Topic Introduction

Generating and Imaging Multicolor Brainbow Mice

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INTRODUCTION

Visualizing the precise morphology of closely juxtaposed cells and their interactions can be highly informative, particularly when studying the complex organization of neuronal and glial networks in the nervous system. To this end, one can use optical approaches to image distinct markers that are differentially distributed among the cells of interest, such as fluorescent proteins of various colors (XFPs). The Brainbow strategies use Cre/*lox* recombination to stochastically express two to four XFPs in a cellular population from a single promoter. Integration of multiple *Brainbow* transgene copies results in combinatorial expression of these XFPs, creating a wide range of hues. In the nervous system, the multicolor labeling thus generated can be used to distinguish adjacent neuronal or glial cells and to verify the identity of neuronal processes while tracing circuitry. This article describes the generation of *Brainbow* transgenes and mice as well as their use to image and digitally reconstruct nerve cells and their interactions in fixed samples. This method also holds potential for studies in other tissues and model organisms as well as live imaging in vivo.

RELATED INFORMATION

A protocol is available for **Generation and Imaging of Brainbow Mice** (Weissman et al. 2011).

OVERVIEW OF THE BRAINBOW APPROACH

The complex circuitry of neuronal processes poses serious challenges to visualizing and understanding the behaviors of individual neurons and their connectivity. For brain studies, one would ideally want to view the precise morphology of multiple (or all) neighboring neurons in a brain circuit. To achieve this goal, a method is needed to highlight neurons while, at the same time, distinguishing them from their neighbors. The Brainbow approach is designed to label cells with distinct fluorescent proteins (FPs), such as cyan fluorescent protein (CFP), yellow fluorescent protein (YFP), or red fluorescent protein (RFP), using a single transgene (Livet et al. 2007; Lichtman et al. 2008) (Fig. 1). On the basis of Cre/*lox*-mediated DNA excision or inversion (Branda and Dymecki 2004), *Brainbow* transgenes trigger the stochastic expression of two to four XFPs in a cellular population, such that each cell randomly adopts one color. If only one copy of the Brainbow construct is present in cells, the recombination choice leads to mutually exclusive expression of XFPs. For example, cell A will express one XFP, whereas cell B will express a different XFP. However, when multiple *Brainbow* transgene copies coexist in cells, each copy makes its own stochastic choice, yielding combinatorial expression of XFPs and creating a wide range of additional colors (Fig. 2). In other words, cell A may express one or a combination of XFPs, whereas cell B may express a different combination or ratio of XFPs.

Because the choice is made in the genome, the entire cell, including all processes, can adopt a single color. These hues allow one to distinguish cells in complex tissues and to visualize their contacts with other cells. In the nervous system, the multicolor labeling provides a method to verify the identity of neuronal processes while tracing them in three-dimensional (3D) image data sets. Individual axons can be distinguished from their neighbors and traced over large distances (Fig. 3). Here, we describe Brainbow strategies, how *Brainbow* transgenes and mice are generated, and the advantages and limitations of this technique.

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FIGURE 1. Principle of Brainbow strategies. In *Brainbow-1.0* and *Brainbow-1.1*, pairs of incompatible (heterospecific) lox variants are interleaved, creating two or three mutually exclusive excision possibilities. Each of these excisions triggers the expression of a distinct XFP. In *Brainbow-2.0*, loxP sites are positioned in opposite orientation, defining an invertible DNA segment in which two XFP genes are placed head to head. This construct can invert as long as Cre is active. When it stabilizes, the XFP gene ending in a sense orientation is expressed. In *Brainbow-2.1*, two invertible units are positioned in tandem, offering additional excision and inversion options, and yielding a total of four expression possibilities.

BRAINBOW STRATEGIES

Several types of *Brainbow* transgenes are available (Table 1; Livet et al. 2007) using Cre-mediated DNA excision (*Brainbow-1.0* and *Brainbow-1.1*), inversion (*Brainbow-2.0*), or both excision and inversion (*Brainbow-2.1*) (Fig. 1). An important parameter that may guide the user's choice of transgene is the number of desired recombination outcomes, which determines how many different XFPs can be expressed in the mice. A second parameter is the source of Cre available to trigger recombination.

FIGURE 2. Mosaic expression of fluorescent proteins in Brainbow mice. (A,B,D,E) *Thy1.2-Brainbow-1.0* line L; (C) line H. Combinatorial expression of FPs is observed throughout the brain. (A) Purkinje neurons of cerebellum; (B) dentate gyrus of the hippocampus; (C) brain stem; (D) cortex (layers 3–5); (E) hippocampus CA1. Scale bars, 125 μ m (A); 150 μ m (B); 40 μ m (C); 100 μ m (D); 40 μ m (E).

FIGURE 3. Circuit tracing using Brainbow multicolor labeling. (A) The confocal data set of the inner granular layer of the cerebellum was resampled in the y–z orientation to provide this view orthogonal to most axons (A1). In this orientation, each cellular component was traced with Reconstruct (A2). Small spots are axons; enlarged, bright objects are mossy fiber rosettes. (B) Three-dimensional reconstruction of cerebellar mossy fiber axons and granule cells. A mossy fiber contact with a granule cell is visible (indicated by the white arrowhead and enlarged in B2). B1 also shows two different rendering options in Reconstruct: Boissonant surface (top, left) and individual traces (bottom, right). Scale bars, 20 μ m (A); 10 μ m (B).

Brainbow-1.0 and *Brainbow-1.1* transgenes lead to dead end products following Cre-mediated DNA excision and are, therefore, largely compatible with any form of Cre, whereas the inversion-based *Brainbow-2.0* and *Brainbow-2.1* transgenes undergo repeated reaction cycles that might lead to chromosome breaks; they, therefore, appear to require transient Cre activity to stabilize their orientation (Table 1). Several strategies are available to limit Cre activity in time (Lam and Rajewsky 1998; Silver and Livingston 2001).

Colors

Depending on the purpose of the experiment, it may be useful to express either a large or a restricted number of XFP combinations or, in some instances, only one XFP per cell. In Brainbow mice, the

Table 1. Brainbow strategies

Brainbow strategy	Principle used for stochastic expression	Total number of transgene configurations (prior to and after recombination)	Brainbow lines available at Jackson Laboratories	Summary of outcomes in available constructs (before Cre → after Cre)
Brainbow-1.0	Excision	3	H, L ^a	R → Y/C
Brainbow-1.1	Excision	4	M ^b	O → R/Y/C
Brainbow-2.0	Inversion	2	—	R → (C ↔ R)
Brainbow-2.1	Inversion and excision	4	R ^c	G → (C ↔ R)/(G ↔ Y)

The nomenclature for construct and mouse lines follows the one used in Livet et al. (2007): (R) red fluorescent protein (RFP); (Y) yellow fluorescent protein (YFP); (C) cyan fluorescent protein (CFP); (O) orange fluorescent protein (OFP); (G) green fluorescent protein (GFP).

^aLine H expresses membrane-targeted YFP and CFP, whereas line L expresses three cytoplasmic XFPs.

^bExpression in this line is mostly restricted to astrocytes and hippocampal mossy fibers; OFP is undetected.

^cExpression is in scattered neurons and astrocytes.

number of those color combinations may be influenced by several parameters—in particular, how many *Brainbow* transgene copies are integrated into the genome and can recombine independently. In mice generated by embryonic stem-cell technology, a single copy of the *Brainbow* construct should be present, yielding only exclusive XFP expression. Conversely, in mice produced by pronuclear injection, multiple tandem transgene copies are likely to integrate (Palmiter and Brinster 1986), enabling a greater range of color combinations. In such an array, transgene copy number may be modulated by intercopy recombination (Garrick et al. 1998). One way to do this is to use a site-specific recombinase such as FLP; to this end, an FRT site has been inserted in several *Brainbow* constructs. In mice bearing tandem *Brainbow* transgene copies, some amount of Cre-mediated intercopy recombination (favored by extended recombination times, high levels of Cre, and short target transgenes) may also occur and could reduce both the intensity of the labeling and the number of color combinations generated. The length of the *Brainbow* transgene, as well as the particular Cre driver line used are, therefore, important parameters to consider when planning an experiment.

Color-Assisted Circuit Tracing

There is a growing interest among neuroscientists to develop tools for the automatic segmentation of 3D data sets. At present, the tracing of multicolor images still relies on human input aided by semiautomated tools. *Brainbow* image data sets can be segmented in this manner, allowing axonal processes to be traced over distances of at least several hundred micrometers (Fig. 3). Such efforts, coupled with the visualization of the neuron's contact with neighboring cells, can provide important information about circuitry, both within and among brain regions. For example, in several instances it is possible to visualize a neuron and immediately determine whether its multiple synaptic inputs arise from distinct (differently colored) cells. This is an advantage over serial reconstruction methods with unlabeled tissues that require tracing nerve processes back to their origin or at least a branch point. There are several current options for digital reconstruction of *Brainbow* data sets, and new programs are under development.

GENERATION OF *BRAINBOW* TRANSGENES

Several *Brainbow* cassettes expressing XFPs from a *Thy1.2* or CMV promoter are available through Addgene.com, which is a nonprofit plasmid-sharing resource. Alternatively, one may assemble a *Brainbow* transgene from basic elements (see Fig. 1).

Promoter

In principle, any promoter can drive *Brainbow* construct expression. We advise the choice of a strong promoter such as *Thy1.2* (Caroni 1997; Feng et al. 2000), which is able to express readily detectable levels of GFP in transgenic mice.

lox Sites

Recombination of *Brainbow-1* constructs relies on incompatible *lox* variants. We advise using *lox2272* (Lee and Saito 1998) and *loxN* (Livet et al. 2007), each of which possesses distinct substitutions at positions 2 and 6 in the spacer of the *lox* sequence. In our experience with expression in mammalian cells, these sites constitute, along with the canonical *loxP*, a set of three efficient and mutually incompatible *lox* variants.

XFPs

A wide palette of FPs is presently available for transgene design (Shaner et al. 2007; Day and Davidson 2009), but few have been tested in transgenic mice. Enhanced green fluorescent protein (eGFP) and enhanced yellow fluorescent protein (eYFP) have been the most successful variants by far. Cyan proteins (eCFP and Cerulean) and red proteins (DsRed2, tdimer2[12], and dTomato) can give good signals, but do not match green and yellow proteins in terms of photostability and longevity in fixed tissues. To facilitate multichannel imaging, one should select XFPs that are spectrally well separated. Cyan (eCFP or Cerulean), yellow (eYFP), and red (DsRed2, d/TdTomato, and mCherry) FPs constitute a first set of three easily distinguishable XFPs. Green (eGFP) or orange (Kusabira, mOrange2), when added to this palette, may require linear unmixing techniques for good optical separation. New proteins in the blue, red, and

far-red range may allow the creation of new and improved transgenes (Ai et al. 2007; Shaner et al. 2008; Shcherbo et al. 2009).

Subcellular Localization Signals

Cytoplasmic XFPs provide a good rendering of the volume of neuronal cell bodies and large neurites (Feng et al. 2000). *Brainbow* line L, which expresses three such proteins is, therefore, recommended for most applications. However, a more restricted repertoire of structures can be highlighted when fusing XFPs to specific localization tags. In particular, membrane-targeted XFPs, such as those used in *Brainbow* line H, are well suited to highlight fine axonal processes (De Paola et al. 2003) and axons of specific neuronal populations, such as cerebellar and hippocampal mossy fibers. However, compared with cytoplasmic proteins, membrane-tagged XFPs often make cell bodies harder to visualize, especially in densely labeled samples. Other useful tags used in mice include nuclear and mitochondrial localization sequences (Misgeld et al. 2007).

Elements for Optimized Expression

Open reading frames in *Brainbow* constructs should have a translation initiation consensus sequence (Kozak 1987), a codon usage optimized sequence (Haas et al. 1996), and an efficient polyadenylation signal (Kakoki et al. 2004).

FRT Site

One *FRT* site, the target sequence for Flp recombinase, can be inserted in a *Brainbow* construct for transgene copy-number reduction in tandem arrays (Garrick et al. 1998). Crossing *Brainbow* animals with germline-expressing Flp mice (Rodriguez et al. 2000) triggers recombination between *FRT* sites located on distinct *Brainbow* copies, thus reducing the transgene array. With large transgenes, this process may sometimes take several generations.

BRAINBOW TRANSGENIC MICE

Several *Thy1-Brainbow* lines (H, L, M, and R) can be obtained from Jackson Laboratories (JAX stock numbers 007901, 007910, 007911, and 007921, respectively; see Table 1). Line L, which expresses three cytoplasmic proteins in a combinatorial manner, should offer the most flexible usage. It shows strong XFP expression, although not as high as in some *Thy1-XFP* lines selected earlier, such as YFP-16, YFP-H, or GFP-M (Feng et al. 2000). Lines H, M, and R, which express mixed cytoplasmic and membrane-targeted XFPs, will likely have more restricted applications.

CRE MICE

Recombination can be triggered with various Cre driver lines, which are available from several locations, including Jackson Laboratories. We use *CAGGS-CreER* mice (Guo et al. 2002) and tamoxifen (Metzger et al. 1995) to create a widespread pulse of recombinase activity in *Brainbow* mice, which robustly triggers expression of XFPs from *Brainbow* transgenes. *Brainbow-1* mice, which can tolerate tonic Cre expression, have also been used with retina- and motor neuron-specific Cre lines.

PROS AND CONS OF BRAINBOW IMAGING

Because they can be genetically encoded, spectrally distinct FPs (XFPs) represent ideal labels for in situ and live imaging studies. Several approaches have emerged for combining two or more of these XFPs in the same animal to distinguish adjacent cells and highlight their interactions. A first set of approaches involves generating several transgenes, each encoding a different color, and coexpressing them in the same animal through various strategies—for example, generation of chimeric animals (Hadjantonakis et al. 2002), interbreeding (Feng et al. 2000; Kasthuri and Lichtman 2003; Walsh and Lichtman 2003), or viral injection (Boldogkoi et al. 2009). A second set of approaches swaps XFP genes expressed from a single locus using Cre- or Flp-mediated excision (Muzumdar et al. 2007) or even interchromosomal recombination (Zong et al. 2005).

Among these methods, Brainbow strategies offer several advantages. First, using the divergent recombination pathways proposed by *Brainbow* transgenes, up to four genes can be stochastically expressed in a cellular population from a single construct. Furthermore, combinatorial expression from multiple transgene copies recombining independently vastly increases the number of expression possibilities. Importantly, it is possible to control whether mutually exclusive or combinatorial expression is obtained by manipulating copy number. In Brainbow mice, cells of a same type, although a priori genetically identical, have a large chance of being labeled with distinct colors, which allows for visualizing their interactions.

This multicolor labeling can be visualized in fixed tissues and also in live conditions with confocal or epifluorescence microscopy (see Livet et al. 2007). However, those techniques are best suited for surface imaging. Multiphoton microscopy allows for increased penetration as well as lower phototoxicity. But for optimal multiphoton excitation of CFP, YFP, and RFP, it appears necessary to either tune the wavelength of the pulsed laser source or simultaneously produce at least two spectrally distinct pulsed excitations. In part, because of these technical issues, the potential of the Brainbow approach for volume live imaging in vitro or in vivo has thus far been largely unexplored. New setups and Brainbow mice should solve these difficulties, with the possible help of spectral unmixing strategies (Ducros et al. 2009).

Current *Brainbow* transgenes could potentially be improved in several aspects; in particular, regarding the photochemical characteristics and expression level of their fluorochromes. Adequate promoters and Cre drivers should allow for expanding *Brainbow* transgene expression to neuronal types and stages not targeted with the current *Thy1.2* promoter. The method appears broadly applicable to other cell types and models—see, in particular, Pan et al. (2011) for studies demonstrating Brainbow in zebrafish. It could, in principle, be used to express genetic markers of any type.

Perhaps the main drawback of the Brainbow method is that, like any optically based method, it is currently limited in resolution by the diffraction of light. *Brainbow* transgenes allow, to some extent, this limit to be bypassed when attributing unambiguous labels to two adjacent cells. However, when several subdiffraction processes overlap in the same focal volume, their individual spectral signatures become difficult to extract (Helmstaedter et al. 2008). One way to overcome this problem is to analyze samples presenting intermediate sparse labeling of neurons. In the future, restricting the combinatorial labeling to synapses, or combining the Brainbow approach with other approaches such as electron microscopy, array tomography, or super-resolution imaging could provide promising methods to overcome the resolution issue (e.g., Kasthuri and Lichtman 2007; Micheva and Smith 2007; Huang et al. 2009; Mishchenko 2010).

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