Brain-on-a-Chip to Nanoformulations

Future of CNS Disorder Management

Rahul Pal, Utkarsh Ravindra Mandage, Sarita Mukesh Beldar, Shital Janardan Patil, Ashwini K. Kankhare *Editors*

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Preface

We are extremely proud and very thankful to offer the revised book, **"Brain-on-a-Chip to Nanoformulations: Future of CNS Disorder Management."** Very complex and very difficult to treat disorders of the central nervous system (CNS) such as Alzheimer's disease, Parkinson's disease, depression, epilepsy, and multiple sclerosis have been the most pressing, disabling, and worldwide medical problems. The brain's complex structure and the blood-brain barrier's (BBB) extreme selectivity represent a major hurdle to conventional drug delivery methods, which is why despite great progress in neuroscience and pharmacotherapy.

Hereun book is about the new technologies that completely and inter-discipline redefine CNS research and therapeutics. The book brings to us advancements in the three scientific fields-nanotechnology, microfluidic platforms, and biomaterials-and points out the transformative methods that are changing the very fabric of disease modeling, diagnosis, and therapy. The spotlight is on, among the others, the nanoparticles based drug delivery systems-liposomes, polymeric nanoparticles, dendrimers, micelles, and hybrid nanoarchitectures-that not only are called drugs' bioavailability but also delivering them exactly to the brain and releasing them slowly and controlled in the CNS; all these the referred systems have shown amazing potential to doing so.

The integration of brain-on-a-chip and organ-on-chip technologies is just as important, as they enable the creation of models that mimic the physiological and human aspects, which can be used to study neuronal activities, drug-brain relations, disease progression as well as the responses to treatments. These miniaturized frameworks are capable of providing the best of the world and the integration of such techniques in the therapeutic process would mean minimizing the risks, making the treatments more accurate, and having them tailored to the individual for whom they are intended.

The concepts and technologies presented in this book have collectively marked the beginning of a new era in precision neurology, which relies on interdisciplinary collaboration and innovation to come up with more effective, targeted, and translational solutions for CNS disorders. This book is meant to be a great help to people, such as, researchers, clinicians, academicians, and industrial professionals who work in the areas of neuroscience, pharmaceutical sciences, biomedical engineering, and translational medicine.

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Chapter 2: Neuroinflammation and Immunomodulation Via Nano-Therapeutics

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Abstract

Neuroinflammation is a characteristic of disorders of the central nervous system (CNS) including Alzheimer, Parkinson, multiple sclerosis, traumatic brain injury, and stroke. The key processes that cause it are: microglial and astrocytic inflammation, cytokine production imbalance, oxidative stress, mitochondrial dysfunction, and dysfunction of the blood-brain barrier (BBB). The traditional therapy measures are not effective since the trip rarely enters into the BBB, there is always a possibility of toxicity in the body, and the target is not selective. Drug delivery strategies developed through nanotechnology will provide new solutions because it allows the targeted delivery to the CNS, regulated drug release and a controllable response to the immune system. Lipid-based nanoparticles, polymeric carriers, inorganic nanomaterials, dendrimers, and nanogels have shown efficacy in preclinical studies with lowering of pro-inflammatory cytokines, increased antioxidant defenses, silencing of pathogenic genes, as well as repair of BBB integrity. Initial clinical trials on nanoformulations of curcumin, methylprednisolone, and glatiramer acetate show have shown enhanced safety, as well as therapeutic outcome in nanoformulations over traditional medications. Nevertheless, the issue of toxicity, lasting bio-distribution and regulatory standardization continues to be such stumbling blocks. New directions related to biomimetic nanocarriers, stimuli-sensitive systems, and CRISPR based nano-delivery vectors appear to promise accuracy in nanomedicine in relation to neuroinflammation. The present review summarizes the molecular pathways involved in neuroinflammation, current nano-therapies, preclinical and clinical data, and the challenges and future directions that are necessary to convert nanomedicine to clinical neurotherapies.

Keywords: *Neuroinflammation, Nanoformulations, Central nervous system disorders, Alzheimer's disease, Parkinson's disease, Cytokines*

1. INTRODUCTION

1.1 OVERVIEW OF NEUROINFLAMMATION

Characteristics The neuroinflammation umbrella term describes the closely controlled, yet situationally specific, innate and adaptive immune responses taking place in the central nervous system (CNS). Neuroinflammation, in contrast to classic peripheral inflammation, is mediated mostly by resident glia (microglia and astrocytes), perivascular/meningeal macrophages, endothelial cells of the neurovascular unit, and contextually by infiltrating peripheral immune cells. Acute, contained responses help clear the debris, remodel the synapses and repair tissues, whereas chronic or unchecked responses cause synapses loss, network dysfunction and nerve degeneration (Ransohoff, 2016; Glass et al., 2010). Microglia, resident macrophages in CNS, change between various activation phenotypes contingent upon injury, aging, and microenvironmental indicators and do not represent a dichotomous system of M1/M2. They monitor synapses, declare an alert through pattern-recognition receptors (e.g., TLRs), and, in case of sustained stimulation, leak cytokines (TNF, IL-1b) reactive oxygen species, complement factors, and proteins that may extend their harm (Salter and Stevens, 2017; Ransohoff, 2016). The class of synapses that is susceptible is complement-tagged ones: in models of Alzheimer disease (AD), C1q/C3 deposition signals synapses to be consumed by microglia, and blockage of this signaling axis protects synapses (Hong et al., 2016; Stevens et al., 2007).

Once viewed as inert supporters, astrocytes actively mediate neuroinflammation in the regulation of glutamate uptake, blood -brain barrier (BBB) activity, and cytokine/chemokine gradients. There are injury-modifiable reactive astrocyte phenotypes in spectrums; example, microglial-induced neurotoxic A1 program has been shown to contribute to synaptic dysfunction (Escartin et al., 2021; Liddelow& Barres, 2017). Misfolded proteins are associated with inflammasome maturation and pathology sustained by influencing misfoldation uptake with cytokin signalling (e.g. NLRP3). The NLRP3-mediated activation of microglia facilitates tau-seeding and tau-spread in tauopathy models; genetic or drug-based NLRP3-inhibition alleviates pathology (Ising et al., 2019). These data, combined, contribute to a paradigm where almost maladaptive glial responses enhance disease processes not only in neurodegenerative diseases but across many disorders in general (Heneka et al., 2015; Ising et al., 2019).

1.2 ROLE OF THE IMMUNE SYSTEM IN CNS DISORDERS

Innate immunity: microglia, astrocytes & complement

In AD, PND, ALS, multiple sclerosis (MS) and TBI, innate immune signatures stand out and play a mechanistic part. DAMs develop around plaques/lesions and are characterised by transcriptional tissue phagocytosis, lipid-metabolic and inflammatory signalling (Deczkowska et al., 2018; Salter and Stevens, 2017). Beneficial synapse-pruning Complement-mediated is complement activated instead of Liigher? What happens to complement in developmental cells is pathologic in activation in adult disease (Hong et al., 2016; Stevens et al., 2007).