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Network-based analysis reveals signatures of IgG autoantibodies targeting G protein-coupled receptors in health and disease

Otavio Cabral-Marques[a], Alexandre Marques[a], Lasse Melvær Giil[b], Roberta de Vito[c], Barbara Elizabeth Engelhardt[c], Jalid Sehouli[d], Harald Heidecke[e], Gabriela Riemekasten[a,*]

[a] *Department of Rheumatology and Clinical Immunology, University of Lübeck, Lübeck, Germany*
[b] *Deaconess Hospital, University of Bergen, Bergen, Norway*
[c] *Department of Computer Science, Princeton University, Princeton, NJ, USA*
[d] *Department of Gynecology, Charité University Hospital, Berlin and Tumor Bank Ovarian Cancer Network (TOC), Berlin, Germany*
[e] *CellTrend GmbH, Luckenwalde, Brandenburg, Germany*
[*] *Corresponding author, email: Gabriela.Riemekasten@uksh.de*

Background: Functional antibodies (ab) against G protein-coupled receptors (GPCR) were found in various diseases and partially in healthy individuals. Their role in physiology and in pathophysiology remains to be identified.

Methods: Sera from 952 patients with different rheumatic diseases were analyzed for the presence of ten different anti-GPCR ab by ELISAs. For deeper ab phenotyping, ab levels against 30 different autoantigens including GPCR, growth factors, and growth factor receptors were studied in sera from 491 healthy controls (HC), 84 patients with systemic sclerosis, 91 with Alzheimer's disease, and 207 with ovarian cancer by ELISAs. Spearman's rank correlation coefficients, hierarchical cluster analyses, network mapping and target interactions using STRING and gene ontology (GO) analyses were performed as well as transwell migration assays.

Results: Specific signatures were identified in different autoimmune diseases and in HC. Ab correlations and clusters of correlations were identified in HC, which were specifically affected by age, sex, and autoimmune and non-autoimmune diseases. Network mapping and GO analysis of ab targets displayed multiple associations and a central role of the endothelin receptor type-A (ETAR) in cell migration and chemoattraction. Indeed, the ab were chemoattractive for immune cells, which could be ameliorated by ETAR blockers.

Conclusions: Our data indicate a functional ab network, which is affected by age, sex, and diseases. The network could affect receptor functions and could guide immune cells or their targets via chemoattraction to organs.

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