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Chapter 12

Febrile status epilepticus-related epilepsy: Neuroinflammation and epigenetics

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Chapter outline

Introduction: The complex origins of febrile status epilepticus (FSE)

As discussed elsewhere in this volume, febrile seizures (FS) are the most common seizure type in infants and young children and are typically short and benign. However, when FS last over 30 min, they are considered febrile status epilepticus (FSE) and portend risk of significant acute and long-term neurological consequences [1]. FSE is not associated with active brain infection and is distinguished from new-onset refractory status epilepticus (NORSE) and febrile infection-related epilepsy syndrome (FIRES) [2,3]. Whereas FSE is

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less common than simple FS, it accounts for 5%–9% of all FS, involving over 25,000 children yearly in the USA [4–6]. Because of its potential impact, an understanding of the origin and consequences of FSE, including neuroinflammatory mechanisms, is imperative.

It is often difficult to separate the relative contribution of genetics and environmental factors in the development of FSE. The former is highlighted by Dravet syndrome, often resulting from a mutation in SCN1A, a gene encoding the alpha subunit of the voltage-gated sodium channel $Na_V1.1$. A long FS or FSE commonly prompts the diagnosis of Dravet syndrome during the first months of life [7,8]. Other mutations may provoke FSE [9], and familial associations indicate a genetic component in many infants and children with FS and FSE [10]. Conversely, a majority of children with FSE have no family history of FSE and a normal prior development, suggesting that environmental factors may contribute to FSE onset. Animal models enable controlled studies that delineate the relative contributions of genetic and environmental factors, and the role of neuroinflammatory mediators in both mechanisms, as discussed in detail in the chapters by Reid, Chen, Henshall, and Kloc in this volume. Indeed, both genetic and environmental factors likely contribute to FSE with differing importance in each child.

Does FSE lead to epilepsy or adverse cognitive outcomes?

Whereas the short-term outcome of FSE is good [11,12], long-term outcomes are more guarded: the risk of epilepsy increases to 30%–40% [13,14]. Notably, whereas the risk of epilepsy is higher in individuals with abnormal development at the time of the FSE, the increased risk (estimated at 14%) [15–17] impacts also children with normal development and no evidence of brain disease and includes generalized [13] or temporal lobe epilepsies (TLE) [18–20]. TLE is often difficult to control with antiseizure medications, and ~30% of patients do not achieve seizure freedom even with optimal management [21]. In addition, emerging information supports deleterious influences of FSE on cognitive function [22]. These facts underlie the importance of understanding the mechanisms for FSE-related epilepsy, because they hold the key for preventing FSE-induced proepileptogenic processes. Experimental models can demonstrate direct causal relationships as well as identify the responsible mechanisms. Several models of FSE have been reported in both mice [23,24] and rats [25–30]. Notably, limbic epilepsy arises after experimental FSE (eFSE) in otherwise normal mice and rats [24,27,31,32], allowing for investigation into the potential mechanisms by which FSE promotes epilepsy, including neuroinflammatory processes.

Neuroinflammation is inherent in the generation of fever and febrile seizures

Neuroinflammation is a response of the brain to threats or insults such as infection, stress, and seizures. This response mainly engages neurons, microglia,

and astrocytes to synthesize and release molecules with inflammatory properties. Inflammatory molecules are inherently involved in the generation of fever [33,34] as well as in the development of FS [35–37]. Two major signaling pathways may be involved in the generation of seizures during fever. First, mice lacking interleukin-1β (IL-1β) receptor type 1 (IL-1R1) display a higher temperature threshold to develop FS than wild-type mice [38], indicating the need for the IL-1β signaling cascade in this hyperexcitability. Second, IL-1β and tumor necrosis factor (TNF) are induced in response to lipopolysaccharide (LPS) administration to immature rats, which promotes seizures in the presence of subthreshold doses of kainic acid [30,39] (see additional information in the chapter by Pittman et al.).

Neuroinflammation is key to the impact of FSE on brain function and hyperexcitability

Neuroinflammation contributes not only to the generation of FS and FSE, but also to the processes resulting from FSE that may culminate in increased vulnerability to epilepsy and cognitive deficits (Fig. 1). This notion is supported both by work in animal models and by the increased levels of inflammatory cytokines and related modulators detected in brain tissue removed from patients with epilepsy [40–44].

The expression and function of numerous constituents of neuroinflammation are modulated in children and rodents experiencing FSE. In children, increased levels of cytokines and chemokines were measured in the plasma and cerebrospinal fluid (CSF) following FSE, and these included TNF, CXCL9, CXCL10, CXCL11, and CCL19. Levels were higher compared to both children with no fever and children who have experienced nonfebrile status epilepticus or chronic seizures [45–47]. More recently, the FEBSTAT study documented elevations of several cytokines, including IL-6 and IL-8 in serum. Remarkably, levels were augmented specifically in serum of children with MRI signal abnormalities who are at greater risk of subsequent epilepsy, supporting a role of inflammatory modulators as both markers and contributors to epileptogenesis [14,48]. In immature rodent models, induction of inflammatory processes by experimental (e)FSE was centered on amygdala, hippocampus, and cortical regions [49,50]. Augmented expression of neuroinflammatory molecules included COX2, TNF, IL-1β, and IL-1R1 [50], as well as markers of glia activation and evidence of breakdown of the blood-brain barrier (BBB) [51].

Of interest, in eFSE, as well as other epileptogenesis models, neuroinflammatory changes often start within minutes of the seizure insult, and increased expression of inflammatory cytokines is also rapid, apparent already at 1 h after the end of eFSE [27,50]. This rapid time course is both a boon and a problem in potential intervention strategies, offering the promise of interfering early in the origin of inflammatory signaling cascades, rather than the need to interfere with the numerous ramifications of multiple interacting signaling pathways further downstream.

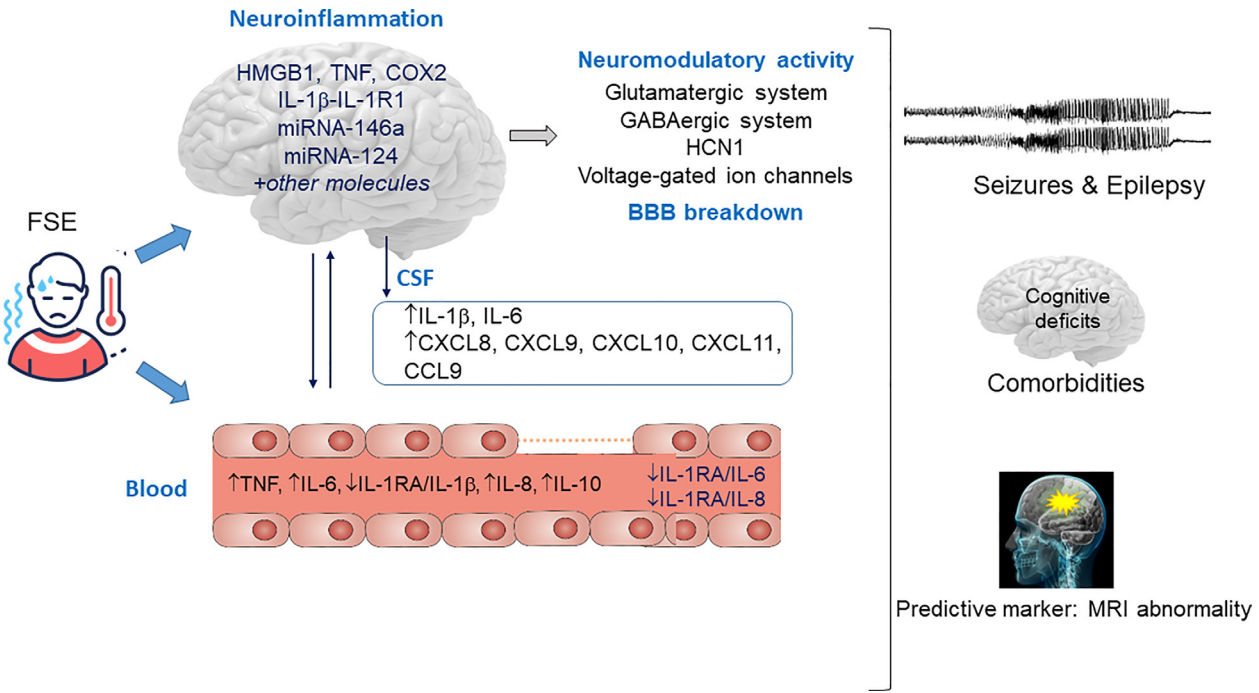

FIG. 1 Inflammatory molecules are involved in the mechanisms underlying fever and febrile seizure generation. FS/FSE sustains brain inflammation, involving production of inflammatory mediators by resident cells (e.g., neuroinflammation). These inflammatory molecules can modify the function of receptor-operated and voltage-gated ion channels implicated in neuronal excitability, thus resulting in cellular dysfunction. Neuroinflammation contributes also to increased BBB permeability. These phenomena alter synaptic transmission, enhance neuronal excitability, and reduce seizure threshold, thus contributing to epileptogenesis and potentially to neurological comorbidities. Increased levels of cytokines and chemokines are measured in blood and cerebrospinal fluid (CSF) after FSE and may have a potential role as predictive markers. Accordingly, changes in selected inflammatory molecules (*highlighted in blue*) are predictive of acute MRI signal abnormalities after FSE, which in turn may predict a greater risk of subsequent epilepsy.

Neuroinflammation in the mechanisms of seizures is involved in changes in seizure threshold likely determined by the neuromodulatory-like functions of various inflammatory molecules, chiefly cytokines and chemokines. In fact, these molecules can rapidly modify, by posttranslational mechanisms, the function of both receptor-operated and voltage-gated ion channels which are implicated in neuronal excitability [52]. Notable examples are the ability of IL-1β to reduce GABAA receptor-mediated currents by activating protein kinase C [53]. Moreover, IL-1β has been implicated in the effect of LPS to reduce HCN1-mediated Ih currents measured in distal dendrites of CA1 pyramidal cells [54]. This is due to modifications in HCN channel trafficking along the dendrites and might have relevance for cognitive deficit and hyperexcitability in FSE and epilepsy [55] (Fig. 1).

Several major inflammatory signaling cascades are implicated in epileptogenesis that may follow FSE

Proepileptogenic insults commonly provoke the subcellular translocation of the damage-associated molecular pattern (DAMP) molecule the high-mobility group box 1 (HMGB1) and its release from brain cells [40]. HMGB1 transport from the nucleus to neuronal dendrites takes place rapidly following eFSE [49] and may influence inflammatory mediators on surrounding cells by binding to Toll-Like receptors (TLRs) and receptors for advanced glycation end products (RAGE) [44,56–59]. Receptor binding, in turn, activates microglia and astrocytes and initiates large-scale inflammatory responses [49,50,56,60–63]. Indeed, structural and molecular changes in microglia and astrocytes occur rapidly following eFSE.

The cytokine IL-1β and its complex signaling cascade are widely implicated in eFSE-related epileptogenesis. IL-1β expression is augmented in neurons and astrocytes in hippocampus of rodents during eFSE. The cytokine is both proconvulsant and proepileptogenic, as its injection into hippocampus increased acute seizures in rodents exposed to intracerebral kainic acid or bicuculline [64,65]. Further, blocking the cytokine's receptor, IL-1R1, or inhibition of caspase 1 to block IL-1β biosynthesis reduced both acute and spontaneous seizures in rodents [66–71]. Notably, the signaling mechanisms of IL-1β and HMGB1 may converge, as both activate common intracellular signaling pathways upon interaction with their respective IL-1R1 and TLR4 [72,73]. The downstream signaling molecules activated by TLR4 and IL-1R1 are poised to initiate long-lasting changes in neurons and glia, because they lead to transcriptional regulation of multiple genes controlled by the transcription factors NF-κB and AP-1. This connection of the initial neuroinflammatory activation with enduring transcriptional changes provides a mechanism for a persistent proepileptogenic state [74,75].

The arachidonic acid-prostanoid cascade, and especially COX2, an inducible enzyme involved in the synthesis of prostaglandins from arachidonic

acid, is rapidly activated by FSE. This is important, because selective inhibition of COX2 in mice increased seizure threshold for chemical convulsants. Following eFSE, mRNA levels of COX1, COX2, the three prostaglandin E synthase enzymes (cPGES, mPGES1, and mPGES2), as well as the prostaglandin E2 (PGE2) receptors (EP1, EP2, EP3α, EP3ß, EP3γ, EP4) were measured. Remarkably, increased expression was selective to constituents of the PGE2 pathway culminating in the EP receptor, namely COX2, EP2, EP3ß, and EP3γ, as observed at 24 h. This selective pathway has been an exciting therapeutic target for neuroprotection and for preventing cognitive deficits [76–80], because blocking the general COX2 pathway has had little effect in rodent models of status epilepticus [42,51,81].

An important link between brain insults including SE and FSE and subsequent epilepsy comprises breakdown and deficits in the function of the BBB [82–84]. The interaction of BBB disruption and neuroinflammation is bidirectional: artificial breakdown of BBB initiates neuroinflammatory processes, chiefly including TGF-β signaling [85–87]. In addition, activated astrocytes and microglia may incite BBB degradation [40,88]. A prominent role for BBB disruption has been demonstrated in humans [82] and in experimental animal models [40,85,89]. Notably, recent work has shown evidence for BBB disruption following experimental FSE [51].

microRNAs: A link between neuroinflammation and epigenetics

The neuroinflammatory response described earlier (as well as other inflammatory pathways) requires both neuronal and glial involvement and an intercellular neuronal-microglial-astroglial communication [57,90–96]. microRNAs (miRNAs) are strong candidates for mediating this communication because they are released from diverse cell types and can be taken up by other cells, for example, via extracellular vesicles (ECVs). ECV may be formed in one cell type, are released into extracellular spaces, and enter and influence other cell types [97–102]. ECV miRNA content is influenced by prolonged seizures [103–105]. Importantly, miRNAs regulate protein translation by repressing their target mRNAs. Thus, they induce large-scale changes in the gene pool translated, a potential key contributor to epileptogenesis. More specifically, miRNAs may regulate neuroinflammatory genes [99,106,107]. Indeed, several major classes of miRNA have been identified in human tissue resected from patients with epilepsy [108]; they mitigate epileptogenesis in several animal models [61,109–111] and constitute a focus of current therapeutic strategies [99,112,113].

In the context of FSE, the abundant neuronal miRNA-124 plays a dual, complex role in neuron-glia interaction [114,115] and in the regulation of transcriptional changes that promote epileptogenesis [74,75]. miRNA-124 levels were drastically reduced within hours after eFSE, and this reduction had dual and opposing effects. First, it enabled upregulation of the transcriptional repressor neuron-restrictive

silencing factor (NRSF), a gene that was originally described in nonneuronal tissues where it suppressed neuron-specific genes [116,117]. In mature neurons, seizures, including FSE, increased NRSF protein levels and activity [118–121] via miRNA-124-mediated mechanisms [74]. Augmented NRSF functions repressed a subset of critical neuronal genes, leading to both proepileptogenic changes and deficits in memory [121,122]. Blocking NRSF binding to chromatin during a few days following FSE rescued the cognitive performance of eFSE rats [123]. Thus, the reduction in miRNA led to neuronal changes that promoted epileptogenesis. By contrast, neuronal miRNA-124 robustly activates microglia provoking major neuroinflammatory processes [74], and the reduction in miR124 levels following eFSE attenuated these effects and hence was antiepileptogenic. The complex dual role of miRNA124 in FSE-related epileptogenesis does not likely position this molecule as a viable therapeutic target [74,75,121–123].

Neuroinflammatory processes as therapeutic targets for prevention of FSE-related epileptogenesis

The previous paragraphs provide strong support for a role of neuroinflammation in insult-related epilepsy in general and in the proepileptogenic events that follow FSE. Therefore, several intervention strategies have targeted specific neuroinflammation pathways as well as broad antiinflammatory agents. For examples, a selective inhibitor of caspase 1 (VX09-765-401), the synthetic enzyme for IL-1β, has shown a beneficial effect on seizure recurrence that persisted for a few weeks after drug discontinuation [124]. Notably, overwhelming cross-talk and homeostatic interactions among the different neuroinflammatory signaling cascades prompted broad antiinflammatory interventions, including glucocorticoids [125,126] and immunoglobulins [127,128], that have been applied in humans with epilepsy. In the context of FSE, the general antiinflammatory agent dexamethasone, employed within hours of the insult in an animal model, significantly attenuated both proepileptic spike series on EEG and eFSE-induced BBB disruption [51]. Application of such disease-modifying antiinflammatory approaches to infants and children with FSE awaits future studies.

In conclusion, neuroinflammation contributes intrinsically to the generation of fever-related seizures in children. Several neuroinflammatory cascades are involved in the mechanisms of pathological changes that follow FSE, which may lead to epilepsy and/or cognitive deficits. Increasing information on the nature of proepileptogenic inflammatory changes in humans and a broad range of experimental model should enable harnessing of this information into tractable therapeutic strategies.

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Further reading

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