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Editorial

Coeliac disease novel histological quantification

Gluten peptides damage the small bowel intestinal epithelial cells, by generating a harmful immune reaction directed against enterocytes in coeliac disease (CD). The small intestinal inflammatory changes following this immune reaction range from sub-microscopic to severe. Accurate classification and objective evaluation of this spectrum of mucosal abnormalities is a challenging task and has been highly controversial. Immune-epithelial cell analysis and the role of its components like intraepithelial lymphocytes (IELs) [1], intestinal epithelial cells (IECs), and relevant cytokines have been debated but are not very accurate in quantifying the CD histology objectively.

Marsh described the natural history of gluten induced mucosal inflammation [2] and delineated the stages of mucosal injury following the harmful adaptive immune response against gluten in CD. The pathological progression from normal to severe architectural distortion in celiac disease pioneered by Marsh soon became after publication a very famous histological classification for CD. Nevertheless, this was never the aim and purpose of the author since the spectrum of normal to severe changes hardly correlate with clinical presentation in CD patients. A milder histology does not always translate into a milder disease phenotype [3]. Similarly, Marsh 0 describing normal individuals [4], can often be associated with sub-microscopic changes that cause malabsorption [5,6] in some patients. In contrast, a severely distorted mucosa may not cause any symptoms in some patients with silent CD. The matter was complicated further with introduction of Marsh III subdivision into a, b and c. This subdivision was based on a small study and never validated in a larger cohort [7]. Although we never found any difference between the most key cytokines, like IFN-γ produced by IELs in active CD, across this subdivision [1,8], they have been subjectively used and consequently far less attention given to the IECs and gene expression.

In this issue of Computers in Biology and Medicine, Charlesworth and colleagues have published a novel gene expression experiment that in conjunction with histological parameters allows more accurate qualitative assessment of changes in duodenal biopsies([9]). This is a novel initiative that evaluated and endorsed histological classification with relevant gene activations. It is recognised that gene expression differences in purified IECs from duodenal mucosa is a unique approach that brings valuable accuracy in the CD histological interpretation. This qualitative assessment would not only be important in assessing complex treatment progression in individual patients, but it might also have a future potential in differentiation and characterizing the entities with milder enteropathy currently considered under microscopic enteritis [5]. Other quantification modalities described and reported so far have their limitations in proving specific quantification of mucosal changes that correlate with other pathological components of CD.

Gene enrichment related analysis highlights a multitude of interactions including immune response, microbial infections, phagocytosis, intestinal barrier function, metabolism, and transportation [10]. This may, at some point, create a powerful discriminant ability for gene expression in defining the histological changes with higher accuracy [11]. The preliminary evidence is promising for a future that provides accurate histological quantification with the reservation that the Marsh III subdivision used in this study is unsubstantiated and lacked established gene expression signatures. Future genome-wide association (GWA) studies will identify new susceptibility variants implicated in the immense complexity of the tissue reactions in CD. Hopefully, in the not so distant future, we may be able to assess the clinical implications, safety and efficacy of these diagnostic strategies, to enable us to refine these equations and implement them in clinical practice.

References

[1] K. Rostami, M.N. Marsh, M.W. Johnson, et al., ROC-king onwards: intraepithelial lymphocyte counts, distribution & role in coeliac disease mucosal interpretation, Gut 66 (12) (2017) 2080–2086.
[2] M.N. Marsh, Gluten, major histocompatibility complex, and the small intestine. A molecular and immunobiologic approach to the spectrum of gluten sensitivity ('celiac sprue'), Gastroenterology 102 (1) (1992) 330–354.
[3] B. Zanini, F. Caselani, A. Magni, D. Turini, A. Ferraresi, F. Lanzarotto, V. Villanacci, N. Carabellese, C. Ricci, A. Lanzini, Celiac disease with mild enteropathy is not mild disease, Clin. Gastroenterol. Hepatol. 11 (3) (2013 Mar) 253–258.
[4] M.N. Marsh, K. Rostami, What is a normal intestinal mucosa? Gastroenterology 151 (5) (2016) 784–788.
[5] K. Rostami, D. Aldulaimi, G. Holmes, et al., Microscopic enteritis: bucharest consensus, World J. Gastroenterol. 21 (9) (2015) 2593–2604.
[6] A. Sbarbati, E. Valletta, M. Bertini, et al., Gluten sensitivity and 'normal' histology: is the intestinal mucosa really normal? Dig. Liver Dis. 35 (11) (2003) 768–773.
[7] K. Rostami, J. Kerckhaert, B.M. von Blomberg, J.W. Meijer, P. Wahab, C.J. Mulder, SAT and serology in adult coeliacs, seronegative coeliac disease seems a reality, Neth. J. Med. 53 (1) (1998) 15–19.
[8] G. Forsberg, O. Hernell, S. Hammarstrom, M.L. Hammarstrom, Concomitant increase of IL-10 and pro-inflammatory cytokines in intraepithelial lymphocyte subsets in celiac disease, Int. Immunol. 19 (8) (2007) 993–1001.
[9] R. Charlesworth, L.L. Agnew, D. Scott, N.M. Andronicos, Equations defined using gene expression and histological data resolve coeliac disease biopsies within the Marsh score continuum, J. Comput. Biol. (2018).
[10] H. Bragde, U. Jansson, M. Fredrikson, E. Grodzinsky, J. Soderman, Celiac disease biomarkers identified by transcriptome analysis of small intestinal biopsies, Cell. Mol. Life Sci. 75 (23) (2018) 4385–4401.
[11] R.P.G. Charlesworth, L.L. Agnew, D.R. Scott, N.M. Andronicos, Celiac disease gene expression data can be used to classify biopsies along the Marsh score severity scale, J. Gastroenterol. Hepatol. (2018).

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