autism spectrum disorder, major depressive disorder, and schizophrenia (Ajamian M et al., 2019). Zonulin-mediated permeability increases are thought to contribute to neuroinflammation in these conditions.

3. Conclusion

Zonulin is an important molecule contributing the pathogenesis of many inflammatory processes in the human body related with intestinal permeability. Recent studies focus on the mechanisms of regulation of the relationship between the intestines and the external environment. The stability of intestinal barrier is the key of all systems of the body. Zonulin may be appreciated as a biomarker in the follow up of autoinflammatory diseaseand predicting inflammatory courses both of which are related with damaged intestinal barrier.

Author Contributions

Idea and design: E.T., S.Y.,
Data collection and processing: E.T.,
S.Y. Analysis and interpretation of data: E.T., S.Y.
Writing of significant part of the article: E.T., S.Y.

Conflicts of interest
None.

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