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Origins of Human Neuropathology: The Significance of Teneurin-Latrophilin Interaction David A. Lovejoy, Antony A. Boucard, Richard P. Tucker, 2020-07-22 We are delighted to introduce this new special issue on The Origins of Neuropathology The Roles of Teneurins and Latrophilins Although the title may seem particularly bold and indeed perhaps presumptuous we the editors think our title well warranted based on the findings and interpretation provided by a dedicated group of researchers who have developed this field over the last 25 years In this publication we introduce the readers to researchers whom have pioneered this field and those whom have played an essential role in developing this research direction Now together their combined work have elucidated a novel ligandreceptor network that evolved during the earliest period of animal evolution and has fostered a new insight into the ancient evolutionary organization of the central nervous system CNS Specifically this work offers a new understanding of several aspects of neuropathology including degenerative psychiatric and mood disorders and furthermore illuminates a fundamental role that teneurins and latrophilins play in cell to cell metabolism that may be associated with various forms of cancer both within and outside of the brain In 1994 the laboratories of Professors Ron Wides in Israel and Ruth Chiquet Ehrismann working in Switzerland independently reported the existence of a novel transmembrane protein and its gene in Drosophila A complex gene protein its closest homologue was that of the tenascins The gene was named either odd or odz or tenascin major ten m by these researchers Subsequent studies indicated that the gene was highly expressed in the brains of vertebrates and the term teneurin was coined to reflect both its relationship with tenascins and with the CNS Around the same time as these studies a novel G protein coupled receptor was identified by Yuri Ushkaryov and his team in the United Kingdom in fact the latrophilins then named C1RL calcium independent receptor for a latrotoxin was first identified by the group of Petrenko at NYU Medical Center in New York USA which was subsequently established as a cognate receptor for the teneurins This receptor was later termed as the latrophilins and more recently Adhesion receptor G protein coupled receptor family L or ADGRL In Part 1 of this publication the early history on the origin and discovery of teneurins has been described by Stefan Baumgartner and Ron Wides Ron Wides and Richard Tucker Recent structural studies by Verity Jackson and her colleagues as well as Demet Arae and Jingxian Li have provided molecular models to understand how teneurins are ensconced in the plasma membrane and play a role in synaptic interaction In addition their work integrates the molecular mechanisms with the early evolution of both teneurins and latrophilins In Part 2 four studies build upon the evolutionary development of teneurins by examining its role in nematodes by Ulrike Topf and Krzysztof Drabikowski a model of teneurin action in the Drosophila nervous system by Alison DePew and associates and two studies on fish Angela Cheung and her colleagues describe the neurological function and expression in zebrafish whereas Ross Reid and his coworkers have described novel actions of the teneurins with respect to metabolism in fish Part 3 of this publication is focused on the latrophilins and is led off by Yuri Ushkaryov and his team

describing the discovery structure and function of the latrophilins This work is followed by a review by Ana Moreno Salinas and colleagues in Antony Boucard's laboratory describing the structure of the latrophilins and its interaction with associated transmembrane proteins with respect to adhesion neuronal function and pathology The following paper by Torsten Schönborg and Simone Prömel links the previous papers with a comparison of teneurin and latrophilin interactions in invertebrates and vertebrates Finally in this section Peter Burbach and Dimphna Meijer provide an interesting overview of the relationship of teneurins and latrophilins with respect to other proteins described in these other papers Together these studies provide a novel understanding of how the teneurins and latrophilins interact in a complex set of associated proteins The next section Part 4 of the publication focuses on the development and maintenance of the CNS in mammals Here Catherine Leamey and Atomu Sawatari lead off with a discussion of the role of teneurin associated neuro circuit formation using knockout studies in mice A detailed review by Luciane Sita and her colleagues in the Bittencourt laboratory frames this and previous studies in a comparative neuroanatomical background and in addition provides a neuroanatomical rationale for new studies associated with other regions of the CNS Building upon these studies David Hogg and his coworkers include a review on the behavioral actions of the teneurin C terminal associated peptide TCAP in mammals and its potential relationship to brain metabolism and forms of neuropathology Finally in this section a study by Gesttner Tessarin in the Casatti laboratory shows for the first time teneurins may be associated with astrocyte function indicating a novel function for teneurins with respect to some glial based disorders in the brain Finally in our last section we have provided some studies on the potential roles of the teneurins and latrophilins with respect to carcinogenesis Although these studies are somewhat removed from our treatise on the role of teneurins and latrophilins with respect to neuronal development maintenance and pathology they provide interesting observations that may be relevant to some types of CNS pathology Thus Boris Rebolledo Jaramillo and Annemarie Ziegler include a review on the relationship of teneurins to several types of cancers This is followed by a research report by Mia Husi and her colleagues suggesting that the TCAP region of the teneurins could play a role in modulating the adhesion of the cancer like cell line HEK293 and finally Sussy Bastias Candia and associates have provided novel data on the role of teneurin 3 with respect to Wnt signalling and have discussed its potential role in neural development and carcinogenesis Overall we posit that the teneurins and latrophilins played a major role in the early evolution of the nervous system and may underlie the etiology of a number of neurological disorders that are thus far misunderstood Indeed we hope that this publication will stimulate further research into the actions of teneurins and latrophilins and lead to novel approaches of understanding and ultimately treatment

Obituary Ruth Chiquet-Ehrismann 1954-2015 A Teneurin Pioneer A major player in the discovery and characterization of teneurins was the Swiss scientist Ruth Chiquet-Ehrismann Dr Chiquet-Ehrismann had a long standing interest in cell-cell and cell-extracellular matrix interactions particularly during development and tumorigenesis She earned her Ph.D. at the ETH Zurich under the mentorship of David C. Turner where she performed early work on the cell and heparin

binding sites of fibronectin Shortly after joining the Friedrich Miescher Institute in Basel as a junior group leader in 1984 Ruth in collaboration with Eleanor J Mackie and Teruyo Sakakura published a paper in *Cell* describing an extracellular matrix glycoprotein that she named tenascin A key observation made in this widely cited paper was the presence of tenascin in the extracellular matrix of embryonic tissues and the stroma of breast cancer but its absence from most normal adult tissues We now know that the original tenascin was the founding member of a diverse gene family and that members of this family promote cell motility proliferation and differentiation in a variety of tissue environments both normal and pathological But in the early 1990s it was unclear how tenascins functioned Specifically its receptors and binding partners were not understood Subsequently Ruth engaged in a multi pronged approach to studying tenascin function in an attempt to identify its homologues in *Drosophila* This work led by her postdoctoral fellow Dr Stefan Baumgartner resulted in the discovery of a novel family of type 2 transmembrane proteins that they named ten a and ten m for tenascin like proteins accessory and major When the homologues of ten a and ten m were found in vertebrates and they were shown to be highly expressed in the nervous system Ruth proposed the name teneurins This name combined the names of the original proteins from *Drosophila* with neurons which appeared to be their most prominent site of expression From that point onward Ruth s research group at the Friedrich Miescher Institute studied two topics the roles of tenascins in cancer and the roles of teneurins in development Using numerous model systems her research included studies of teneurins in arthropods *Drosophila* nematodes *C elegans* and chordates birds and humans Key firsts that came from Ruth s laboratory include the cloning and sequencing of human teneurins experimental evidence of teneurin processing by furin and the potential nuclear localization of the intracellular domain the ability of teneurins to promote growth cone spreading patterning defects in teneurin knockout animals a description of the ancient origins of teneurins via horizontal gene transfer the complementary expression patterns of different teneurins during development the cytotoxic properties of the teneurin C terminal domain and the presence of homotypic adhesion domains in teneurins Since 1994 Ruth s group published 24 papers on the cloning expression origins and functions of teneurins Contributing to these papers were 15 graduate students and postdoctoral fellows often with the expert technical guidance of Jacqueline Ferralli Marianne Brown Luedi and Doris Martin This work has provided a foundation for a new generation of researchers in the field of teneurins Ruth Chiquet Ehrismann passed away at her home near Basel on September 4 2015 She is survived by her husband and collaborator Matthias Chiquet three children Daniel Patrice and Fabian and an expanding cohort of grandchildren Richard P Tucker Davis California

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