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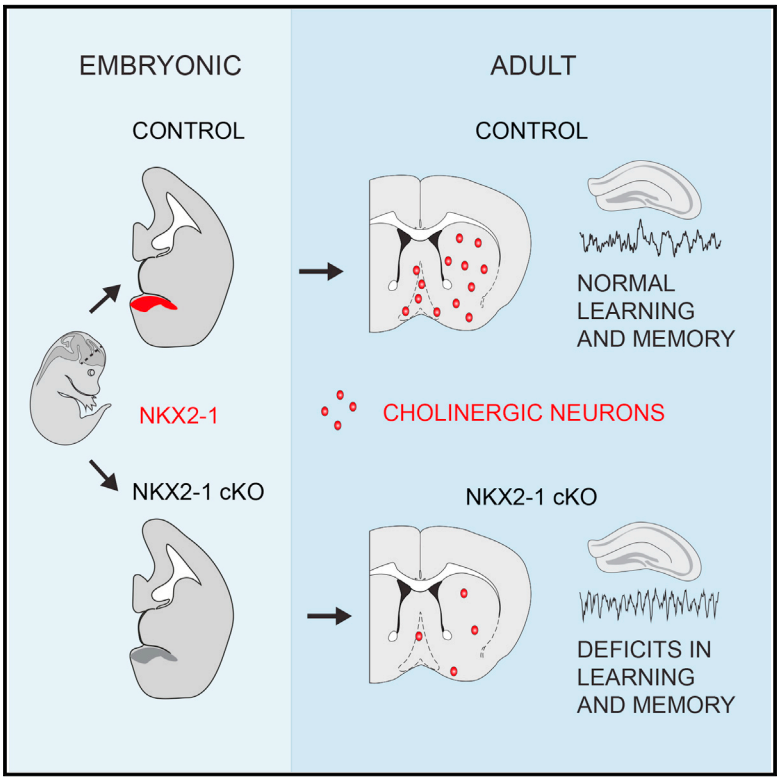
NKX2-1 Is Required in the Embryonic Septum for Cholinergic System Development, Learning, and Memory

Graphical Abstract



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In Brief

NKX2-1 is a highly conserved patterning gene in the developing forebrain, mutations in which can lead to a spectrum of disorders including cognitive deficiencies. Using genetic fate mapping and intersectional deletion, Magno et al. demonstrate a requirement for embryonic septal NKX2-1 in forebrain cholinergic system development and learning and memory.

Highlights

- Forebrain cholinergic neuron subsets originate from septal NKX2-1^{+ve} progenitors
- Septal *Nkx2-1* deletion causes widespread loss of forebrain cholinergic neurons
- Severe deficits in learning and memory in septal *Nkx2-1* conditional mutant mice
- Hippocampal network activity alterations in the absence of embryonic septal NKX2-1

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NKX2-1 Is Required in the Embryonic Septum for Cholinergic System Development, Learning, and Memory

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SUMMARY

The transcription factor NKX2-1 is best known for its role in the specification of subsets of cortical, striatal, and pallidal neurons. We demonstrate through genetic fate mapping and intersectional focal septal deletion that NKX2-1 is selectively required in the embryonic septal neuroepithelium for the development of cholinergic septohippocampal projection neurons and large subsets of basal forebrain cholinergic neurons. In the absence of NKX2-1, these neurons fail to develop, causing alterations in hippocampal theta rhythms and severe deficiencies in learning and memory. Our results demonstrate that learning and memory are dependent on NKX2-1 function in the embryonic septum and suggest that cognitive deficiencies that are sometimes associated with pathogenic mutations in NKX2-1 in humans may be a direct consequence of loss of NKX2-1 function.

INTRODUCTION

Nkx2-1 (also known as *Ttf1*, *Titf-1*, or *Tebp*) is a widely conserved homeobox-encoding "hub gene" with a high degree of connectivity and functional significance during embryogenesis (Kang et al., 2011). Mutations in *NKX2-1* in humans account for over 50% of cases presented with the rare autosomal dominant movement disorder benign hereditary chorea (BHC) (Inzelberg et al., 2011; Kleiner-Fisman and Lang, 2007; Peall and Kurian, 2015). More recently, psychiatric symptoms, as well as cognitive deficiencies that include mental retardation (Gras et al., 2012), learning difficulties (Gras et al., 2012), and memory deficits (Sempere et al., 2013) have been identified in individuals with mutations in NKX2-1, raising the possibility that NKX2-1 may be required for development of the cognitive system.

NKX2-1 orchestrates the development of the medial ganglionic eminence (MGE)—one of the main sites of expression of this gene—by repressing alternative neuroepithelial identities and activating MGE-specific transcriptional programs (Butt et al., 2008; Kessaris et al., 2014; Sandberg et al., 2016; Sussel et al., 1999). In the absence of NKX2-1, the MGE becomes respecified into alternative lateral ganglionic eminence (LGE)-like fates and downstream MGE-specific genes, some of which are direct targets of NKX2-1, fail to be activated (Du et al., 2008; Sandberg et al., 2016; Sussel et al., 1999). Hence, NKX2-1 constitutes one of the main factors that pattern the ventral forebrain and parcellate its germinal zones into functionally distinct progenitor pools.

The NKX2-1 neuroepithelial zone has been subdivided into several subdomains based on the combinatorial expression of a number of transcription factors (Flames et al., 2007). Although there is little evidence to date for entirely distinct neuronal fates arising from each domain, there are clear biases in neuronal subtype generation: for example, the dorsal MGE generates many more somatostatin (SST)-expressing cortical interneurons than parvalbumin (PV)-expressing ones compared to the ventral MGE (Flames et al., 2007; Fogarty et al., 2007). Similarly, preoptic area (POA) progenitors expressing NKX2-1 generate neurons of the globus pallidus, but only few interneurons for the cortex (Flandin et al., 2010). NKX2-1 is also expressed in the septal neuroepithelium (Flames et al., 2007; Rubin et al., 2010), where its function and the identity of neurons derived from it remain unexplored.

The adult septal complex and, in particular, the medial septum and vertical limb of the diagonal band (MSvDB), which contain the septohippocampal projection system, constitute one of the major subcortical brain areas that regulate learning and memory (Brandner and Schenk, 1998). Septohippocampal projections orchestrate hippocampal physiology by modulating synaptic plasticity and transmission (Colom, 2006; Drever et al., 2011; Nicoll, 1985). At a network level, the MSvDB provides a rhythmic input that drives the synchronous firing of hippocampal neurons, producing a prominent oscillatory brain activity known as theta rhythm (Buzsáki, 2002; Colom, 2006; Yoder and Pang, 2005). Hippocampal theta can be detected during voluntary movement (Whishaw and Vanderwolf, 1973) or highly aroused states (Buzsáki, 2005) and has been associated with navigation, spatial learning, and memory processes in humans and other species

