Heterogeneity of neurons in the cortex

Re-interpretation of the findings in terms of the IPL mechanism

Studies of cortical neurons show significant heterogeneity in transcriptomic analyses (Tasic et al., 2016; Cembrowski et al., 2016; Tasic et al., 2018; Hodge et al., 2019). In fact, these findings show that there won't be two neurons with the same sets of transcripts within them. The above findings naturally raise the question, "What is the functional importance of such a finding?" The actual operational mechanism of the nervous system is expected to provide clues for a suitable explanation. Based on the IPL mechanism, this heterogeneity is necessary for the formation of IPL fusion between spines that belong to different neurons at one stage of development supported by the diffusion of dye injected into on neuron to neighboring neurons.

In the mouse, neuronal precursor cells in the ventricular zone (VZ) undergo cell division. While in the VZ, **100% of precursors** in G2 and S phases of the cell cycle couple together and form clusters (Bittman et al., 1997). During this stage, injection of dye into one cell spread to neighouring cells (Bittman et al., 1997). **This indicates the formation of fusion pores between these cells.** This is followed by death of nearly 70% of these cells and survival of the remaining 30% cells (Blaschke et al., 1996). The surviving 30% of cells are expected to have acquired an adaptation, most probably during inter-cellular coupling. The adaptation most likely prevents any future coupling between neurons that may result in inter-neuronal fusion. This adaptation is suitable for maintaining IPLs (that generated inner sensations) and prevents any IPL fusion. Aging can be viewed as resulting from gradual loss of this adaptation. Augmented formation IPL fusion events can lead to pathological changes such as those observed in neurodegenerative disorders (Vadakkan, 2019). For example, pathological changes of neurofibrillary tangles and amyloid plaques can result from precipitation of proteins & leakages of certain precipitated proteins through defective fusion pores to the extracellular matrix space in Alzheimer’s disease

If neurons are not heterogeneous, then fusion between them will not evoke cellular reactions, which is responsible for cell death of **majority** of neurons. Most importantly, this IPL fusion is expected to trigger an adaptation in surviving neurons, responsible for restricting IPL fusion to the stage of IPL hemifusion. Thus, neuronal heterogeneity can be viewed as a marker of an adaptation that occurred during those last stages of the developmental of the nervous system. It is most likely that maintaining heterogeneity is essential for maintaining the above adaptation throughout the life-span of the neurons. This prompts us to make a testable prediction that, any deficiencies in maintaining this adaptation will trigger IPL fusion between heterogeneous neurons, which can explain aging and other disease associated neurodegeneration.

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