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Schizophrenia: The 'BLOC' May Be in the Endosomes

Pearl V. Ryder[1] and **Victor Faundez**[2,3]

[1]Graduate Program in Biochemistry, Cell, and Developmental Biology, Emory University, Atlanta, GA 30322

[2]Department of Cell Biology, Emory University, Atlanta, GA 30322

[3]Center for Neurodegenerative Diseases, Emory University, Atlanta, GA 30322

Abstract

Genome-wide association studies have identified multiple genetic polymorphisms associated with schizophrenia. These polymorphisms conform to a polygenic disease model in which multiple alleles cumulatively increase the risk of developing disease. Two genes linked to schizophrenia, *DTNBP1* and *MUTED*, encode proteins that belong to the endosome-localized **B**iogenesis of **L**ysosome-related **O**rganelles **C**omplex-1 (BLOC-1). BLOC-1 plays a key role in endosomal trafficking, and as such has been found to regulate cell surface abundance of the D2 dopamine receptor (DRD2), the biogenesis and fusion of synaptic vesicles, and neurite outgrowth. These functions are pertinent to both neurodevelopment and synaptic transmission, processes tightly regulated by selective cell surface delivery of membrane proteins to and from endosomes. We propose that cellular processes, such as endosomal trafficking, act as convergence points where multiple small effects from polygenic genetic polymorphisms pileup to trigger schizophrenia.

Schizophrenia is a devastating mental illness that can lead to the inability to live independently within our society. Genetic factors and their interactions with the environment account for 80% of the susceptibility for disease emergence [1]. The identity of these genetic factors is the subject of intense scrutiny. Recent genome-wide studies suggest that the risk of developing schizophrenia is polygenic, with multiple common allelles each contributing a small effect [2]. Such studies have identified a plethora of polymorphisms associated with the illness. Moreover, the genes identified as associated with schizophrenia have markedly diverse functions; they include genes implicated in signal transduction, growth cone guidance, pre- and post-synaptic neurotransmission, and vesicular membrane protein trafficking [2–7].

Pathogenic hypotheses for schizophrenia have tended to emphasize individual genes of "interest" [1, 8]. Broadly, these hypotheses fall into two main categories: neurochemical or neurodevelopmental [8, 9]. The neurochemical hypotheses focus on alterations in neurotransmitter systems, such as dopamine, glutamate or GABA, and are substantiated by neurotransmitter abnormalities found in the brains of affected individuals, as well as the mechanism of action for pharmacological agents used in treating or inducing schizophrenia

Address correspondence to: Victor Faundez, Department of Cell Biology, Emory University School of Medicine, 615 Michael Street, Room 446, Atlanta, GA 30322, Telephone: 404-727-3900, Fax: 404-727-6256, faundez@cellbio.emory.edu.

symptoms [9, 10]. The neurodevelopmental hypotheses encompass structural alterations in the brain of schizophrenic patients that emerge early in life [9, 11]. Here, we discuss studies by several groups that focus on the biogenesis of lysosome-related organelles complex-1 (BLOC-1) [12–14]. These studies implicate endosomal trafficking to and from the plasma membrane as a cellular mechanism that could link the neurochemical and neurodevelopmental hypotheses of schizophrenia.

Eight subunits constitute the BLOC-1 complex: dysbindin, muted, pallidin, cappuccino, snapin, BLOS1-3 [15]. This complex is present on transferrin-receptor positive endosomes, where it regulates membrane protein targeting to synaptic vesicles, lysosomes, and lysosome-related organelles [13, 16, 17]. BLOC-1 subunits are tightly bound, as evidenced by the observation that all of the dysbindin and pallidin protein in the brain copurify as a complex with the predicted molecular mass of the BLOC-1 complex [12]. Mice with genetic defects in BLOC-1 subunits further highlight the tight structural organization of BLOC-1 complex. Most null alleles of genes encoding BLOC-1 subunits lead to almost identical cell and organism phenotypes [18–21]. Among these phenotypes, the absence of any one of the BLOC-1 subunit proteins triggers the disappearance of all other BLOC-1 protein complex subunits [12, 18, 19, 22].

Two of the BLOC-1 complex subunits, dysbindin (encoded by *DTNBP1*) and muted (encoded by *MUTED*), have been associated with increased risk of schizophrenia [23, 24]. Several population genetic studies have replicated the association of *DTNBP1* variants with schizophrenia [3, 8]. Importantly, dysbindin mRNA and protein abundance are decreased in the brain of schizophrenics [25, 26]. Based on these data, the hypothesis that BLOC-1 is implicated in the pathogenesis of schizophrenia leads to three predictions. First, BLOC-1-deficient mice should have neurological phenotypes consistent with the disease. Second, genetic polymorphisms in *DTNBP1* associated with schizophrenia should trigger reduced levels of dysbindin in the brain of schizophrenic patients. Finally, brain tissue from schizophrenics with decreased dysbindin protein levels should also possess reduced levels in other BLOC-1 subunits, irrespective of whether these other BLOC-1 subunit genes were to carry disease-associated polymorphisms. The first prediction has been documented in dysbindin deficient mice, *sandy*, which display impaired social interactions and working memory both phenotypes consistent with schizophrenia [11, 27–29]. Similarly, *DTNBP1* disease-associated polymorphisms decrease the levels of *DTNBP1* transcripts in human cortex [30], thus supporting the second prediction. However, there is neither evidence to support the last prediction nor is there information about the developmental stage at which deficiencies in BLOC-1 function may impact the brain in schizophrenic patients.

Key observations of Ghiani *et al.* [12] suggest that BLOC-1 function may be required in the neonatal period, an observation consistent with the neurodevelopmental hypothesis of schizophrenia. First, they found that brain dysbindin and pallidin protein levels were the highest perinatally and declined in adulthood. Second, they described that loss of BLOC-1 in pallidin-null mice led to neurite outgrowth defects in primary cultured hippocampal neurons [12]. However, the effects of BLOC-1 extend beyond developmental processes. For instance, Iizuka *et al.* found that BLOC-1 decreases the cell-surface abundance and activity of the D2 dopamine receptor (DRD2). In neuronal cells where BLOC-1 was down-regulated by

siRNA, the surface abundance of DRD2 and receptor-dependent signal transduction increased [31]. Intriguingly, *DRD2*, which encodes DRD2, is, like dysbindin, considered a candidate schizophrenia susceptibility gene [8]. Indeed, the D2 dopamine receptor plays a central role in the well-known dopamine hypothesis of schizophrenia, which postulates that increased dopaminergic neurotransmission is causative of disease [10]. In this context, increased surface levels of DRD2 receptors in neurons induced by defective expression of BLOC-1 would favor enhanced dopaminergic neurotransmission. Furthermore, genetic polymorphisms in the *DRD2* gene may potentiate this enhanced dopaminergic neurotransmission. BLOC-1-dependent endosomal trafficking mechanisms in neurons may not limited to modulation of the DRD2 receptor, instead affecting the surface levels of diverse membrane proteins and thereby altering neuronal responsiveness to extracellular cues.

Although the precise endosomal processes affected by BLOC-1 deficiency are unclear, two non-exclusive mechanisms may contribute to the increased abundance of these proteins at the cell surface. Evidence indicates that BLOC-1 regulates the sorting of selected membrane proteins into vesicles either by itself or in association with the adaptor complex AP-3 [13, 16, 32, 33]. In fact, mouse models carrying null mutations in subunits of either BLOC-1 or ubiquitous AP-3 increase the content of specific synaptic vesicle proteins, most prominently VAMP7-TI, an endosomal SNARE (soluble N-ethylmaleimide-sensitive factor attachment protein receptor) [13]. BLOC-1 also affects membrane fusion [12, 14]. Mice lacking dysbindin, and therefore the BLOC-1 complex, have slower quantal synaptic vesicle release and lower synaptic vesicles release probability [14]. This may be related, at least in part, to the ability of BLOC-1 complexes to bind and regulate the subcellular distribution of endosomal SNAREs [12, 13, 33], membrane proteins that control the selectivity of membrane fusion along the endocytic route and between endosomal-derived organelles and the cell surface, such as synaptic vesicles [34]. Regardless, either defective biogenesis or fusion of synaptic vesicles could decrease synaptic availability of neurotransmitter, a notion consistent with the glutamatergic and GABAergic neurochemical hypotheses of schizophrenia which postulate decreased activity of these neurotransmitter systems in schizophrenia brains [10].

An attractive aspect of an endosomal hypothesis is its ability to accommodate the polygenic nature of the genetic association data. For example, one-third of the 29 genes considered top scores for increased schizophrenia susceptibility in genetic association meta-analyses are either regulated by or participate in endosomal mechanisms [3] (see Table 1). Furthermore, the products of several genes identified as contributors to the risk of developing schizophrenia in recent genome wide studies are either regulated or participate in endosomal trafficking (Table 1). Consider two gene products from table 1: VMAT1 (encoded by *SLC18A*)[35], which is involved in presynaptic storage of dopamine in vesicles, and DRD2 (encoded by *DRD2*), a postsynaptic dopamine receptor. Recognizing how polymorphisms in these two genes fit to the dopaminergic hypothesis is straightforward. However, under the umbrella of an endosomal hypothesis we can understand how the products of several of the genes in table 1 could regulate dopaminergic neurotransmission. The subcellular distribution of VMAT1 and DRD2 could be under control of proteins involved in endosomal sorting and vesiculation encoded by genes such as *DTNBP1* (dysbindin), *CLTCL1* (clathrin isoform-1),

and *CENTG2* (ARF1 GTPase activating protein-1 (AGAP1)). The clathrin isoform encoded by the *CLTCL1* gene is deleted from chromosome 22 of schizophrenia patients [4]. Clathrin and clathrin adaptor complexes orchestrate the formation of vesicles from multiple compartments in cells, including endosomes [36]. AGAP1, the protein encoded by *CENTG2,* regulates the recruitment of AP-3 to endosomal membranes, a necessary step in the formation of vesicles from endosomes [37]. Importantly, AGAP1 directly interacts with AP-3, which in turns associates with both clathrin and BLOC-1 to form vesicles from endosomes [37, 38]. Thus, under a polygenic model of schizophrenia, disease-associated alleles in *SLC18A,* for example, could have small and clinically silent individual effects in either the protein levels or the function of VMAT1. Minor VMAT1 phenotypes could be further potentiated and rendered clinically significant by the compounded effect of multiple other disease-associated alleles affecting, for example, mechanisms regulating dopamine receptor surface levels. Such genes will include those genes encoding BLOC-1 subunits and other molecules involved in endosomal sorting and vesiculation, such as clathrin, AP-3 and AGAP1.

Endosomal trafficking controls cell surface receptor numbers in most cell types. Trafficking qualitatively and quantitatively affects signal transduction and cell surface composition in developing and adult organisms [39]. In neurons, endosomal trafficking mechanisms define pre- and post-synaptic composition and function by controlling the biogenesis of synaptic vesicles as well as the subcellular distribution of neurotransmitter transporters and receptors [40, 41]. Focusing on endosomal trafficking builds a conceptual bridge among traditional models of schizophrenia pathogenesis. Although we have focused on the BLOC-1 complex and its role in endosomal trafficking, analysis of present and future genetic data may define other fundamental cellular machineries or processes that could contribute to disease pathogenesis. We believe that focusing on cellular mechanisms rather than isolated genes of “interest” will facilitate the formulation of hypotheses with unique predictions amenable to exploration in the genomes and brain tissue of affected individuals.

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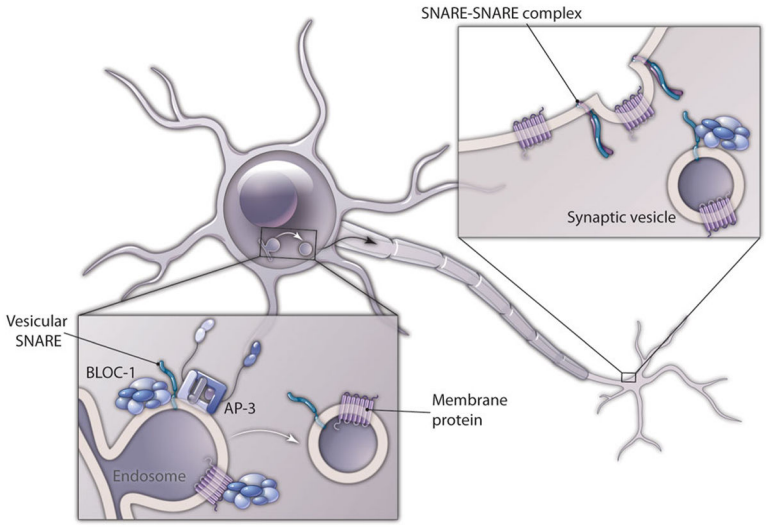

Figure 1. Putative events regulated by BLOC-1-dependent mechanisms in neurons

Diagram depicts the **b**iogenesis of **l**ysosome-related **o**rganelles **c**omplex (BLOC)-1 possible sites of action. BLOC-1 modulates sorting of membrane proteins and SNAREs either alone or in conjunction with AP-3 at endosomes in the cell body impacting the composition of presynaptic secretory organelles. Additionally, BLOC-1 binds and may regulate SNARE-dependent membrane fusion at the nerve terminal.

Table 1
Schizophrenia Susceptibility Genes Related to Endocytic Trafficking

Selected supporting references are listed with capital letters in the right hand column. The following studies are included SzGene study [3], the studies that identified microdeletions in chromosomes 22 (Chr22) and 15 (Chr15) [4, 7], genome wide association studies (GWAS) conducted on the Molecular Basis of Schizophrenia Study (MGS GWAS) [5], the Stefansson's genome wide association study [6] and the International Schizophrenia consortium genome wide association studies (ISC GWAS) [2]. A) Mol Psychiatry. 2007;12:74–86. B) J Cell Biol. 1994;127:1419–33. C) Nat Rev Neurosci. 2007;8:413–26. D) Crit Rev Biochem Mol Biol. 2007;42:3–14. E) J Biol Chem. 2007;282:15778–89. F) Eur J Neurosci. 2006;24:1395–403 and Eur J Pharmacol. 2007;572:83–93. G) Adv Exp Med Biol. 2007;600:1–11. H) Mol Cell Neurosci. 2005;28:335–46. I) Mol Biol Cell. 2006;17:4027–38. J) Mol Biol Cell. 2004;15:3181–95. K) Mol Biol Cell. 2008;19:1942–51. L) J Biol Chem. 2004;279:51250–7. M) J Biol Chem. 2005;280:25769–79. N) Pflugers Arch. 2002;444:795–800. O) J Cell Biol. 2008;181:1179–93. P) J Cell Sci. 2006;119:1203–11. Q) Trends Neurosci. 2002;25:379–81. R) Biochim Biophys Acta. 2008;1782:99–108. S) Exp Cell Res. 2009;315:683–96. T) Science. 2009;325:213–7.

GENE	Study	Gene Product Name	Regulated by or Involved in Endosome Traffic
DISC1	SzGene	Disc1	A
SLC18A1	SzGene	VMAT1	B
GRIN2B	SzGene	NMDA receptor subtype 2B	C
GABRB2	SzGene	GABA A receptor, beta 2	D
DRD1	SzGene	Dopamine receptor 1	E
DRD2	SzGene	Dopamine receptor 2	F
DRD4	SzGene	Dopamine receptor 4	Not explored
PLXNA2	SzGene	Plexin A2	G
NRG1	SzGene & Stefansson GWAS	Neuregulin 1	H
DTNBP1	SzGene	Dysbindin	I
CLTCL1	Chr 22 ISC	clathrin, heavy chain-like 1	J
SEPT5	Chr 22 ISC	Septin 5	K
SCARF2	Chr 22 ISC	scavenger receptor F 2	L
SNAP29	Chr 22 ISC	SNARE SNAP29	M
P2RXL1	Chr 22 ISC	purinergic receptor P2X 6	N
CHRNA7	Chr 15 ISC	cholinergic receptor, nicotinic, a7	O
CENTG2	MGS GWAS	AGAP1	P
NTRK3	MGS GWAS	TRKC	Q
ADPR2	MGS GWAS	adiponectin receptor 2	R
ERBB4	MGS GWAS	Neuregulin receptor 4	S
MHC locus	MGS, ISC, Stefansson GWAS	MHC gene products	T