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Fig4 deficiency: A newly emerged lysosomal storage disorder?

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ABSTRACT

FIG4 (Sac3 in mammals) is a 5′-phosphoinositide phosphatase that coordinates the turnover of phosphatidylinositol-3,5-bisphosphate ($PI(3,5)P_2$), a very low abundance phosphoinositide. Deficiency of FIG4 severely affects the human and mouse nervous systems by causing two distinct forms of abnormal lysosomal storage. The first form occurs in spinal sensory neurons, where vacuolated endolysosomes accumulate in perinuclear regions. A second form occurs in cortical/spinal motor neurons and glia, in which enlarged endolysosomes become filled with electron dense materials in a manner indistinguishable from other lysosomal storage disorders. Humans with a deficiency of FIG4 (known as Charcot-Marie-Tooth disease type 4J or CMT4J) present with clinical and pathophysiological phenotypes indicative of spinal motor neuron degeneration and segmental demyelination. These findings reveal a signaling pathway involving FIG4 that appears to be important for lysosomal function. In this review, we discuss the biology of FIG4 and describe how the deficiency of FIG4 results in lysosomal phenotypes. We also discuss the implications of FIG4/$PI(3,5)P_2$ signaling in understanding other lysosomal storage diseases, neuropathies, and acquired demyelinating diseases.

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1. Introduction

Phosphatidylinositol-3,5-bisphosphate ($PI(3,5)P_2$) is one of the seven known phosphoinositides that are involved in the regulation of intracellular organelle trafficking in mammalian cells (Fig. 1A). One of the key proteins that regulates the concentration of $PI(3,5)P_2$ is known as the FIG4 phosphatase (alternatively known as SAC3 in mammals). Recent discoveries of recessive *FIG4/SAC3* gene mutations causal for neurodegeneration, abnormal lysosomal

Abbreviations: $PI(3,5)P_2$, phosphatidylinositol-3,5-bisphosphate; CMT4J, Charcot-Marie-Tooth disease type 4J; kD, kilodalton; PI3P, phosphatidylinositol-3-phosphate; *plt*, pale tremor; CNS, central nervous system; PNS, peripheral nervous system; DRG, dorsal root ganglion; TRPML1, transient receptor potential mucolipin-1; LEL, late endolysosome; EM, electron microscopy; OL, myelinating oligodendrocyte; OPC, oligodendrocyte precursor cell; ALS, amyotrophic lateral sclerosis.

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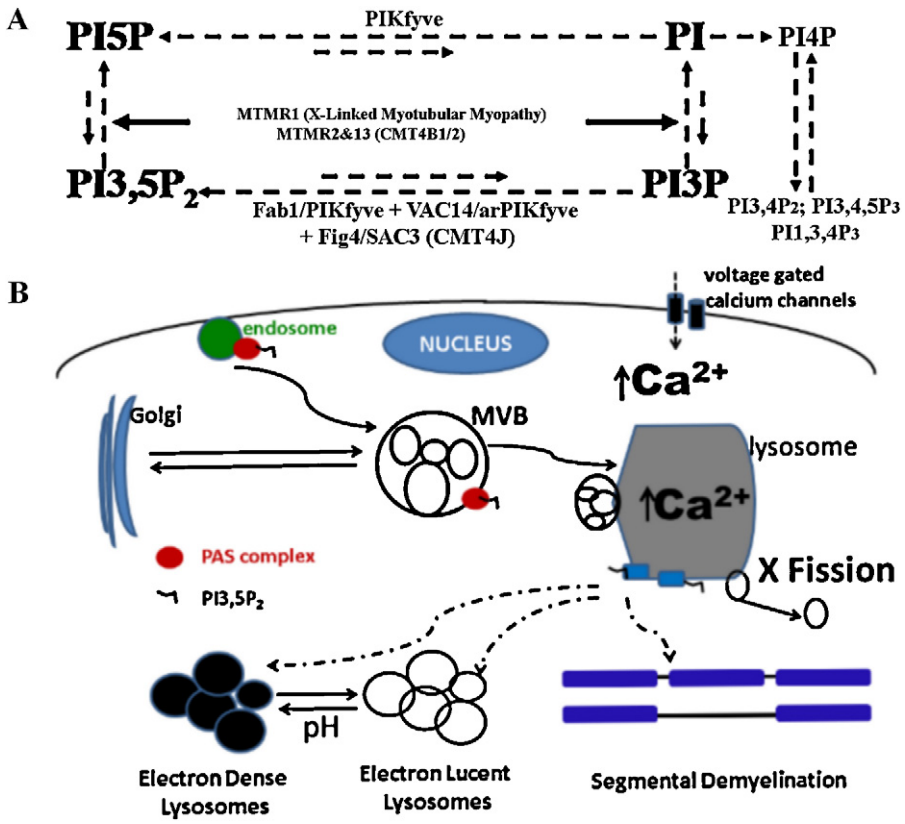

Fig. 1. (A) A diagram of phosphotidylinositide metabolism. PI = phosphotidylinositol. Relevant enzymes to this paper are marked. Their related diseases are shown in parenthess. Notice that all pathways involved in 4-phosphate are simplified since they are not relevant to this review. (B) A hypothetical mechanism in Fig4 deficiency is illustrated.

storage, and segmental demyelination in humans have substantiated its importance in neuronal functions and myelination. These pathological findings during FIG4 deficiency are reminiscent to what has been described in other lysosomal storage diseases, supporting the role of endolysosomal pathway dysregulation in the neurological disease. In this review, we will first discuss the clinical presentation, electrophysiological alterations, and endolysosomal pathology in patients and rodents with Fig4 deficiency. We will then describe how FIG4/SAC3 controls PI(3,5)P_2 abundance and endolysosomal trafficking in tandem with other PI(3,5)P_2 regulatory proteins. Finally, we will discuss how these molecular events might involve in the abnormal lysosomal accumulation in this neurological disease. For in-depth reviews of Fig4 and PI(3,5)P_2, refer to (Dove et al., 2009; Ho et al., 2012).

2. Clinical presentation of CMT4J

In humans, the *FIG4/SAC3* gene is localized to chromosome 6q21 and it encodes a protein of approximately 103 kDa comprised of 907 amino acids (Chow et al., 2007). CMT4J is an inherited peripheral neuropathy that is caused by autosomal recessive mutations of the *FIG4* gene. Typically, the disease is caused by the combination of a *FIG4* null allele and a missense *FIG4*^{I41T} mutation in the other allele (Chow et al., 2007; Nicholson et al., 2011; Zhang et al., 2008). These recessive mutations result in a loss of function of FIG4/SAC3 and a deficiency of PI3,5P_2. While the missense mutant *FIG4*^{I41T} allele still produces a partially functional phosphatase, the mutation results in an increase of FIG4/SAC3 cytosolic degradation (Ikonomov et al., 2010). Thus, the *I41T* point mutation consequently exerts a loss of function effect (Lenk et al., 2011).

The deficiency of FIG4/SAC3 in CMT4J patients manifests in rapidly progressive asymmetric muscle weakness with minimal or absent sensory symptoms. This renders CMT4J as a special subtype of CMT since most forms of CMT manifest as slowly progressive, symmetric and length-dependent polyneuropathies (Patzko and Shy, 2011). Symptomatic onset of CMT4J can range from early childhood to adulthood. Similarly, the severity of the CMT4J phenotype can vary from mild neurological impairment to fatal outcomes (Nicholson et al., 2011). It is currently unknown what genetic factors, if any, modify the onset and severity of CMT4J. While early onset patients can develop gait abnormalities with asymmetric limb involvement that appear as soon as the patients begin walking in childhood, late onset patients may develop subtle abnormalities for years that are insufficient to prompt them to seek medical attention (Nicholson et al., 2011; Zhang et al., 2008).

The most prominent clinical finding in CMT4J patients is typically muscle weakness with atrophy. In almost all cases, the severity of the weakness/atrophy is conspicuously asymmetric. There are mild sensory abnormalities, such as reduced sensation to touch and/or pin-prick in distal limbs. Deep tendon reflex may also be mildly decreased. Interestingly, however, central nervous system abnormalities have not been observed in patients with CMT4J (Nicholson et al., 2011; Zhang et al., 2008). This issue will be discussed further in the next section. On neurological examination, dysfunction of the cranial nerves is uncommon and these patients usually display normal cognitive function. Their brain MRI scans show no abnormalities (Nicholson et al., 2011; Zhang et al., 2008).

Most CMT4J patients have been examined by electrophysiological studies. Nerve conduction studies show prolonged distal latencies and reduced conduction velocities indicative of demyelination. Unlike most CMT1 patients, who have uniform slowing of conduction velocities with little variation from one nerve to another or from one limb to another, CMT4J patients have decreased conduction velocities that are often non-uniform or