Journal Club

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Somatostatin Diversity in the Inhibitory Population

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Review of Ma et al. (http://www.jneurosci.org/cgi/content/full/26/19/5069)

For some time, there has been great interest in defining the canonical cortical circuit. To do this, all of the types of neurons that comprise this basic circuit must be identified. Neocortical neurons can be distinguished based on their neurotransmitter phenotype as excitatory (glutamatergic) or inhibitory (GABAergic), but these categories show diverse functions and morphologies. For inhibitory interneurons, recent estimates of the number of subtypes reach the mid-teens (Gupta et al., 2000). It has been hypothesized that each subtype has a distinct cortical function and could be specifically affected in diseases such as schizophrenia (for review, see Lewis et al., 2005).

GABAergic interneurons have been classified based on their axonal targeting, electrophysiological properties, or expression of calcium-binding proteins such as parvalbumin (PV) or neuropeptides such as somatostatin (SOM). Interneurons have mostly been categorized electrophysiologically based on spiking responses to current step injections as fast-spiking (FS), regular-spiking, low-threshold spiking (LTS), irregular, bursting, and stuttering. However, subtypes identified by one set of criteria have not necessarily segregated cleanly based on other criteria. For example, SOM-expressing neurons exhibit a high degree of anatomical and electrophysiological variability.

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The recent *Journal of Neuroscience* paper by Ma et al. (2006) sheds some light on variability among SOM+ neurons. Novel transgenic mouse lines were made that expressed green fluorescent protein (GFP) under control of the GAD67 promoter. Two lines, X94 and X98, were compared with the frequently used GIN line, in which GFP expression is driven by a smaller fragment of the GAD67 promoter. In each line, GFP appeared to label a distinct population of somatostatin-containing neocortical interneurons (Fig. 1*A*). These inhibitory neuron subtypes varied with respect to their anatomical layering [Ma et al. (2006), their Figs. 1 (http://www.jneurosci.org/cgi/content/full/26/19/5069/F1) and 4 (http://www.jneurosci.org/cgi/content/full/26/19/5069/F4)], expression of calbindin [Ma et al. (2006), their Fig. 2 (http://www.jneurosci.org/cgi/content/full/26/19/5069/F2) and Table 1 (http://www.jneurosci.org/cgi/content/full/26/19/5069/T1)], and axonal projections [Ma et al. (2006), their Figs. 3 (http://www.jneurosci.org/cgi/content/full/26/19/5069/F3) and 4 (http://www.jneurosci.org/cgi/content/full/26/19/5069/F4)]. The cells from the GIN line appeared to have properties intermediate to X94 and X98 neurons.

Ma et al. then characterized the GFP+ neurons electrophysiologically [Ma et al. (2006), their Table 2 (http://www.jneurosci.org/cgi/content/full/26/19/5069/T2)]. Of the 15 properties analyzed, nine were good predictors of grouping, and six were not (resting potential, threshold, spike amplitude, sag slope, adaptation, and frequency–current slope). The nine informative parameters included three passive properties [input resistance, membrane time constant, rheobase (current intercept of frequency–current curve)] and six active properties (action potential rise rate, action potential decay rate, spike width, steady-state spiking frequency, initial spiking frequency, afterhyperpolarization amplitude). Most of the heterogeneity could be accounted for by segregation of the neurons into distinct groups (Fig. 1*B*): GFP+ cells in the X98 line were consistent with Martinotti cells, whereas cells labeled in the X94 line appeared to be a novel subtype of "quasi-FS" stuttering cells [Ma et al. (2006), their Table 2 (http://www.jneurosci.org/cgi/content/full/26/19/5069/T2) and Fig. 5 (http://www.jneurosci.org/cgi/content/full/26/19/5069/F5)].

Importantly, Ma et al. (2006) used multiple unbiased forms of analysis to determine whether there were actually distinct subtypes. The methods included analysis of correlation of variance [Ma et al. (2006), their Table 2 (http://www.jneurosci.org/cgi/content/full/26/19/5069/T2) and Fig. 7*a–d* (http://www.jneurosci.org/cgi/content/full/26/19/5069/F7)], principle component analysis [Ma et al. (2006), their Fig. 7*e* (http://www.jneurosci.org/cgi/content/full/26/19/5069/F7)], and discriminant function analysis [Ma et al. (2006), their Fig. 7*f* (http://www.jneurosci.org/cgi/content/full/26/19/5069/F7)]. The groups established by the unbiased analysis of electrophysiological properties correlated very well with the observed neurochemical and morpholog-

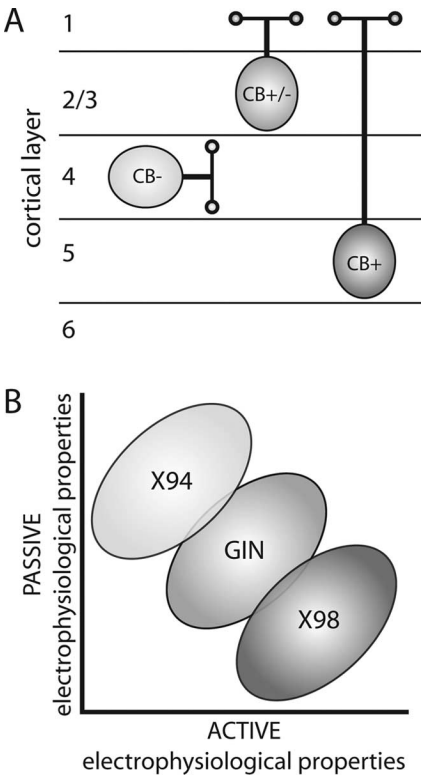

Figure 1. SOM+ neurons labeled in X94, GIN, and X98 transgenic mice have distinct laminar distributions and electrophysiological properties. ***A***, X94 (left), GIN (middle), and X98 (right) somas reside in layers 4, 5, and 2/3, respectively. X94 axons terminate in layer 4, whereas GIN and X98 axons project to layer 1. ***B***, Principle components analysis places X94, GIN, and X98 neurons into separate groups based on combined active and passive membrane properties.

ical distinctions [Ma et al. (2006), their Table 3 (http://www.jneurosci.org/cgi/content/full/26/19/5069/T3)]. It will be interesting to similarly analyze other subtypes, such as PV or FS cells, to determine how many distinct subtypes might be included in the previously defined classes.

Unfortunately, Ma et al. (2006) did not examine the synaptic properties. Gupta et al. (2000) characterized the synaptic, morphological, and intrinsic spiking behaviors of cortical interneurons and divided the cells into 14 distinct types based on combinations of these properties. Martinotti cells were included in the analysis; however, it is not clear where X94 cells fit into this classification scheme. Recently, microarray analysis of neurons derived from four lines of transgenic mice, including the GIN mice used by Ma et al. (2006), demonstrated that several previously defined neuronal types have distinct gene expression profiles (Sugino et al., 2006). Pools of genes distinguished the neuronal types better than older neurochemical definitions. In addition, hierarchical relationships between the gene expression profiles were observed, with neurons of closer origin and function expressing a larger number of similar genes. Despite the electrophysiological differences between X94, X98, and GIN neurons, the types of neurons studied by Sugino et al. (2006) are unlikely to be as similar to one another as the three SOM-expressing subtypes. It would be interesting to see whether gene expression profiles of the X94, X98, and GIN neurons are highly distinct. Although the expression of 26 ion channel genes has been examined in Martinotti cells (Wang et al., 2004), microarray comparisons of neurons from the mouse lines generated by Ma et al. (2006) should lend additional insight into which ion channels give each class of neuron its distinctive properties. Perhaps microarray analysis and/or identification of the regulatory sequences controlling the differential expression of GFP in each line would also lead to the discovery of a biochemical marker that would uniquely identify these neuronal subtypes.

The use of transgenic mice to label subsets of neurons has been invaluable in the study of interneuron subtypes. The work presented by Ma et al. (2006) suggests that this approach will continue to provide insight. To make the best use of such data, we need to maintain a constant interchange between physiological and molecular studies of subtypes, use standardized measurements and unbiased analysis, and generate a database of the results that is readily accessible to the neuroscience community.

References

Gupta A, Wang Y, Markram H (2000) Organizing principles for a diversity of GABAergic interneurons and synapses in the neocortex. Science 287:273–278.

Lewis DA, Hashimoto T, Volk DW (2005) Cortical inhibitory neurons and schizophrenia. Nat Rev Neurosci 6:312–324.

Ma Y, Hu H, Berrebi AS, Mathers PH, Agmon A (2006) Distinct subtypes of somatostatin-containing neocortical interneurons revealed in transgenic mice. J Neurosci 26:5069–5082.

Sugino K, Hempel CM, Miller MN, Hattox AM, Shapiro P, Wu C, Huang ZJ, Nelson SB (2006) Molecular taxonomy of major neuronal classes in the adult mouse forebrain. Nat Neurosci 9:99–107.

Wang Y, Toledo-Rodriguez M, Gupta A, Wu C, Silberberg G, Luo J, Markram H (2004) Anatomical, physiological and molecular properties of Martinotti cells in the somatosensory cortex of the juvenile rat. J Physiol (Lond) 561:65–90.