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Myeloid-derived suppressor cells are good biomarkers of fingolimod efficacy in multiple sclerosis

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Introduction: The increasing number of available treatments for multiple sclerosis (MS) highlights the need for biomarkers for individualized medicine. Fingolimod (FTY720), an oral disease modifying treatment approved for relapsing-remitting MS, acts as a sphingosine-1-phosphate receptor modulator preventing lymphocyte egress from lymphoid tissues. However, it has been described that it promotes the immunosuppressive activity of Myeloid-Derived Suppressor Cells (MDSCs), a cell type which can be used as biomarker of disease severity in MS and of the degree of demyelination and axonal damage extent in its animal model, experimental autoimmune encephalomyelitis (EAE).
Objective/aim: We interrogate whether the abundance of MDSCs at the onset of EAE or prior to start treatment in MS patients can be related to a better response and higher efficacy to fingolimod.
Methods: In EAE, treatment with vehicle or FTY720 was orally administered for 14 days in an individualized manner, i.e. the day wheneach mouse began to develop clinical signs. Peripheral blood from EAE mice was collected previous to treatment and human peripheral blood mononuclear cells (PBMCs) were collected from MS patients at baseline, 6 and 12 months after fingolimod treatment. In both cases, different immune cell populations were analyzed by flow cytometry. According to the clinical response, a patient was considered as responder when met two or more criteria of NEDA-3 12 months after treatment.
Results: MDSC content in the peripheral blood of FTY720 treated animals was associated with a milder EAE disease course with a less demyelination and axonal damage. However, a small proportion of the FTY720 treated mice showed a clinical course similar to vehicles (non-responders), which was invariably associated to a very low abundance of MDSCs prior to treatment initiation. Remarkably, higher MDSC abundance also revealed to be an important parameter to distinguish EAE mice prone to respond to FTY720 with a higher efficacy. Cox regression analysis showed that FTY720 effectiveness was related to MDSC abundance and independent of other clinical or immunological variables. Lastly, a higher MDSC abundance in MS patients at baseline allows the identification of responders to fingolimod treatment after 12 months of follow-up.
Conclusion: In sum, our data indicate that MDSCs may be good biomarkers for fingolimod responsiveness and treatment efficacy in MS.
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