Springer Series in Translational Stroke Research

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Preface

Studies of cerebral white matter are arguably the stepchild of the neurobiology of disease. Accounting for over half the brain volume of the adult human, it would be surprising if cerebral white matter structure was not intimately involved in disease progression for most neurological disorders of the brain. Yet the learned reader of the scientific literature might justifiably conclude that brain insults affect neurons, and that neuronal protection and repair should be the main targets for translational neuroscience.

The field of white matter biology and disease is emerging to fill this scientific void. Fueled by new imaging modalities, molecular tools and cellular and animal models, studies of white matter development, injury, and repair are beginning to generate new concepts of disease progression in Alzheimer's disease, new descriptions and biomarkers of axonal pathology in traumatic brain injury and stroke, and a more detailed understanding of white matter health in normal aging. The chapters in this book explore these new developments in each of these categories: normal white matter structure and imaging; developmental white matter injury and its unique anatomical and temporal profile; progressive white matter degeneration as a major component of Alzheimer's disease and, surprisingly, normal aging; white matter energy dynamics, axonal support, and ischemic injury; acute structural white matter insults in stroke and head trauma; and progressive white matter injury in toxic exposures.

Neuroscience is a field driven by technology. Our emerging understanding of white matter health, disease, and repair is no exception to this principle. Chapters in this book review the MRI sequences that have provided structural insight into white matter tracts, such as diffusion tensor imaging, high angular resolution MRI, NMR spectroscopy, and their combination in multimodal MRI in humans and preclinical models. These approaches clearly provide indices of white matter structure in ischemia, head injury, and neurodegenerative diseases and might provide biomarkers for clinical stratification of patients for treatment.

One of the most important areas of study in white matter disease is the field of white matter progenitor biology. The most abundant progenitor cell in the brain, the

oligodendrocyte progenitor cell (OPC), is a card-carrying member of the white matter club. Originally and literally described as a precursor to mature oligodendrocytes, these cells have in fact a far more complicated biology, with multipotent potential to differentiate into neurons, with an ability to form synapses, and a capacity to recognize injury, migrate, and participate in scar formation (the "reactive OPC"). These principles are reviewed and the tools necessary for detailed study of the OPC are discussed.

Though it is tempting in the Preface to this book to push the "white matter-centric" view far so as to draw out distinct and neglected biological principles of CNS disease, the study of white matter injury reaches its most important points when integrated back into a more whole neurobiology of disease. Several principles discussed in these chapters illustrate this point. At a system's level, in Alzheimer's disease the integrated function of white matter tracts and overlying neuronal areas are key to understanding disease progression. On a cellular level the myelinated axon interacts with its neighboring oligodendrocyte to form an axoglial unit. This unit interconnects metabolic shuttling, cell-adhesion signals, and triggers compartmentalization in both the axon and its nodes with the oligodendrocyte that is key to normal signal propagation. In traumatic brain injury, stroke, periventricular leukomalacia, and other brain injuries the axoglial unit is disturbed, and this can be progressive even after the initial insult is completed. These points are clearly made throughout this book.

If the Preface as a beginning is anything it leads into the chapters and then beyond, in this case to the more robust study of white matter structure, function, disorder and recovery. The latest tools for this journey are described, from genetic cellular fate-mapping to MRI imaging and network analysis. New principles are set, and these now need future examination, such as the cognitive dysfunction of aging, acute injury, and progression; white matter progenitor biology and tissue repair; and subcellular energy dynamics and signaling. The reader, like the editors and authors before him, is set on this journey. A more famous beginning lead into a journey and an examination of the principles beyond, "Somewhere in La Mancha, in a place whose name I do not care to remember, a gentleman lived not long ago, one of those who has a lance and ancient shield on a shelf and keeps a skinny nag and a greyhound for racing." With a relatively new conception of the importance and role of white matter disease it is time to lower the lance and charge.

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