Potential role of long noncoding RNA GAS5 in rapamycin-induced reversion of glucocorticoid resistance

M. Lucafò[1,2], V. Bravin[1], A. Tommasini[2], A. Di Silvestre[2], S. Martelossi[2], A. Ventura[1,2], G. Decorti[3], S. De Iudicibus[1,2]

[1]Dept of Medicine, Surgery and Health Sciences, University of Trieste, Italy
[2]Institute for Maternal and Child Health - IRCCS "Burlo Garofolo", Trieste, Italy
[3]Dept of Life Sciences, University of Trieste, Italy

Glucocorticoid (GC) resistance is a major driver of therapeutic failure in immune-mediated diseases and there is presently no means to predict this phenomenon in advance. Recent reports showed that the long noncoding RNA (lncRNA) GAS5 interacts with the GC receptor (GR) DNA-binding domain (DBD) and suppresses GC-induced transcriptional activity. Data published from our laboratory have demonstrated a role for GAS5 in modulating GC response, suggesting that this lncRNA could be considered a marker of GC resistance.
Rapamycin, the inhibitor of mTOR, reverses GC resistance in vitro: we have investigated the association between the GAS5 levels and the effect of methyl-prednisolone (MP) alone and in combination with rapamycin in PBMCs obtained from healthy donors, considering the individual variability in the anti-proliferative efficacy of GCs.
The effect of MP at 250 ng/ml, rapamycin at 100 nM and rapamycin plus MP was determined by [methyl-3H] thymidine incorporation assay on PBMCs proliferation for 72 h. Subjects were divided into two groups based on whether their $I_{250ng/ml}$ values were above the median ($I_{250ng/ml}$ median value 54%; good responders MP_GR) or below (poor responder, MP_PR).
In MP_PR PBMCs the combination of MP with rapamycin enhanced the growth inhibitory effect (median inhibition 91%) compared to rapamycin (58%, $p<0.001$) or MP alone (36%, $p<0.001$), and the same trend was observed in MP_GR (81%; 75%, $p<0.05$; 61%, $p<0.001$). GAS5 expression was measured in the same cells: a significant upregulation of GAS5 was observed in MP_PR group after treatment with MP in comparison with MP_GR ($p=0.0427$). When MP_PR cells were treated with rapamycin plus MP, a GAS5 downregulation was observed to levels not significantly different from MP_GR group. In conclusion, the combination of rapamycin with MP restores GC effectiveness in MP_PR subjects through the downregulation of this lncRNA, confirming the role of GAS5 as a pharmacogenetic marker of GC response.