PBMC FROM A SUBPOPULATION OF CELIAC PATIENTS RESPOND TO GLIADIN WITH INTERLEUKIN-8 PRODUCTION THAT IS CXCR3-DEPENDENT

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Recently we have identified and characterized the chemokine receptor, CXCR3, as a receptor for gliadin. Binding of gliadin to CXCR3 induces a MyD88-dependent activation of the zonulin pathway and a subsequent increase in intestinal permeability.

Aim: Our aim was to study the role of CXCR3 in the immune response in peripheral blood mononuclear cells (PBMC) from healthy donors (HD) and celiac disease (CD) patients after challenge with gliadin.

Methods: PBMC from 21 CD patients on a gluten-free diet and 10 HD were cultured in the presence of pepsin/trypsin-digested gliadin (PTG, 1 mg/mL) for 24 hours. In a subset of wells, PBMC were pre-incubated with blocking anti-CXCR3 monoclonal antibody (10 μg/mL) or its appropriate isotype control (10 μg/mL). Supernatants were analyzed for their content in IL-6, IL-8, IL-10, TNFα and IFNγ.

Results: All cytokines were produced at higher level in CD patients compared to controls, and production of IL-6, IL-10, TNFα and IFNγ was not influenced by blocking of the CXCR3 chemokine receptor. Conversely, gliadin induced IL-8 production only in a subgroup of individuals, namely 30% of healthy controls and 43% of CD patients. Interestingly, gliadin-induced IL-8 secretion was abrogated when CXCR3 was blocked prior to gliadin stimulation in the CD group, but <u>not</u> in the control group. See Table below:

Group	**Non-Responders**		**Group**	**Responders**		
	Medium	**PTG**		**Medium**	**PTG**	**αCXCR3+PTG**
HD (N=7)	1.4±0.1*	2.7±0.1	HD (N=3)	0.3±0.2	98.8±15.2	82.6±11.5
CD (N=12)	4±2.2	2.2±0.2	CD (N=9)	2.2±0.2	179.2±30.2	2.7±0.1**

* IL-8 values are expressed as ng IL-8/1x10^6 PBMC

** P<0.001 compared to CD responders exposed to PTG

Conclusions: Compared to controls, PBMC from CD patients respond to gliadin with production at higher level of IL-6, IL-8, IL-10, TNFα and IFNγ. A subgroup of individuals responds to gliadin with the production of IL-8 that is CXCR3-dependent only in CD patients but not in healthy controls.