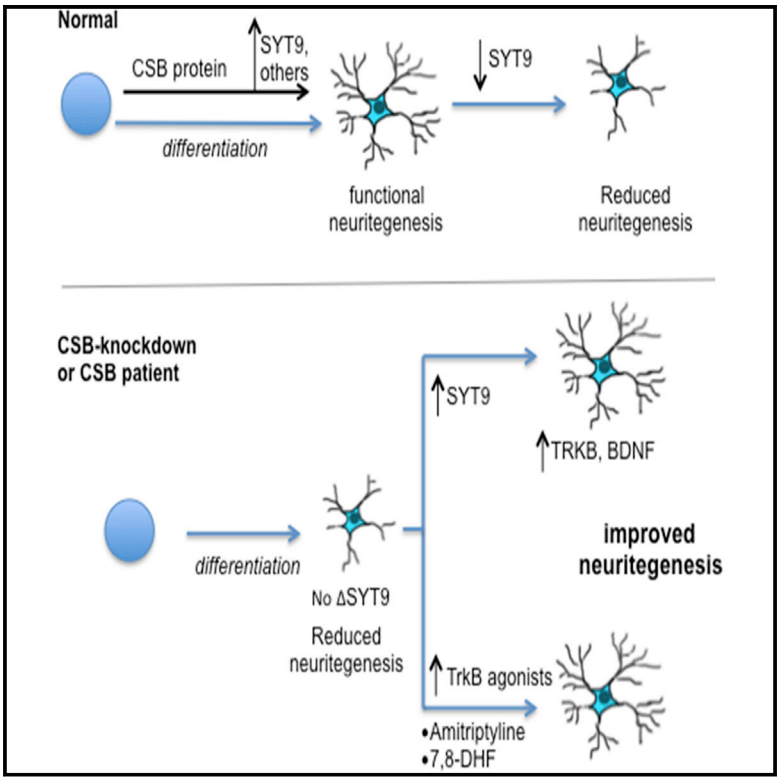
Cell Reports

Pharmacological Bypass of Cockayne Syndrome B Function in Neuronal Differentiation

Graphical Abstract



Highlights

- Neuritogenesis defects in CS cell lines can be overcome by overexpression of SYT9
- SYT9 is crucial for neuritogenesis and involved in neurotrophin (BDNF) signaling
- Neuritogenesis defects in CS cell lines can be overcome by BDNF treatment
- They can also be overcome by treatment with amitriptyline, an FDA-approved BDNF mimic

Authors

Yuming Wang, Jace Jones-Tabah, Probir Chakravarty, Aengus Stewart, Alysson Muotri, Rebecca R. Laposa, Jesper Q. Svejstrup

Correspondence

jesper.svejstrup@crick.ac.uk

In Brief

Wang et al. show that Cockayne syndrome cell lines have defects in gene regulatory loops, resulting in sub-optimal neurotrophin signaling and explaining their defects in neurogenesis. These defects can be overcome by Synaptotagmin 9 overexpression or by treatment with NTRK2 (TrkB) agonists, pointing to future disease intervention.

Accession Numbers

GSE58072

Wang et al., 2016, Cell Reports *14*, 2554–2561
March 22, 2016
http://dx.doi.org/10.1016/j.celrep.2016.02.051

OPEN ACCESS
CellPress

Cell Reports
Report

Pharmacological Bypass of Cockayne Syndrome B Function in Neuronal Differentiation

Yuming Wang,[1,6] Jace Jones-Tabah,[2] Probir Chakravarty,[3] Aengus Stewart,[3] Alysson Muotri,[4,5] Rebecca R. Laposa,[2] and Jesper Q. Svejstrup[1,*]

[1]Mechanisms of Transcription Laboratory, Clare Hall Laboratories, The Francis Crick Institute, South Mimms, Hertfordshire EN6 3LD, UK
[2]Department of Pharmacology and Toxicology, University of Toronto, 1 King's College Circle, Toronto, ON M5S 1A8, Canada
[3]Bioinformatics & Biostatistics Group, The Francis Crick Institute, 44 Lincoln's Inn Fields, London WC2A 3LY, UK
[4]Department of Pediatrics
[5]Department of Cellular and Molecular Medicine
University of California, San Diego, 2800 Torrey Pines Scenic Drive, La Jolla, CA 92037, USA
[6]Present address: State Key Laboratory of Ophthalmology, Zhongshan Ophthalmic Center, Sun Yat-sen University, Guangzhou 510060, China
*Correspondence: jesper.svejstrup@crick.ac.uk
http://dx.doi.org/10.1016/j.celrep.2016.02.051

SUMMARY

Cockayne syndrome (CS) is a severe neurodevelopmental disorder characterized by growth abnormalities, premature aging, and photosensitivity. Mutation of Cockayne syndrome B (CSB) affects neuronal gene expression and differentiation, so we attempted to bypass its function by expressing downstream target genes. Intriguingly, ectopic expression of Synaptotagmin 9 (SYT9), a key component of the machinery controlling neurotrophin release, bypasses the need for CSB in neuritogenesis. Importantly, brain-derived neurotrophic factor (BDNF), a neurotrophin implicated in neuronal differentiation and synaptic modulation, and pharmacological mimics such as 7,8-dihydroxyflavone and amitriptyline can compensate for CSB deficiency in cell models of neuronal differentiation as well. SYT9 and BDNF are downregulated in CS patient brain tissue, further indicating that sub-optimal neurotrophin signaling underlies neurological defects in CS. In addition to shedding light on cellular mechanisms underlying CS and pointing to future avenues for pharmacological intervention, these data suggest an important role for SYT9 in neuronal differentiation.

INTRODUCTION

Cockayne syndrome (CS) is a hereditary, multisystem disease, characterized by neurological and developmental impairment as well as sun sensitivity and progeroid-like features (Brooks, 2013). Despite the accumulating knowledge on the role of the main causative gene, *Cockayne syndrome B* (*CSB*), in the control of various biological processes, an understanding of its role in CS has been missing. Indeed, a lack of effective mechanism-based therapeutic approaches means that CS is devastating, with a large number of symptoms related to nervous system deficiencies and often resulting in death within the first decade of life.

CSB is a member of the SWI2/SNF2 family of ATP-dependent chromatin remodeling factors (Troelstra et al., 1992; Citterio et al., 1998), and its mutation accounts for the vast majority (~80%) of CS cases. Certain mutations in the CS genes can also give rise to the clinically less severe UV-sensitive syndrome (UVSS) (reviewed in Spivak, 2005). CSB is a multi-functional factor. Indeed, it has been implicated not only in transcription-coupled nucleotide excision repair (TC-NER) and base excision repair but also in mitochondrial function and regulation of transcription (reviewed in Weidenheim et al., 2009; Brooks, 2013; Scheibye-Knudsen et al., 2013; Vélez-Cruz and Egly, 2013; Vermeulen and Fousteri, 2013).

Studies of the molecular mechanisms underlying human disease have often relied on animal models. Intriguingly, while mice lacking *Csb* show sun sensitivity, they do not display the same severe growth retardation, neurologic defects, or high early mortality that is characteristic of human CS patients (van der Horst et al., 1997). Thus, the mouse model appears to provide an excellent model for UVSS, while it is arguably somewhat less helpful for our understanding of CS. Interestingly, recent studies in different human cell differentiation systems showed that a lack of functional CSB represents a barrier to neuronal cell differentiation (Ciaffardini et al., 2014; Wang et al., 2014). For example, we reported that direct reprogramming of CS fibroblasts to neurons is defective and that little or no differentiation of neuroblastoma cells to neuron-like cells was observed in the absence of CSB (Wang et al., 2014). This correlated with gene expression defects in neuronal gene networks (which were not observed in the mouse), suggesting that transcription defects, rather than DNA repair- or mitochondrial defects, underlie the severe neurologic symptoms of CS (Wang et al., 2014). However, the mechanism and important downstream implementing factors remained unknown. Crucially, without knowledge of these