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EDITORIAL

Neuroinflammation in neurodegeneration: role in pathophysiology, therapeutic opportunities and clinical perspectives

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Accumulating evidence support that chronic innate neuroinflammation mediated by microglia and astrocytes is a common feature across neurodegenerative disorders, including Alzheimer's disease (AD), frontotemporal dementia (FTD), Parkinson's disease (PD) and amyotrophic lateral sclerosis (ALS), and play a complex role in their pathophysiology. Whereas in healthy conditions microglia display key beneficial functions that are crucial for maintaining CNS homeostasis, their chronic activation in neurodegeneration results in their altered functionality, which is thought to ultimately play an instrumental detrimental role in disease pathogenesis. Strategies targeting such neuroinflammatory processes are currently a strongly and rapidly emerging field of research in the quest for innovative therapeutic approaches in AD and other neurodegenerative disorders. In this special issue gathering key experts and opinion leaders in the field, authors provide overviews focusing on the cellular and molecular bases of neuroinflammatory processes in neurodegeneration, their complex detrimental and beneficial roles in disease pathophysiology, and their growing and promising interest as potential targets for innovative therapeutic approaches as well as new molecular imaging biomarkers of relevant clinical interest.

In a first review, Guillot-Sestier and Town (2017) discuss the immunopathological similarities and underlying common neuropathological processes shared by neurodegenerative disorders, including AD, PD, ALS, and prion disease. Among these, they address the contribution of exosomes to pathogenic protein accumulation and spreading as well as their immune modulatory activity, receptor-mediated innate immune activation of mononuclear phagocytes and astrocytes, and complement pathway activation. Importantly, the authors discuss the complex detrimental role of key anti-inflammatory mediators in neurodegeneration, and highlight the concept that aberrant innate immune pathways can be targeted for return to homeostasis, in the perspective of rewiring cerebral innate immunity and coaxing mononuclear phagocytes into clearing neurotoxic misfolded proteins.

A series of three reviews then subsequently focuses on selected inflammatory pathways emerging as key instrumental players in the pathophysiology of neurodegeneration and other neuroinflammatory disorders. Dansokho and Heneka (2017) discuss recent findings regarding the role of Toll-like receptors and NOD-like receptors signaling and inflammasomes activation in AD. They highlight the critical role of these pathways in microglia-mediated neuroinflammatory processes in the course of AD pathogenesis, and underline their potential as valuable therapeutic targets in such neurodegenerative disorders. Mendiola et al. review recent advances of our understanding on the multifaceted roles of proinflammatory cytokine IL-1β in perpetuating immune responses and contributing to disease severity in a variety of CNS disorders, including neurodegenerative diseases, multiple sclerosis, traumatic brain injury, and diabetic retinopathy (Mendiola and Cardona 2017). Then, Taylor et al. (2017) address the complex role that type-I interferons (IFNs) play in the control and regulation of neuroinflammation in chronic neurodegeneration. Authors highlight that the complexity of type-I IFN signaling together with the differential effects it has in the central and peripheral nervous systems, ultimately lead to different outcomes with both beneficial and detrimental impacts. Yet, prolonged type-I IFN exposure in the CNS may possibly contribute to promote the pathophysiological process in several neurodegenerative disorders, including AD in which type-I IFN signaling may act as a critical modulator of disease-promoting neuroinflammatory processes.

In an another review, Baufeld et al. (2017) then go on by giving a broad overview of the current knowledge on the

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differential contributions of resident microglia and peripherally derived mononuclear phagocytes in the common neurodegenerative diseases AD, PD, and ALS, as well as multiple sclerosis, which may be regarded as a combination of inflammatory processes and neurodegeneration. Authors summarize and discuss common and newly described markers for distinguishing resident microglia and infiltrating monocytes, and how their expression profiles change in neurodegenerative diseases. They extensively review experimental studies in mouse models as well as clinical data addressing the respective contribution of both cellular populations in each of the aforementioned neurodegenerative disorders.

Subsequently, Franco Bocanegra et al. (2017) elegantly address the key question of the relevance of AD-like mouse models with respect to aging- and disease-associated innate neuroinflammation. The authors review the prominent similarities and differences in neuroinflammatory processes and microglia, regarding genetics, morphology/phenotypes, and functionality, between human AD and experimental mouse models. They highlight the key importance of particularly taking into account the limitations of these models when interpreting experimental findings on neuroinflammatory processes and their role in disease pathophysiology. This will remain a crucial point for better translating such preclinical data into clinically relevant pathophysiological processes and potential therapeutic approaches.

Finally, Lagarde et al. (2017) provide an extensive overview of the current state-of-art of in vivo PET imaging of neuroinflammation, as well as available and emerging MRI-based alternative approaches. Authors describe the most widely used PET tracers targeting the 18 kDa translocator protein (TSPO) as the main current target, the methodological issues in tracer quantification, and summarize the results obtained by TSPO PET imaging in AD, as well as AD-associated neurodegenerative disorders, psychiatric disorders and aging. Interestingly, they question the meaning of PET imaging data in the context of a highly multifaceted role of neuroinflammatory processes in neurodegeneration. Authors highlight that PET imaging of neuroinflammation is a promising approach, which needs further development for better deciphering the complex role of neuroinflammatory processes in the pathophysiology of AD, as well as for monitoring the clinical effect of new therapeutic strategies.

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