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PROMEMO Lecture

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Auditorium A, bldg. 1162, room 013

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Autism and "Astro"logy: New insights from recordings in human cortical neurons

Abstract:
Important insights into the pathophysiology of fragile X syndrome (FXS), a common monogenic cause of autism spectrum disorder, have emerged from analyses of rodent models. These findings, however, have been less effective in developing therapeutic interventions, thereby highlighting the need for model systems of human origin. Moreover, many studies have focused on neurons, and the role of glia remains largely unexplored in FXS. Here, we used human 5 pluripotent stem cells to examine the potential role of astrocytes in physiological abnormalities in FXS neurons. FXS cortical neurons, co-cultured with FXS astrocytes, fired spontaneous bursts of action potentials that are more frequent, but shorter in duration, compared to control neurons co-cultured with control astrocytes. However, bursts fired by FXS neurons, co-cultured with control astrocytes, are indistinguishable from control neurons. Conversely, control neurons exhibit 10 aberrant firing in the presence of FXS astrocytes. Thus, the genotype of astrocytes determines the physiological phenotype of neurons. Strikingly, astrocytic conditioned medium by itself, from either control or FXS astrocytes is capable of eliciting the same spontaneous burst firing patterns that would be observed if astrocytes were physically present in co-cultures. Further analysis of a mechanistic basis of this effect revealed that the astroglial-derived protein, S100β, restores normal 15 firing by reversing the suppression of a persistent sodium current in FXS neurons. Together, these results identify an important cell non-autonomous contribution of astrocytes in correcting aberrant electrical activity in human FXS neurons, thereby suggesting a framework for exploring new therapeutic strategies aimed at neuron-glia interactions.

Hosts: Marco Capogna and Sadegh Nabavi, PROMEMO

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