Mini-Symposium

Singing Mice, Songbirds, and More: Models for FOXP2 Function and Dysfunction in Human Speech and Language

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In 2001, a point mutation in the forkhead box P2 (FOXP2) coding sequence was identified as the basis of an inherited speech and language disorder suffered by members of the family known as "KE." This mini-symposium review focuses on recent findings and research-in-progress, primarily from five laboratories. Each aims at capitalizing on the FOXP2 discovery to build a neurobiological bridge between molecule and phenotype. Below, we describe genetic through behavioral techniques used currently to investigate FoxP2 in birds, rodents, and humans for discovery of the neural bases of vocal learning and language.

Key words: **basal ganglia; birdsong; brain development; chromatin immunoprecipitation; Forkhead; FOXP2; language; motor learning; song; speech; zebra finch**

Language is unique to humans, so how can neuroscientists study its molecular basis? The discovery that mutations in the human gene encoding forkhead box P2 (FOXP2), a transcription factor, result in speech and language deficits (Lai et al., 2001; MacDermot et al., 2005) provides a molecular toehold into exploration of the neural mechanisms for language. However, whose nervous system should be traversed? Humans must be explored, especially for understanding how human brains uniquely recombine a finite set of sounds to generate infinite meaning (Hauser et al., 2002). Another component of language, vocal learning, is also rare but not unique to humans. Vocal learners are animals with a talent for modifying innate vocalizations to imitate or create new sounds. Human speech and birdsong are the best characterized exemplars of vocal learning, and the experimentally tractable songbird has provided molecular and physiological insights. In contrast, transgenically tractable rodents are not thought to learn their vocalizations; however, the recent discovery that male mice produce ultrasonic sounds that are song like (Holy and Guo, 2005) reopens the question of whether such songs are learned.

Given the complexity of language and the variety of speech and language disorders (which affect up to 1 in 20 children), no single tissue or animal model is likely adequate for discovery of the neural bases. Fortunately, a model system need not capture every aspect of a behavior or disorder to be useful. Below, scientists, whose interests range from basic brain–behavior relationships to human cognitive specializations, apply their expertise and model systems to gain understanding of the neural basis of vocal learning and language. Given the firm association between FOXP2 mutations and language deficits, these scientists aim to identify the gene targets of this transcriptional regulator and to investigate the evolutionary, developmental, and real-time roles of FoxP2 in bona fide vocal learners, with a prospective of developing additional models.

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Investigating *FOXP2* mutations: humans, cell lines, and mutant mice (S. E. Fisher)

Genetic mapping in an unusual multigenerational family exhibiting a monogenic communication disorder (Fisher et al., 1998) provided the first link between *FOXP2* and language (Lai et al., 2001). Affected members of the "KE" family carry a heterozygous point mutation, yielding an amino acid substitution (R553H) in the DNA-binding domain of the FOXP2 protein. This tiny change correlates with a multifaceted phenotype (Marcus and Fisher, 2003; Vargha-Khadem et al., 2005) that includes profound deficits in learning and production of complex sequences of mouth movements, impairing speech (verbal dyspraxia), as well as wide-ranging problems with language, extending beyond expressive domains (Watkins et al., 2002a). Despite knowing the primary cause of this disorder, we have little understanding of how FOXP2 exerts its influence(s) on the brain. The Fisher laboratory and collaborators are using three complementary strategies to bridge this gene–brain gap.

Additional studies in humans

To date, insights into the *FOXP2*-associated disorder come predominantly from behavioral and neuroimaging studies of a single mutation, R553H, on one background, that of the KE family. These early efforts identified anomalies in subcortical structures (including caudate and cerebellum) (Watkins et al., 2002b) and

abnormal patterns of cortical activation during language-based tasks (Liegeois et al., 2003). To more fully reveal complex genotype–phenotype relationships, we screened the entire coding region of *FOXP2* in 49 probands diagnosed with verbal dyspraxia. We found a novel nonsense mutation (R328X) that truncates the protein and segregates with disorder in relatives of the proband (MacDermot et al., 2005). Detailed phenotypic studies of the family are underway. We and others are also studying cases of chromosomal rearrangement involving the *FOXP2* locus. These include translocations (Lai et al., 2001; Shriberg et al., 2006) as well as deletions that involve multiple genes (Liegeois et al., 2001; Zeesman et al., 2006).

Cell lines

Given the ethical and practical limitations to human studies, analyses of FOXP2 function using human neuron-like cells grown in the laboratory, although potentially "reductionist," can be highly informative. Such systems enabled us to assess disturbances in subcellular localization, DNA binding, and transactivation properties associated with the R553H and R328X mutations (Vernes et al., 2006). Moreover, *in vitro* models can be used to identify other elements in FOXP2-related pathways. For example, the Fisher laboratory and that of D. H. Geschwind have each used chromatin immunoprecipitation to isolate fragments of DNA that are directly bound by FOXP2 protein in living neurons, allowing us to successfully isolate downstream targets (see below, section by D. H. Geschwind).

Mouse models

Orthologs of FOXP2 are highly conserved across distant vertebrates in both coding sequence and CNS expression (Lai et al., 2003; Haesler et al., 2004; Teramitsu et al., 2004; Bonkowsky and Chien, 2005). Expression patterns suggest that FOXP2 in a common vertebrate ancestor may have influenced the emergence of circuits involved in sensory processing, sensorimotor integration, and control of skilled coordinated movements (Scharff and Haesler, 2005; Fisher and Marcus, 2006). Mice are highly effective systems for genetic manipulation, and we produced an allelic series of mice that carry *Foxp2* point mutations identical to those producing language disorders in humans. These models are important for studying etiological pathways at multiple levels (molecular, cellular, morphological, developmental, electrophysiological, and behavioral). Furthermore, although songbirds presently represent the model of choice for uncovering mechanisms involved in vocal learning (see below, sections by S. A. White and C. Scharff), mice still offer perspectives about the roles of genes in vocalizations. For example, a recent study by another group (Shu et al., 2005) reported that ablation of *Foxp2* in their targeted knock-out correlated with a reduction in the number of isolation calls made by mouse pups when removed from their mother, although no abnormalities in call structure were noted. Accordingly, we are in the midst of performing detailed analyses of the vocalizations in our *Foxp2* mutant lines. Intriguingly, Holy and Guo (2005) have discovered that vocalizations of adult male mice are more complex than previously appreciated and share characteristics of birdsong (see below, section by T. E. Holy). Whether or not such vocalizations are learned, it will be interesting to determine whether/how *Foxp2* mutations affect the properties of these "mouse songs."

Investigating FOXP2 function in cognition: genomic screening for FOXP2 targets in humans (D. H. Geschwind)

Evidence from many sources demonstrates a strong but complex genetic component for language that consists of many loci and interacts with environmental factors (Fisher et al., 2003). Although rare, monogenic disorders of speech and language, such as those caused by FOXP2 mutation, provide a unique window through which to study the biological basis of speech and language in health and disease. Thus, one of the goals of the Geschwind laboratory is to identify downstream targets of FOXP2 that may be relevant to human brain development, so as to learn more about the molecular events driving this complex process. Development of regional identity in the mammalian telencephalon occurs over a protracted period and is modifiable until the middle to late stages of neurogenesis and migration (in humans, 10–25 weeks gestation) (Barbe and Levitt, 1995; McConnell, 1995; Rakic, 1995; Fishell, 1997; Nothias et al., 1998; Rakic and Lombroso, 1998; Rubenstein and Beachy, 1998). This is thus a critical time to identify and study gene products involved in the development of human higher functions such as speech and language (Geschwind and Miller, 2001; Geschwind et al., 2002; Sun et al., 2005), including the effects of FOXP2 on the basal ganglia and cortex.

The Geschwind laboratory has developed a staged genomic screening approach using chromatin immunoprecipitation coupled to microarray analysis (ChIP–Chip) to identify potential neural targets of human FOXP2, both *in vitro* and *in vivo*. ChIP–Chip enables the genome-wide study of direct interactions between a protein and the chromosomal sites to which it binds, in the context of the normal chromatin structure of living tissue (Ren et al., 2000; Ren and Dynlacht, 2004). Briefly, cells or tissues are treated with a crosslinking agent, and then an antibody recognizing the protein of interest is used to selectively immunoprecipitate protein–DNA complexes. After reversing crosslinks, the recovered DNA is hybridized to arrays containing DNA from thousands of human genes, allowing systematic identification of transcription factor binding sites. For these experiments, we made high-affinity, specific polyclonal antibodies based on unique C-terminal regions of FOXP2. *In vitro*, ChIP exploited SH-SY5Y human neuroblastoma cells, after induction of FOXP2 expression via BDNF/retinoic acid treatment, whereas *in vivo*, ChIP involved material from human basal ganglia and inferior frontal cortex at midgestation. In each case, experiments were performed in triplicate, and the DNA that was pulled down was hybridized to microarrays containing ~700 bp of the promoter regions and 300 bp from the intronic regions of ~6000 human genes (Aviva Systems Biology Corporation, San Diego, CA). Target sequences are found in genes from a variety of gene ontology categories, including those involved in neural development.

ChIP–Chip can identify regions of transcription factor binding at high specificity (Ren et al., 2000; Ren and Dynlacht, 2004; Kim et al., 2005). However, it does not determine whether binding has a functional effect on the putative target gene or whether binding results in transcriptional repression or activation. In the last stage of this genomic screening experiment, we used small interfering RNA and overexpression *in vitro* to demonstrate functional effects of FOXP2 binding on target genes suggested by ChIP–Chip. The function and expression of these genes vis-à-vis the development of circuits involved in speech and language and disorders disrupting them (e.g., autism; specific language impairment) are now important avenues of our research.

Dynamic regulation of *FoxP2* during singing (S. A. White)

The corticostriatal abnormalities that accompany verbal dyspraxia in humans bearing *FOXP2* mutations implicate FOXP2 in the ontogenesis of neural circuitry involved in speech and language. Accordingly, the powerful strategies outlined above use

FOXP2 as a molecular entry point toward understanding how the brain develops this capacity. The White laboratory and that of C. Scharff (see below, section by C. Scharff) have used songbirds as behaviorally relevant and physiologically accessible models to determine whether FOXP2 additionally functions during vocal learning and in adulthood (Scharff and White, 2004). To address the question of a real-time role during vocalization, the White laboratory has examined *FoxP2* mRNA expression in zebra finches, a songbird species in which males sing stable, unchanging songs to court females. Any alteration in *FoxP2* within the song control regions of adult singers would thus reflect real-time changes rather than the developmental or seasonal ones, discussed below.

Male zebra finches offer another potential insight to a behavioral role of FoxP2 because they display two basic types of singing: "directed" singing is when a male performs to a female; "undirected" singing is when a male practices alone or sings in the presence of, but not toward, conspecifics (Zann, 1996). These acoustically similar yet socially distinct vocal behaviors allowed us to address whether any mature function of FoxP2 is purely motor or also contingent on social context (Jarvis et al., 1998).

We found that *FoxP2* mRNA declines rapidly and specifically within the striatal song control region Area X when males sing but is stable in nonsinging birds. Furthermore, this decline occurs when males practice alone but not when they perform to females (Teramitsu and White, 2006). This real-time regulation of *FoxP2* during vocalization, dependent on social context, suggests that FoxP2 functions beyond development and beyond pure motor control. Obtained from a humble grass finch, these data nonetheless support the conclusion that human *FOXP2* mutations entail more than motor deficits (Watkins et al., 2002a) and suggest, by analogy, postdevelopmental roles for FOXP2 in human speech.

FoxP2 in brain evolution, development, and vocal learning: more perspectives from the birds (C. Scharff)

FOXP2 has undergone recent positive selection in human history (Enard et al., 2002; Zhang et al., 2002). Given the established finding that *FOXP2* mutations lead to speech and language disorders, it is tempting to speculate that the adaptive evolution of human *FOXP2* may have related to the emergence of modern speech capacities (Enard et al., 2002; Zhang et al., 2002). Among birds, however, there is no evidence that Darwinian selection of changes in the FoxP2 protein sequence contributed to vocal learning in some, but not other, avian species (Webb and Zhang, 2005). Given this evolutionary difference, can findings from songbirds really be relevant to the role of FOXP2 in human speech? Perhaps. To begin, despite some differences, the FoxP2 protein of songbirds is astonishingly similar to mammalian FoxP2: for example, the zebra finch and human sequences share 100% identity within the DNA-binding domain (Haesler et al., 2004; Teramitsu et al., 2004). A strong conservation like this often indicates shared function. Furthermore, the FoxP2 expression pattern in the brain of many birds that learn their songs by imitation is very similar to that of rodents and humans, including expression within the same cell types, such as striatal medium spiny neurons (Scharff and Haesler, 2005). FoxP2 is expressed early in the embryo and remains "on" in some regions into adulthood. What does this have to do with speech? It suggests that FoxP2 is necessary to allow brain regions involved in vocal behavior to develop properly during embryonic life (see above, sections by S. E. Fisher and D. H. Geschwind). If so, does it fulfill a related, or a different, role later in life, after the brain has finished its "construction phase"?

To address the latter question, the Scharff laboratory examined *FoxP2* mRNA expression in young male zebra finches. We found that, when the birds are in full swing of learning to sing, there is more *FoxP2*, bilaterally in Area X (Haesler et al., 2004), the striatal region known to be vital for song learning (Sohrabji et al., 1990; Scharff and Nottebohm, 1991). This finding suggests that FoxP2 might be directly involved in the learning, but perhaps this is just coincidence. However, adult canaries also have higher *FoxP2* expression in Area X exactly during those months of the year when they remodel their song after having previously sung very stable song to woo females (Haesler et al., 2004). Coincidence again? To find out whether FoxP2 is required for song behavior, we need to get rid of it, at the right time, in the right place. Because knock-out technology is not yet available for songbirds, we use RNA interference to downregulate *FoxP2* in Area X. These studies, still ongoing, should soon provide answers to the following questions. Can zebra finches still sing normal song after growing up with less FoxP2 in Area X than normally present? Even more interestingly, will they still copy the song of an adult male tutor? By selecting an animal model (here, a songbird) that exhibits key aspects of the behaviors affected in humans with *FOXP2* mutations (here, vocal learning), the potential for observing the effects of functional intervention can be realized.

Analyzing the ultrasonic songs of male mice (T. E. Holy)

Although the most widely appreciated vocalizations of mice are audible, it has been known for several decades that mice and other rodents also vocalize at ultrasonic frequencies. In the Holy laboratory, we recorded and analyzed the vocalizations of a sizable population of adult males. When the recordings were computationally shifted into the range of human hearing, these vocalizations were found to be subjectively reminiscent of bird songs.

To objectively determine the extent of similarity with bird songs, individual syllables were analyzed quantitatively (Holy and Guo, 2005). Mouse syllables can be classified into distinct types, with several different approaches yielding consistent classifications. These vocalizations are also structured in time. During a bout of vocalization, syllable types are arranged in nonrandom order, with the most obvious characteristic being that particular types tend to be repeated several times before a new syllable type is uttered. Finally, individual mice show reproducible biases in terms of their syllable type usage and degree of repetitiveness, traits that reliably distinguish them from other males. Consequently, these vocalizations have many of the characteristics that have been described for birdsong.

Recently, we further examined the stimulus triggers for these songs. Previous work has shown that males vocalize in the presence of females and also when they encounter mouse pheromones, chemosensory cues detected by the olfactory system. We examined whether the songs uttered in the presence of male cues are different from those triggered by female cues. We find that the songs differ greatly in terms of degree (with far more singing triggered by female than by male cues) but do not find any consistent difference in the character of the songs. Together, these discoveries increase the attractiveness of mice as model systems for study of vocalizations (see above, section by S. E. Fisher).

Conclusion

The first report of *FOXP2* as a monogenetic locus of a speech and language disorder has enabled great strides in the design and execution of experiments that bring us closer to understanding the biological basis of vocal learning and language. These reflect

the creativity and power of comparative and integrative approaches for understanding behavior, including those that are cognitively complex.

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