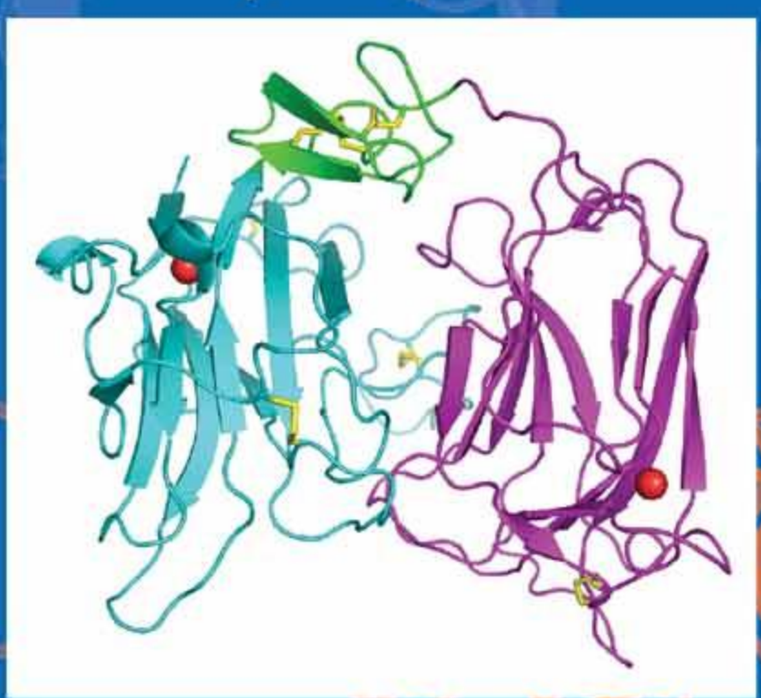
S. Hossein Fatemi
Editor

Reelin Glycoprotein



Structure, Biology and Roles in Health and Disease

Springer

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To my father, S. Mehdi Fatemi, and to my family, S. Ali Fatemi, M.D., Naheed Fatemi, Parvin Fatemi, S. Mohammad Fatemi, Neelufaar Fatemi, Maryam Jalali-Mousavi, and last but not least, my mother, Fatemeh Parsa Moghaddam, whose love and support have enabled me to complete this work.

Foreword

By inviting me to contribute a short foreword to this superb collective work on the biology of Reelin, Dr Fatemi gives me a nice opportunity for some reminiscence and speculation. The first reeler mutation appeared in 1948 in Edinburgh, and reeler mice were for many years the only genetic model of cortical malformation. The model became popular in the mid sixties and seventies, thanks to the vision of Sidman and his colleagues, especially Caviness and Rakic. However, in the following years, reeler fell a bit out of fashion because the gene was not characterized. Only a few groups, such as those of Mikoshiba and myself, persisted in studying reeler mice. This changed dramatically when D'Arcangelo and Curran cloned the Reelin gene in 1995. The next few years saw rapid progress with the identification of the adaptor Dab1 by Howell and Cooper in 1997, and of reelin receptors by Herz in 1999. Since 1999, as is often the case after a golden period, progress has been slower. Still, we have witnessed very significant progress that is nicely covered in this book. We understand more about the biochemistry and structure of Reelin, and most probably a full structure of the native protein will be defined in the coming years. Reelin has been studied during brain development in several species, and this resulted in a somewhat clearer view of its importance during brain evolution. Similar comparative studies of Dab1 and receptors would be needed, however, and I doubt that they will be done soon. We know a lot about Reelin expression in the embryonic and adult brain, even though the basic mechanisms that control Reelin synthesis and secretion, particularly by Cajal-Retzius cells, need to be defined better. The proximal steps in the signal elicited by Reelin have basically been worked out, and interactions between proximal signaling by Reelin and other important pathways are being elucidated at increasing pace. In addition, several papers appear regularly that describe expression of Reelin where it is not really expected, generating new hypotheses on what are probably several different functions of a large protein. Whether these various functions use the canonical Reelin signaling pathway or additional pathways that remain to be identified is another theme of interest for the next few years. Last but not least, a large body of evidence has accumulated that hints at a role of Reelin in psychiatric disorders.

Notwithstanding this vast body of exciting data, however, we are still in the dark about some key issues, among which I would mention two that appear particularly

important – at least to me. First and foremost, even though Reelin receptors and signaling components have been identified, we still do not know what Reelin does to immature neurons. The concept that Reelin provides a stop signal has been useful but is reaching its operational limit. Presumably, we all agree that Reelin somehow instructs neurons to arrest migration and take position in early architectonic patterns (cortical plate, Purkinje cell layer, etc. …). However, how this happens remains unknown. Does Reelin modulate expression of adhesion molecules on the surface of neurons, radial glia, or both, as I always imagined? Alternatively, does Reelin signaling impact on the cytoskeleton, thereby "freezing" the architecture of end-migration neurons? Does Reelin signaling recruit or hijack other signaling pathways such as Notch, as recently proposed by the Rakic group? Second, what is the function of Reelin after maturation and in the mature brain. What does Reelin do when it is secreted by cortical interneurons? Related to this are clearly the questions about the actions of Reelin in learning and behavior, and in psychiatric diseases. To address this, we need to inactivate Reelin and/or its partners in neurons after normal maturation, using, for example, floxed alleles and Cre-ER technology. As far as I know, these tools are only being developed.

As this superb book outlines, the Reelin field is at a crossroad. Following a rapid initial phase, with cloning of Reelin, identification of Dab1 and receptors, each of which owed quite a lot to serendipity, progress has been much slower and difficult. Whether future breakthrough will also occur unexpectedly (maybe the next knockout…) or will result from more rational approaches, is anybody's guess. But one thing is more predictable, namely that this timely book will prove very useful and will end up on the bookshelf of all investigators with an interest in the Reelin puzzle. We should all be grateful to Dr Fatemi and his staff for editing it so carefully.

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Preface

Reelin glycoprotein is a major secretory protein with important roles in embryogenesis and during adult life. Reelin gene mutations or deficiency of the protein product cause abnormal cortical development and Reelin signaling impairment in brain. Since the first discovery of the reelin mutant mouse in 1951 by Falconer, and later discovery of the gene for Reelin in 1995, there has been an explosion of new knowledge about this important molecule. As of this writing, a search of public library of medicine cites over 665 published papers on Reelin.

Thus, it became apparent that a book dealing with this topic and presenting contributions from an international panel of experts would be timely and necessary. In the following twenty eight chapters, various authors will present up-to-date discussions of the state of the knowledge on various aspects of Reelin such as reelin gene, its receptors, downstream effector molecules in Reelin signaling cascade, chemistry and structure of Reelin, comparative anatomy of reelin, presence of Reelin in various body tissues, Reelin mutations, and abnormalities of Reelin production in neuropsychiatric disorders and cancer.

It is hoped that this book serves as a foundation for analysis of this emerging novel protein for all interested neuroscientists and clinicians.

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