Immunology of stroke: from animal models to clinical trials

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Over recent years, fascinating novel aspects in stroke immunology have been elucidated, examples being alternative immigration routes of hematogenous immune cells, mechanisms of immune-cell intercellular communication, and the epigenetic regulation of inflammation in stroke. The scope of this Special Collection is to keep the readers updated with novel insights in the fast-developing field of stroke immunology.

Acute ischemic stroke evokes an immediate inflammatory response, which involves complex cellular and molecular mechanisms. Among the cellular components, local microglia occupy the pole position and are activated within hours after stroke onset.[1] This early microglial response is primed by damage-associated molecular patterns (DAMPs), which are released from dying neuronal and non-neuronal brain cells and activate microglia and perivascular endothelial cells *via* pattern recognition receptors similar to toll-like receptors (TLRs) (Gülke *et al.*). In a comprehensive review, Gülke and colleagues discuss destructive and protective properties of the most important DAMPs following stroke, with special emphasis on the interplay between DAMPs and microglia. Subsequent to the early microglial activation, an army of hematogenous immune cells with predominantly detrimental effects invades the ischemic brain parenchyma.[1–3] In experimental models of acute stroke, mice devoid of T cells and mice with impaired leukocyte trafficking had smaller infarct volumes and better functional outcomes.[2–4] However, due to the high risk of systemic infections, the depletion of immune cells is not applicable in the clinical setting, and studies evaluating the effects of antibodies, which inhibit the transendothelial immigration across the compromised blood–brain barrier, such as fingolimod, natalizumab and enlimomab, yielded conflicting results.[5–8] The latter might be explained by recent revolutionary findings demonstrating that a majority of hematogenous immune cells invade the brain *via* alternative immigration routes like the choroid plexus and meninges, which exhibit a different expression pattern of leukocyte adhesion molecules.[9,10] In a comprehensive review, Benakis and colleagues[9] detail these alternative immune-cell immigration routes and potential implications for the development of future stroke therapies. Enzmann and colleagues, who observed that neutrophils mostly accumulate within the neurovascular unit and the subarachnoid space, but do not invade into the brain parenchyma, suggest that neutrophils cause neuronal cell death by clogging drainage pathways and subsequent accumulation of toxic metabolites rather than through direct cytotoxic effects. In contrast, Hermann and colleagues visualized the migration of neutrophils into ischemic brain parenchyma by intravital two-photon microscopy combined with conventional immunohistochemistry and propagated direct cytotoxic effects. For the study of dynamic interactions of neutrophils with brain parenchymal cells, Hermann and colleagues suggest the use of transgenic mice, such as mice expressing the red fluorescent reporter protein tdTomato under the granulocyte-specific Ly6G locus. The use of inflammatory molecules as biomarkers for an early diagnosis of stroke is discussed by Ramiro *et al.*, whereas Fanning and colleagues characterize the prevalence of inflammatory molecules in perioperative infarction, and Dzyubenko and colleagues focus on the interplay between neuroinflammatory cascades and extracellular matrix remodeling in the ischemic brain.

Apart from immune-cell activation and immigration, the involvement of neurotransmitter signaling in modulation of neuroinflammation has emerged as another topic of interest. One of the principal neurotransmitters in the central nervous system is dopamine, which is constantly released in the brain and is physiologically involved in motor control and

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higher brain functions. Interestingly, immune-cell populations express different dopamine-receptor subtypes, with an expression pattern influenced by the immune cells' activation status (Talhada *et al.*). As detailed by Talhada and colleagues, exposure to dopamine or dopamine-receptor agonists generally decreases devastating effects of immune cells, whereas a reduction of dopaminergic inputs facilitates a pro-inflammatory state. Apart from dopaminergic signaling, cholinergic, purinergic and glutamatergic signaling are also involved in the modulation of neuroinflammation (Martin *et al.*). In a thorough review, Martin and colleagues evaluate the suitability of cholinergic, purinergic and glutamatergic agents as biomarkers for neuroinflammation and as treatments to attenuate the inflammatory response following stroke. Further hopeful treatment strategies are presented by Dreikorn *et al.* The concept of thromboinflammation, which describes the pathological link between thrombus formation and inflammation in the development of ischemic stroke, prompted Dreikorn and colleagues to systematically review the evidence of immunotherapeutic agents approved for multiple sclerosis in preclinical and clinical stroke studies. Their systematic review of the literature yielded 5 clinical and 47 preclinical trials, mostly showing beneficial effects (Dreikorn *et al.*). Difficulties in translating those promising immune-modulatory strategies from bench to bedside are outlined by Drieu *et al.* Immunological and nonimmunological effects of stem-cell-derived extracellular vesicles on the ischemic brain are discussed in an intriguing review by Doeppner *et al.* In an Original Research contribution, Luger and colleagues present the effects of either fingolimod or beta-adrenoceptor blockade on glucose tolerance and cerebral ceramide metabolism in a mouse model of transient middle-cerebral-artery occlusion (tMCAO).

Although most articles on stroke focus on the inflammatory response afterwards, inflammation may also be a primary cause, as it is the case in primary angiitis of the central nervous system (PACNS). PACNS accounts for 3–5% of strokes in patients aged $<$ 50 years and is associated with particularly high relapse rates and mortality rates (Beuker *et al.*). The identification of PACNS mimics is often challenging, and large randomized controlled trials on treatment regimens are lacking. A comprehensive overview of existing data on diagnostics, differential diagnoses and treatments of this devastating disease is provided by Beuker *et al.*

Despite optimal stroke care, there remain remarkable differences in the extent of damage induced during stroke between patients. Over recent years, these interindividual variations in susceptibility and vulnerability to cerebral ischemia have drawn increasing attention toward the role of epigenetics in stroke pathophysiology. Ng and colleagues highlight the contribution of epigenetic mechanisms to postischemic neuroinflammation and neuronal cell death and explain how inflammatory mediators can be regulated in an epigenetic context through deoxyribonucleic acid methylation, histone modifications and microribonucleic acids. Ng and colleagues discuss approaches to epigenetic interventions for stroke, involving not only epigenetic-related drugs but also positive lifestyle practices such as dietary restrictions and healthy eating.

In summary, our Special Collection gathers substantial contributions from leading laboratories working in the fields of stroke and neuroinflammation, providing fascinating insights into the most recent developments in the rapidly expanding field of stroke immunology.

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Conflict of interest statement

The authors declare that there is no conflict of interest.

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