Characterization of non-coding RNA as molecular markers during glucocorticoid treatment in children with inflammatory bowel disease

M. Lucafò[1], A. Di Silvestre[2], S. Martelossi[3], S. Naviglio[3], A. Ventura[1, 3], G. Stocco[4], G. Decorti[1], S. De Iudicibus[3]
[1]Dept of Medicine, Surgery and Health Sciences, University of Trieste, Italy
[2] PhD School in Science of Reproduction and Development, University of Trieste, Italy
[3]Institute for Maternal and Child Health - IRCCS "Burlo Garofolo", Trieste, Italy
[4]Dept of Life Sciences, University of Trieste, Italy

The incidence of inflammatory bowel disease (IBD) is increasing in recent years, in particular in children and adolescent, and it is currently estimated that 20%–30% of patients experience onset of their symptoms under 20 years of age. To date, a curative pharmacological therapy for IBD does not exist: in spite of the introduction in therapy of highly effective biological agents, glucocorticoids (GCs) are still employed to induce remission in moderate to severe IBD, but considerable inter-individual differences in their efficacy and side effects have been reported. Given the high incidence of suboptimal response, associated with a significant number of side effects, that are particularly severe in paediatric patients, the identification of subjects that are most likely to respond poorly to GCs is extremely important. However, the mechanisms of this variability are scarcely understood and there is presently no means to predict the response in advance; in this context, non-coding RNAs (ncRNAs), in particular long non-coding RNAs (lncRNAs) and microRNAs (miRNAs) represent a new and promising field of research.

Recent results obtained in our laboratory suggest a role for the lncRNA growth arrest-specific 5 (GAS5) in modulating GC response in peripheral blood mononuclear cells (PBMCs). GAS5 interacts with the activated GR, preventing its association with GREs, and consequently suppressing its transcriptional activity. We have demonstrated that PBMCs resistant to GCs express higher levels of GAS5 in comparison with good responders, and hypothesized that upregulation of GAS5 could interfere with GR activity, leading to the resistance phenotype observed.

Nineteen IBD paediatric patients (mean age at enrolment 12.8 years, 14 ulcerative colitis and 5 Crohn's disease, 9 males and 10 females) were enrolled at the Paediatric Clinic of IRCCS Burlo Garofolo in Trieste in a prospective study, and treated with prednisone 1 to 2 mg/kg/day for 30 days. Peripheral blood was obtained from these patients at diagnosis (T0) and after 4 weeks of steroid treatment (T4). RNA was extracted from patients' PBMC at T0 and T4, and used to analyze ncRNA profiles.

Patients were classified on the bases of their clinical response into 2 groups: steroid resistant (SR; n=3) and steroid sensitive (SS; n=16). SS subjects were further stratified into steroid dependent subjects (SD; n=7).

GAS5 expression was measured in these patient groups: a significant downregulation of GAS5 was observed in SS group after treatment with GCs in comparison with SR group ($p=0.0128$) and SD ($p=0.0224$).

We hypothesize that, in SR patients, abnormally high levels of Gas5 expression, through the interaction with the DNA binding domain of the activated GR, results in the suppression of GC transcriptional activity, reducing their effectiveness.

If these results are confirmed in a larger number of subjects, GAS5 should be considered a novel pharmacogenomic biomarker useful for the personalization of GC therapy in paediatric IBD and to elucidate molecular pathways that underline these diseases.