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"Neuroinflammation in epilepsy: mechanisms and therapeutic perspectives"



Prof. Annamaria Vezzani - The Mario Negri Institute for Pharmacological Research, Milano, Italy

The lack of treatments which can prevent epilepsy development or improve disease prognosis represents an unmet and urgent clinical need. The development of such drugs requires a deep understanding of the mechanisms underlying disease pathogenesis. In the last decade, preclinical studies in models of acute seizures and of chronic epilepsy highlighted that neuroinflammation arising in brain areas of seizure onset and generalization is a key contributor to neuronal hyper-excitability underlying seizure generation. Microglia and astrocytes are pivotal cells involved in both the induction and perpetuation of the inflammatory response to epileptogenic injuries or seizures; other cell contributors are neurons, cell components of the blood brain barrier and leukocytes.

From the clinical standpoint, neuroinflammation is now considered an hallmark of epileptogenic *foci* in various forms of focal onset pharmacoresistant epilepsies. Moreover, pharmacological studies in animal model with drugs targeting specific inflammatory molecules, and changes in intrinsic seizure susceptibility of transgenic mice with perturbed neuroinflammatory mechanisms, have demonstrated that neuroinflammation is not a bystander phenomenon but has a pathogenic role in seizures, cell loss and neurological comorbidities.

Understanding the role of neuroinflammation in seizure pathogenesis is instrumental for a mechanism-based discovery of selective therapies targeting the epilepsy causes rather than its symptoms, thereby allowing the development of novel disease-modifying treatments. Notably, clinical translation of laboratory findings may take advantage of anti-inflammatory drugs already in medical use for peripheral autoinflammatory or autoimmune disorders.

I will report key preclinical and clinical findings supporting a role for brain inflammation in the pathogenesis of seizures. I will also highlight the emerging proof-of-concept studies showing signs of clinical efficacy of target-specific anti-inflammatory interventions in epilepsies of differing etiologies. I will discuss the need for biomarkers and novel clinical trial designs for anti-inflammatory therapies that have a mechanism of action very different than standard antiepileptic drugs.