Zagreb, 30th of April 2015.

Dear Editors,

I am writing to submit our manuscript entitled “**Differential expressions of ABC Transporters and Cytokines in the inflamed and unaffected tissues in Crohn’s disease”** for consideration for publication in Periodicum Biologorum.

We feel that better understanding of the expression of ABC efflux transporters in the lining of the gastrointestinal tract is of major importance because their expression at different segments of the gut mucosa is not the same. This should be taken into consideration when performing experiments based on evaluation of their expression in inflammatory bowel diseases. Since these transporters can affect the bioavailability of drugs used in the therapy of inflammatory bowel diseases, contribute to gut barrier homeostasis and regulate cellular redox status, we feel that the results of this study could contribute to better understanding of the disease pathogenesis.

The importance of our study raises form the fact that the experiment was conducted on three different Crohn’s disease groups, namely newly diagnosed patients, patients with active disease undergoing therapy and those in remission. The selection of this groups provide not only the new insight into pathological events, but also the influence of therapy introduction and subsequent resolution of inflammation on the expression of efflux transporters, cytokines and their negative regulators, SOCS molecules, in the intestinal tissue samples.

We show that the inflamed intestinal mucosa was depicted by an overall reduction in MDR1 expression irrespective of the disease stage. MRP1 was reduced at the time of diagnosis and normalize to control levels with therapy introduction. BCRP expression was significantly reduced only in treated group. The expression of examined efflux transporters did not differ between defined groups along colon and rectum mucosa. Also, in inflamed intestine mucosa we found a transitory increase in IFN-γ and IL-17A mRNA expression levels in treated group. However, increased IFN-γ, IL-2 and IL-1β mRNA expression were also found in unaffected colon mucosa. Furthermore, for the first time, we analyzed SOCS1 and SOCS3 expression in inflamed and unaffected mucosal tissues at different disease stages and found change in expression that follows the pattern of cytokines expression. However, the levels of SOCS expression imply inadequate STAT pathways regulation.

Our results point to involvement of MDR1 and MRP1 in the pathogenesis of CD, which could be also true for BCRP.

This manuscript, including related data, figures and tables, has not been previously published. It describes original work and is not under consideration by any other journal. All authors approved the manuscript and this submission, and have no competing interests. All authors have made substantial contributions to all of the following: (1) the conception and design of the study, or acquisition of data, or analysis and interpretation of data, (2) drafting the article or revising it critically for important intellectual content, (3) final approval of the version to be submitted. I would like to stress that all authors concur with the submission.

Thank you for receiving our manuscript and considering it for review. We appreciate your time and look forward to your response.

Kind regards,

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