

# Neural Regeneration Research

September 2022,  
Volume 17, Number 9

## Repurposed anti-cancer epidermal growth factor receptor inhibitors: mechanisms of neuroprotective effects in Alzheimer's disease

Page 1913

ISSN 1673-5374

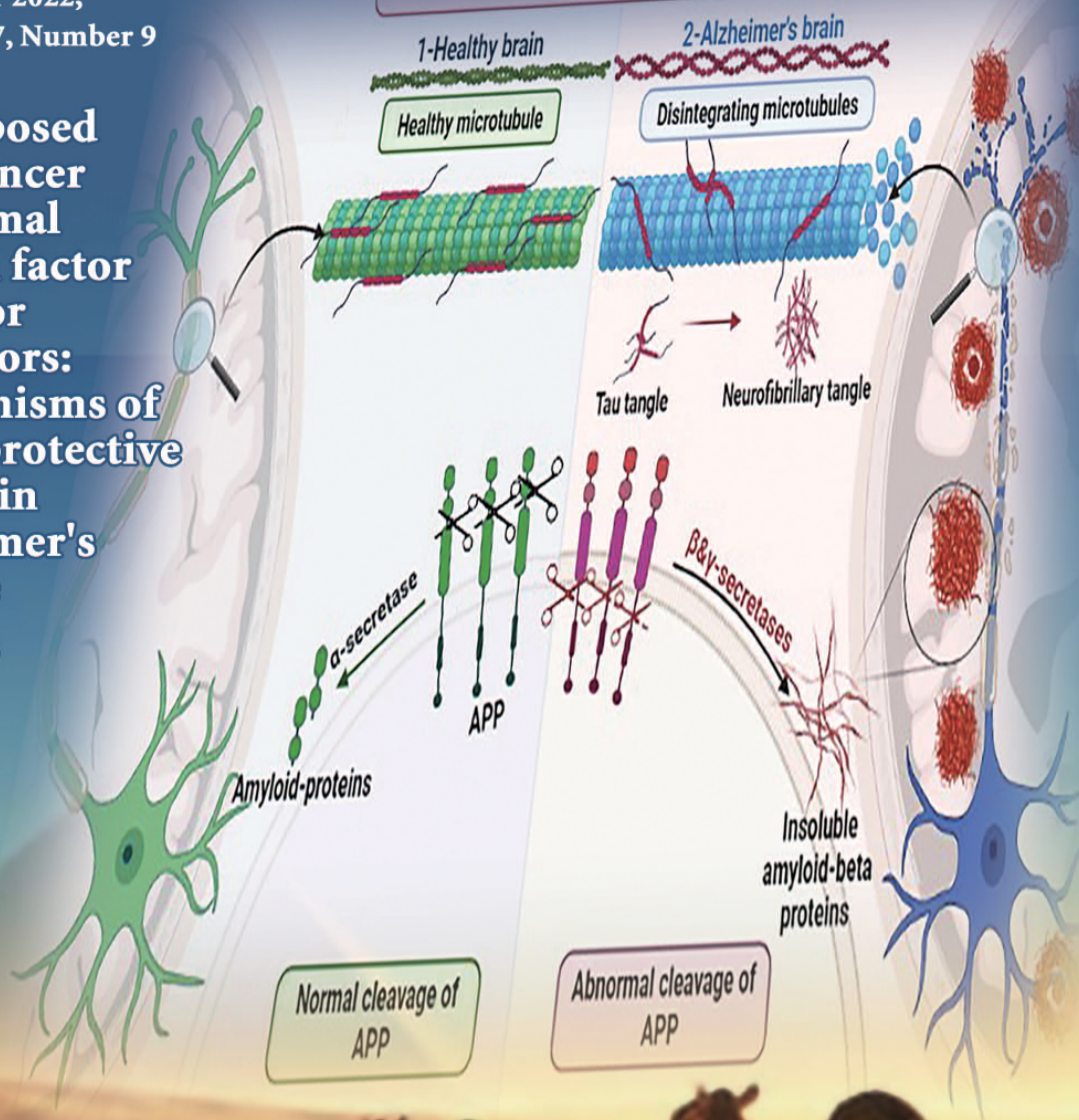
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### PATHOPHYSIOLOGY OF ALZHEIMER'S DISEASE



# Early life stress-induced neuroinflammation and neurological disorders: a novel perspective for research

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Childhood maltreatment (CM) has been consistently linked with numerous detrimental outcomes concerning physical and psychological health. However, few studies have explored vulnerability to neurological disorders after CM. Early life adversity, in the form of poverty, stress and abuse, has been associated with decline in cognitive function and dementia later in life (Short and Baram, 2019). Robust preclinical data suggest that early life stress (ELS) may increase the risk and worsen the course of neurological disorders such as Alzheimer's (AD) and Parkinson's (PD) diseases, and traumatic brain injury (TBI) (Lesuis et al., 2018; Short and Baram, 2019; He et al., 2020; Catale et al., 2021; Sanchez et al., 2021).

The biological mechanisms underlying this connection are still not clear. One possible candidate mediator is the immune system. Neuroinflammatory and immune processes have been proposed as key regulators of disease and recovery progression in many pathologies affecting the central nervous system (CNS). ELS has lifelong effects on inflammation and immune system reactivity. Clinical research has delineated a specific "immune phenotype" which characterizes blood of people exposed to CM and involves persistent low-grade inflammation, accelerated immunosenescence, and possibly an impairment in cellular immunity (Elwenspoek et al., 2017). These immune changes have been linked to the susceptibility of CM individuals to psychiatric and neurological disorders, since immune processes and neuroimmune communication are crucial for development and normal functioning of the CNS. It has been proposed that ELS permanently reprograms innate immune cells and/or the stress systems, i.e., sympathetic nervous system and hypothalamus-pituitary-adrenal (HPA) axis that regulate immune responses (Elwenspoek et al., 2017), leading to exaggerated inflammatory reactions to successive insults. This reprogramming may be responsible for exaggerated/dysfunctional neuroinflammatory responses to protein aggregates and tissue damage, leading to initiation and/or exacerbation of CNS pathologies in individuals with a history of CM. Moreover, ELS may facilitate neurological disorders by altering immune pathways that influence and regulate maturation of the brain, in particular microglia. In maltreated individuals, aberrant neuronal function and synaptic plasticity may provoke premature senescence and vulnerability to insults in circuits affected by neurodegenerative diseases and injury.

Microglia, the resident immune cells of the brain, are good candidate mediators of developmental and long-term effects of ELS.

Accumulating evidence suggests that ELS can prime microglia responses to future challenges (microglia priming), and/or may accelerate the priming effect of senescence on microglia, leading to premature loss of or alteration in microglia physiological roles. Primed microglia may show abnormal responses (e.g., increased/decreased/atypical phagocytosis and cytokine signaling) to aberrant neuronal products and glial and peripheral immune signaling, aggravating neurodegeneration and synaptic loss (Lesuis et al., 2018; Desplats et al., 2020). ELS can also interfere with microglial developmental roles, with consequences on neurodevelopmental processes of synaptic refinement and circuit organization, possibly causing aberrant brain maturation (Catale et al., 2020).

In this perspective, we will discuss preclinical and what little clinical literature is available regarding mechanisms of interaction between ELS, neuroinflammation, and neurological damage arising from AD, PD, and TBI. Finally, we will provide different mechanistic hypotheses and a novel point of view that could spur further research.

**ELS, AD, and neuroinflammation:** Some longitudinal and retrospective clinical studies have demonstrated an association between dementia and AD or cognitive decline, and adverse childhood factors (Radford et al., 2017). Preclinical studies have investigated the effects of different adverse early life experiences on AD-related processes in rodent models of the disease, showing that ELS, in the form of maternal separation or limited nesting material, accelerates/aggravates cognitive impairment and amyloid  $\beta$  ( $A\beta$ ) neuropathology (formation of amyloid beta plaques). Various candidates have been suggested as mediators of these effects, with support from animal and human findings. These include increased HPA axis reactivity and circulating glucocorticoids, blood-brain barrier disruption, and neuroinflammation/microglia activation (Lesuis et al., 2018). All these systems interact with each other: for example, glucocorticoids can change the activity of microglia and other immune cells, and microglia and neuroinflammation can disrupt blood-brain barrier integrity, leading to hypoxia and subsequent neuronal injury that worsens with disease progression. AD pathogenesis has been associated with aberrant microglia functionality. Microglia clear soluble  $A\beta$  oligomers and  $A\beta$  fibrils from the brain through the secretion of  $A\beta$ -degrading enzymes and through phagocytic uptake and subsequent degradation. Loss of microglial phagocytic capacity may lead to inefficient clearance of  $A\beta$ , which is a



pathogenic hallmark of sporadic AD (Lesuis et al., 2018). It has been shown that adverse early life experiences prime microglia and neuroinflammatory responses to subsequent exposure to  $A\beta$ . These aberrant responses are associated with worse  $A\beta$  neuropathology (Lesuis et al., 2018; Desplats et al., 2020). ELS induces long-lasting changes in neuronal components regulating cognition and plasticity, such as dendritic morphology, spine number, and synaptic proteins, mainly in brain structures associated with cognition and memory function (e.g., hippocampus and prefrontal cortex). It has been proposed that some of these changes are mediated by ELS-induced microglia activation (Catale et al., 2020). Our group showed that ELS could alter dopaminergic functionality in the ventral tegmental area (VTA) and that this was mediated by stress-induced microglia activation (reviewed in: Catale et al., 2020). Interestingly, dopaminergic neurodegeneration in the VTA, associated with microglia activation, has been recognized as an early pathophysiological event in AD (Nobili et al., 2017).

**ELS, PD, and neuroinflammation:** No clinical study so far has specifically evaluated the effect of child maltreatment on susceptibility to PD. One prospective study found that symptoms related to altered adaptation to stress (vital exhaustion) were significantly associated with the risk of developing PD (Clark et al., 2014). It has been hypothesized that stress-related dysfunctions may contribute to etiology of preclinical non-motor symptoms of PD (such as depression) and may worsen motor symptoms in PD patients (Desplats et al., 2020; He et al., 2020). Several preclinical rodent studies support the link between ELS, mainly in the form of maternal separation, and increased susceptibility of dopaminergic, striatal, and hippocampal regions to pathogenic factors of PD, such as the neurotoxin 6-hydroxydopamine (He et al., 2020). Based on preclinical data, it has been suggested that ELS may impact developmental trajectories of dopaminergic neurons and circuits, inducing susceptibility to depression and subsequently PD (He et al., 2020). No study on ELS and PD so far has investigated the contribution of microglia to these processes. Increased number of microglia and microglia activation have been consistently reported in postmortem PD brains and transgenic animal models of PD, particularly in the vicinity of dopaminergic neurons primed for degeneration (Desplats et al., 2020). Both central and peripheral inflammation has found to be responsible for pathogenic processes in familial and sporadic PD onset. Indeed, pathological  $\alpha$ -synuclein accumulation triggers neuroinflammation, associated with infiltration of T cells and activation of microglia, which leads to oxidative stress promoting dopaminergic neuron degeneration that will in turn sustain neuroinflammation, in a deleterious loop (Desplats et al., 2020). In one study, the combination of ELS and 6-hydroxydopamine treatment induced increased pro-inflammatory and reduced anti-inflammatory cytokines expression in the striatum of rats (Dallé et al., 2017). ELS may exacerbate PD pathology by making the neuronal compartment more vulnerable to insults (He et al., 2020), but also by priming microglia responses to  $\alpha$ -synuclein and other PD-related pathological processes.



Interestingly, microglia regulate developmental wiring and refinement of the dopaminergic system and may therefore mediate its abnormal maturation after ELS.

**ELS, TBI, and neuroinflammation:** No clinical study has evaluated the impact of child maltreatment on TBI responses so far. However, it is known that pre-injury mental condition and stress exposure are risk factors for a poorer outcome after TBI. Recently, our group (Catale et al., 2021) and Sanchez et al. (2021) have shown for the first time that ELS aggravates outcomes in two different rodent models of TBI. Sanchez et al. (2021) demonstrated that early maternal separation, combined with TBI in adulthood, resulted in persistent learning and memory deficits, exacerbated cortical atrophy, and hyperactivity of the HPA axis in response to stress. Authors hypothesized that high microglial activation and proinflammatory molecules expression mediate ELS-induced HPA axis changes and worsening of TBI outcomes (Sanchez et al., 2021). Indeed, CNS injury is characterized by peripheral immune cell infiltration to the damaged tissue with activation of brain resident astrocytes and microglia, which has been observed in both animal models and patients. Invasion of blood monocytes and lymphocytes seems to be detrimental, whereas long-lasting activation of microglia could be either harmful or beneficial. Our group showed that peri-adolescent social stress hampered the neuroinflammatory milieu and functional recovery one week after focal brain injury in adulthood through developmental microglia activation (Catale et al., 2021). We found that ELS permanently altered microglia responses such that, after injury, they produced an exaggerated remote inflammatory response – higher expression of pro-inflammatory cytokines, phagocytic markers, and NLRP3 inflammasome – associated with increased cell death and worse functional recovery. Notably, pharmacological prevention of microglia/macrophage activation during ELS exposure significantly reduced microglia responses, cell death and improved functional recovery. Conversely, pharmacological treatment administered in adulthood after TBI was ineffective in reducing inflammation and cell death or improving functional recovery (Catale et al., 2021). Therefore, we reasoned that ELS worsened outcomes to TBI through a combination of microglia priming and microglia-mediated alteration in brain maturation, that might be critical not only for later susceptibility to disease, but also for shaping neurological recovery after injury.

**Conclusion and future directions:** Accumulating evidence supports a direct link between ELS, neuroinflammation/microglia activity, and vulnerability to neurological disorders. Mechanistically, three possible models of interaction can be hypothesized from these data:

- 1) ELS may permanently alter microglia (and peripheral immune cells) activity, leading to dysfunctional neuroinflammatory responses to tissue damage and/or protein aggregates. These responses could initiate or exacerbate CNS pathologies.
- 2) ELS may impair developmental functions of microglia, causing aberrant neuronal and

synaptic activity and incorrect wiring. This altered brain maturation may account for premature senescence and vulnerability to insults, particularly in sensitive circuits affected by neurodegenerative diseases and injury, thus initiating or exacerbating CNS pathologies.

3) Combining the first two models, in a third “synergistic” model ELS could alter microglia and the immune system both in the short term, leading to atypical brain maturation, and in the long term, priming their responses to secondary insults. Then, in the presence of aggregates or injury, aberrant neuroimmune communication between a primed immune system and an altered neuronal substrate could drive initiation or exacerbation of CNS pathologies.

This third model is for us the most exciting and promising because it takes into account both the complexity of the brain and the experimental data. Further experiments are needed to explore these three models and to disentangle the possible mechanisms and pathways underlying the described processes. Previous animal studies have mainly employed pharmacological or genetic strategies that prevented excessive microglia and immune activation induced by early stress to “normalize” the pathological phenotypes observed after ELS. However, it would be interesting to examine whether therapeutical approaches that boost or restore microglia homeostatic functions after/during ELS could prove effective in reducing stress-related outcomes.

Studying the interaction between ELS, immune system, and neurodegeneration/TBI is difficult and requires technical tools and controlled manipulation that are currently possible only by using animal models. Human studies are strongly limited by potential confounders whose effects are difficult to detect and analyze, but which can profoundly influence response to early stress, such as genetics, gene-environment interaction, developmental timing of exposure to adversity, and combination of different types of stress. These variables can and should be controlled in animal studies, since different ELS procedures have differential effects on microglia outcomes and neurodevelopment (Catale et al., 2020; Short and Baram, 2019). Nonetheless, more clinical studies focusing specifically on the contribution of maltreatment to susceptibility to neurological disorders are needed to develop tailored, more effective treatments for a possible vulnerable subpopulation.

*We thank Rhys David Talbot for editing an English draft of this manuscript.*

*This work was supported by the Italian Ministry of Health, Young Researcher Grant, No. GR-2009-1576820 (to VC) and by Linea D.1. 2019 Università Cattolica del S. Cuore (to MTV).*

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Date of submission: July 2, 2021

Date of decision: August 13, 2021

Date of acceptance: September 9, 2021

Date of web publication: February 8, 2022

https://doi.org/10.4103/1673-5374.335152

**How to cite this article:** Catale C, Carola V, Viscomi MT (2022) Early life stress-induced neuroinflammation and neurological disorders: a novel perspective for research. *Neural Regen Res* 17(9):1971-1972.

**Availability of data and materials:** All data generated or analyzed during this study are included in this published article and its supplementary information files.

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**Open peer reviewers:** Anne Albrecht, Otto-von-Guericke-University Magdeburg, Germany; Gürsel Çalıřkan, Otto-von-Guericke University, Germany.

**Additional file:** Open peer review report 1.

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*P-Reviewers:* Çalıřkan G, Albrecht A; *C-Editors:* Zhao M, Liu WJ, Qiu Y; *T-Editor:* Jia Y