

Promising Targets and Strategies to Control Neuroinflammation (Part II)

Neuroinflammation is the condition in which inflammation occurs in the central nervous system (CNS: brain and spinal cord), leading to the activation of microglia and astrocytes. Its role in several central pathologies is nowadays well-known, including neurodegenerative diseases like Alzheimer's disease (AD), Parkinson's disease (PD), multiple sclerosis (MS) and amyotrophic lateral sclerosis (ALS) [1]. In fact, neuroinflammation has the role of restoring homeostasis in the CNS when an injury occurs. On the contrary, sustained inflammation is detrimental, and this typically occurs in and characterizes neurodegenerative diseases. The formation of protein aggregates distinctive to neurodegenerative diseases is one of the stimuli that exacerbate neuroinflammation [2]. Thus, searching for targets involved in the control of the neuroinflammatory condition in these still incurable diseases continuously attracts the scientific community's attention. In particular, several enzymes and receptors have been investigated for their role in neuroinflammation and neurodegeneration. In this thematic issue, promising targets and their ligands are discussed with strategies to develop entities able to control neuroinflammation.

In particular, in this second part of the thematic issue, the discussed targets by eminent research groups are G protein-coupled receptors and the mitochondrial translocator protein TSPO. The first contribution, "A_{2A} Adenosine Receptor Antagonists and their Potential in Neurological Disorders" by Lambertucci *et al.*, highlights the neuroprotective effects mediated by the A_{2A} adenosine receptor antagonists summarizing most relevant and promising compounds along with their preclinical and clinical studies in neuroinflammation related diseases [3].

The second contribution, titled "Interplay Between Endocannabinoid System and Neurodegeneration: Focus on Polypharmacology," by Seghetti *et al.* is focused on the most recent studies evaluating the role of cannabinoids in neurodegenerative diseases, especially on the potential for a multitarget strategy [4].

The third contribution, titled "Translocator Protein 18-kDa: A Promising Target to Treat Neuroinflammation-related Degenerative Diseases," by Tremolanti *et al.* reviews recent findings on the potential immunomodulatory effects of TSPO ligands against neuroinflammation, taking into consideration some pathologies of the nervous system in which inflammatory events are crucial for the onset and progression of the disease [5]. The last contribution, titled "Essential Principles and Recent Progress in the Development of TSPO PET Ligands for Neuroinflammation Imaging," by Viviano *et al.* focuses on TSPO. This review discussed the design and development of TSPO PET ligands useful for assessing active gliosis associated with brain lesions following injury or disease [6].

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REFERENCES

- [1] Kwon, H.S.; Kho, S-H. Neuroinflammation in neurodegenerative disorders: the roles of microglia and astrocytes. *Transl. Neurodegener.*, **2020**, *9*(1), 42.
- [2] Currais, A.; Fischer, W.; Maher, P.; Schubert, D. Intraneuronal protein aggregation as a trigger for inflammation and neurodegeneration in the aging brain. *FASEB J.*, **2017**, *31*(1), 5-10.
- [3] Lambertucci, C.; Marucci, G.; Catarzi, D. Colotta, V.; Francucci, B.; Spinaci, A.; Varano, F.; Volpini, R. A_{2A} Adenosine Receptor Antagonists and their Potential in Neurological Disorders. *Curr. Med. Chem.*, **2022**, *29*(28), 4780-4795.
- [4] Seghetti, F.; Gobbi, S.; Belluti, F.; Rampa, A.; Bisi, A. Interplay Between Endocannabinoid System and Neurodegeneration: Focus on Polypharmacology. *Curr. Med. Chem.*, **2022**, *29*(28), 4796-4830.
- [5] Tremolanti, C.; Germelli, L.; Barresi, E.; Da Pozzo, E.; Simorini, F.; Castellano, S.; Taliani, S.; Da Settimo, F.; Martini, C.; Costa, B. Translocator Protein 18-kDa: A Promising Target to Treat Neuroinflammation-related Degenerative Diseases. *Curr. Med. Chem.*, **2022**, *29*(28), 4831-4861.
- [6] Viviano, M.; Barresi, E.; Siméon, F.G.; Costa, B.; Taliani, S.; Da Settimo, F.; Pike, V.W.; Castellano, S. Essential Principles and Recent Progress in the Development of TSPO PET Ligands for Neuroinflammation Imaging. *Curr. Med. Chem.*, **2022**, *29*(28), 4862-4890.

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