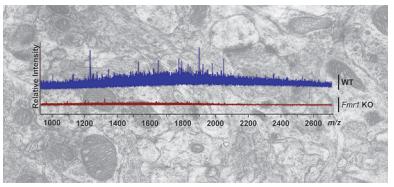
Signaling and Fragile X Syndrome

Fragile X syndrome is an inherited disorder distinguished by mental retardation and autism-like behaviors. The cause of this disorder is the failure to transcribe the gene for the fragile X mental retardation protein. Annangudi et al. (DOI: 10.1021/cn900036x) explore neurotransmitter and neuropeptide release in mouse models and report that mice without the ability to synthesize intact fragile X mental retardation protein show impaired neuropeptide release.

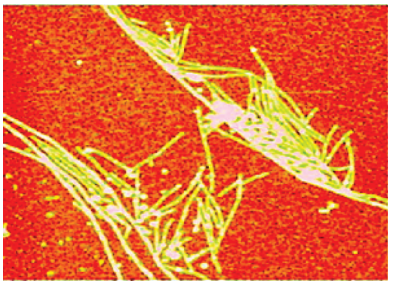
The authors were able to characterize a large number of peptides released in a stimulation-dependent manner using new sampling approaches in mass spectrometry. The authors note that release of biogenic amines does not differ between the brain slices of wild-type and knockout mice. An mRNA cargo of the fragile X mental retardation protein involved in vesicle release was also found to be depressed by ~50% in knockout mice. The authors suggest a role for cell−cell signaling in the progression of Fragile X syndrome.



Alzheimer's Disease and Congo Red

Alzheimer's disease is the most common form of dementia and a leading cause of death in the United States. One pathological hallmark of Alzheimer's disease is the presence of senile plaques. Senile plaques are protein aggregates mainly composed of the amyloid β peptide in which the peptide has formed fibrous protein aggregates known as amyloid fibrils. Molecular entities formed during the fibrillation process are currently believed to be responsible for neuronal toxicity. Inhibition of the amyloid β aggregation process may offer a viable therapeutic approach to treat Alzheimer's disease.

The histological dye Congo red is a widely used antiamyloid agent, known to suppress amyloid β-peptide formation. Bose et al. (DOI: 10.1021/cn900041x) present an explanation of how Congo red suppresses amyloid β toxicity. Ultimately, this knowledge may assist in the rational design of novel inhibitors of amyloid β aggregation.



Chemical Genetics and Neuritogenesis

A growing number of neuropsychiatric disease susceptibility genes have been shown to alter the fundamental process of neuritogenesis. However, there is inadequate understanding of the underlying molecular mechanisms. Cell culture systems that satisfy the need both for quantitative analysis and chemical screening might serve as platforms in the discovery of small-molecule probes that target molecular circuitry integral to the pathophysiology of neuropsychiatric disease. Now, Kuai et al. (DOI: 10.1021/cn900046a) use a chemical genetics approach to discover novel small-molecule probes of the neuregulin-1 and ErbB4 receptor signaling pathway so essential to many aspects of nervous system development and plasticity.

Using a quantitative, high-throughput, automated microscopy-based assay, the authors demonstrate that neuregulin-1 and nerve growth factor act synergistically to enhance neuritogenesis. The authors also find pathway-selective inhibitors of neuregulin−ErbB4 signaling that do not affect nerve growth factor signaling, Taken together, the results of this chemical genetic screen provide new small-molecule probes to potentially identify new targets for the treatment of neuropsychiatric disorders.

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