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Abstracts

Articles appearing in the July 2019 issue

Harmful neutrophil subsets in patients with ischemic stroke: Association with disease severity

Objective To better understand the functional state of circulating neutrophils in patients with ischemic stroke (IS) for planning future clinical trials.

Methods We analyzed by flow cytometry activation state of circulating neutrophils and the distribution of neutrophil peripheral subsets in 41 patients with acute IS less than 6 hours before admission and compared them with 22 age-matched healthy controls.

Results Our results demonstrated continuous basal hyperactivation of circulating neutrophils during acute IS, characterized by lower L-selectin expression and higher CD11b expression at the cell surface, increased ROS production by neutrophils, and greater circulating levels of neutrophil elastase. Neutrophil hyperactivation was associated with deregulation of the equilibrium between apoptotic and necrotic. Patients also had higher percentages than controls of the overactive senescent ($CXCR4^{bright}$/$CD62L^{dim}$) neutrophil subset and increased percentage of neutrophils with a reverse transendothelial migration ($CD54^{high}CXCR1^{low}$) phenotype. Importantly, neutrophil alterations were associated with the clinical severity of the stroke, evaluated by its NIH Stroke Scale score.

Conclusion Altogether, our results indicate that during acute IS, the inflammatory properties of circulating neutrophils rise, associated with the expansion of harmful neutrophil subsets. These changes in neutrophil homeostasis, associated with disease severity, may play an instrumental role by contributing to systemic inflammation and to the blood-brain barrier breakdown. Our findings highlight new potential therapeutic approaches of stroke by rebalancing the ratio of senescent to immunosuppressive neutrophils or decreasing reverse neutrophil transmigration or both.

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α4-integrin deficiency in B cells does not affect disease in a T-cell–mediated EAE disease model

Objective The goal of this study was to investigate the role of CD 19^+ B cells within the brain and spinal cord during CNS autoimmunity in a peptide-induced, primarily T-cell–mediated experimental autoimmune encephalomyelitis (EAE) model of MS. We hypothesized that $CD19^+$ B cells outside the CNS drive inflammation in EAE.

Methods We generated $CD19.Cre^{+/-}$ α4-$integrin^{fl/fl}$ mice. EAE was induced by active immunization with myelin oligodendrocyte glycoprotein peptide (MOG_{p35-55}). Multiparameter flow cytometry was used to phenotype leukocyte subsets in primary and secondary lymphoid organs and the CNS. Serum cytokine levels and Ig levels were assessed by bead array. B-cell adoptive transfer was used to determine the compartment-specific pathogenic role of antigen-specific and non–antigen-specific B cells.

Results A genetic ablation of α4-integrin in $CD19^{+/-}$ B cells significantly reduced the number of $CD19^+$ B cells in the CNS but does not affect EAE disease activity in active MOG_{p35-55}-induced disease. The composition of B-cell subsets in the brain, primary lymphoid organs, and secondary lymphoid organs of $CD19.Cre^{+/-}$ α4-$integrin^{fl/fl}$ mice was unchanged during MOG_{p35-55}-induced EAE. Adoptive transfer of purified $CD19^+$ B cells from $CD19.Cre^{+/-}$ α4-$integrin^{fl/fl}$ mice or C57BL/6 wild-type (WT) control mice immunized with recombinant $rMOG_{1-125}$ or $ovalbumin_{323-339}$ into MOG_{p35-55}-immunized $CD19.Cre^{+/-}$ α4-$integrin^{fl/fl}$ mice caused worse clinical EAE than was observed in MOG_{p35-55}-immunized C57BL/6 WT control mice that did not receive adoptively transferred $CD19^+$ B cells.

Conclusions Observations made in $CD19.Cre^{+/-}$ α4-$integrin^{fl/fl}$ mice in active MOG_{p35-55}-induced EAE suggest a compartment-specific pathogenic role of $CD19^+$ B cells mostly outside of the CNS that is not necessarily antigen specific

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S. Engel, M. Friedrich, M, Muthuraman, et al. 2019;6:e595. doi.org/10.1212/NXI.0000000000000595

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Dimethyl fumarate–induced lymphopenia in MS due to differential T-cell subset apoptosis

M. Ghadiri, A. Rezk, R. Li, et al. 2017;4:e340. doi.org/10.1212/NXI.0000000000000340

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E. Staun-Ram, E. Najjar, A. Volkowich, A. Miller. 2018;5:e508. doi.org/10.1212/NXI.0000000000000508

