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Molecular basis of neurodegeneration and neurodevelopmental defects in Menkes disease

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ABSTRACT

ATP7A mutations impair copper metabolism resulting in three distinct genetic disorders in humans. These diseases are characterized by neurological phenotypes ranging from intellectual disability to neurodegeneration. Severe ATP7A loss-of-function alleles trigger Menkes disease, a copper deficiency condition where systemic and neurodegenerative phenotypes dominate clinical outcomes. The pathogenesis of these manifestations has been attributed to the hypoactivity of a limited number of copper-dependent enzymes, a hypothesis that we refer as the oligoenzymatic pathogenic hypothesis. This hypothesis, which has dominated the field for 25 years, only explains some systemic Menkes phenotypes. However, we argue that this hypothesis does not fully account for the Menkes neurodegeneration or neurodevelopmental phenotypes. Here, we propose revisions of the oligoenzymatic hypothesis that could illuminate the pathogenesis of Menkes neurodegeneration and neurodevelopmental defects through unsuspected overlap with other neurological conditions including Parkinson's, intellectual disability, and schizophrenia.

Introduction

Genetic defects in the trans-Golgi copper-transporter P-ATPase, ATP7A, cause three distinct X-linked recessive disorders: occipital horn syndrome (OMIM 304150), *s*pinal *m*uscular *a*trophy, distal, *X*-linked *3* (SMAX3, OMIM 300489), and Menkes disease (OMIM 309400) (Kaler, 2011). More than 350 different mutations affecting the ATP7A gene have been described (Moller et al., 2009; Tumer, 2013). These disease-associated mutations are quite heterogeneous in their genomic location and the type of DNA defect and, unlike other genetic disorders, there are no recurrent genetic defects that account for a significant number of cases (Tumer, 2013). Milder mutations in ATP7A result in occipital horn syndrome in which connective tissue and bone abnormalities predominate and patients lack the severe neurological phenotypes of Menkes disease (Das et al., 1995; Kaler et al., 1994). Yet another ATP7A-related disease is SMAX3, in which missense mutations not severe enough to perturbate systemic copper status cause a non-demyelinating spinomuscular atrophy (Kennerson et al., 2010; Takata et al., 2004). At the far end of the spectrum is Menkes disease in which the most severe loss-of-function mutations result in a multisystemic metabolic disorder of copper deficiency. Here we focus in Menkes disease, first described in 1962 in a single family that in two generations accumulated five male infants affected by intellectual disability, failure to thrive, prominent neurological manifestations, neurodegeneration, epilepsy, and 'peculiar white hair' (Menkes et al., 1962). Menkes disease is a rare affliction with an incidence of 1/140,000 to 1/300,000 (Gu et al., 2005; Tonnesen et al., 1991). Although this disease has been studied for more than 50 years and its metabolic foundations are known (Kaler, 2011; Menkes, 1988), we contend that the pathogenic mechanisms underlying neurodegeneration and neurodevelopmental defects remain poorly understood. In this review, we explore neuropathogenic hypotheses and argue that some of the classic ideas invoked to explain Menkes disease phenotypes, although logical, remain speculative and inadequate. We propose an updated modified hypothesis in light of newer findings to account for the neurological manifestations of ATP7A loss-of-function mutations.

Our interest in Menkes disease pathogenesis extends beyond this genetic disorder. Because the neurological symptoms associated with Menkes disease are common to other neuropsychiatric disorders of childhood and adulthood (Kaler, 2011; Menkes, 1988), it is increasingly recognized that Menkes disease studies may shed light into the mechanisms of other prevalent disorders. Menkes pathogenesis mechanisms can thus be a tool to understand: a) neuronal mechanisms where copper participates either as a micronutrient or a toxicant; b) pathways of neuronal cell death triggered by altered metabolic homeostasis; c) mechanisms that cells use to respond to neurotoxic anticancer agents such as platinum compounds, which bind to ATP7A (Gregg et al., 1992;

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Inesi et al., 2014; Liu et al., 2012; Rabik and Dolan, 2007); d) regulatory mechanisms of key receptors and channels involved in neurotransmission and neurodegeneration. These include N-methyl-D-aspartate (NMDA) receptors, voltage-gated calcium channels, APP, and the prion protein to mention few (Gaier et al., 2013a; Hung et al., 2010; Kaler, 2011; Stys et al., 2012); and e) mechanisms of development that could account for defective cell positioning observed in Menkes gray matter (Mendelsohn et al., 2006).

Clinical and pathological characteristics of Menkes disease

Menkes disease manifests itself between two to twelve months after birth with hypotonia, failure to thrive, focal and generalized seizures, impaired cognitive development, and brain atrophy at the expense of the gray and white matter. Hypotonia at birth evolves into spastic paresis. Systemic features associated with the disease include the characteristic hypopigmented "kinky hair", which at the microscopic level reveals pili torti (twisted hairs), monilethrix (beaded hairs) and thickening or weak nodes that cause hair fragility (trichorrhexis nodosa). In addition, affected Menkes infants exhibit sagging facial appearance, micrognathia and arched palate, laxity of the skin (cutis laxa) and joints, reduced bone density, bladder diverticula, aneurysms, vascular tortuosity, and bluish irises. This constellation of clinical features permits a high confidence of Menkes diagnosis when associated with serum copper deficiency and X-linked recessive transmission (Bankier, 1995; Gu et al., 2012, 2005; Kaler, 2011; Kodama et al., 2012; Menkes, 1988; Menkes et al., 1962; Prasad et al., 2011).

Menkes disease neuropathology

Menkes is characterized by widespread atrophy of the gray and white matter. At the light microscopic level there is focal degeneration that extends to all layers of the cerebral cortex. Neuronal cell loss is most pronounced in the cerebral cortex but affects the hippocampus, striatum, hypothalamus and thalamus to a variable degree. In the cerebral cortex neuronal cell loss is commonly associated with astrocytosis (Barnard et al., 1978; Ghatak et al., 1972; Hirano et al., 1977; Menkes et al., 1962; Vagn-Hansen et al., 1973).

The cerebellum also shows astrocytosis, although this is more variable compared to the cerebrum. The cerebellum also exhibits marked atrophy in Menkes patients, a feature that is also observed in copper deficient animals giving rise to enzootic ataxia (Suttle, 2012). The Menkes cerebellum also shows scattered loss of Purkinje cells and pronounced reductions in neuronal numbers in the molecular and granular layers. The most prominent Purkinje cell phenotypes are defective cell positioning or heterotopia and abnormal cell architecture (Fig. 1) (Ghatak et al., 1972; Hirano et al., 1977; Menkes et al., 1962; Vagn-Hansen et al., 1973). The heterotopia is characterized by irregular alignment of Purkinje cells and displacement within the molecular and granular layers of the cerebellar cortex (Barnard et al., 1978; Ghatak et al., 1972; Hirano et al., 1977; Menkes et al., 1962; Purpura et al., 1976; Vagn-Hansen et al., 1973). In addition, Purkinje cell dendrites are markedly swollen with an aberrant pattern of dendritic arborization (Fig. 1) (Hirano et al., 1977; Purpura et al., 1976; Yamano and Suzuki, 1985). Sprouts directly extending from the Purkinje cell body, some of which resemble spines, appear less frequently with the age of the individual (Hirano et al., 1977). In addition to architectural phenotypes, the cell bodies of Purkinje cells contain clusters of mitochondria, which possess dense granules in their matrix and altered cristae (Iwane et al., 1990; Nagara et al., 1980; Onaga et al., 1987; Yoshimura and Kudo, 1983). This mitochondrial ultrastructure is important as it provides a morphological correlate to mitochondrial enzymatic defects, which has been postulated to underlie the neurodegeneration. However, despite their prominent mitochondrial ultrastructural pathology, the overall neurodegeneration of Purkinje cells is mild (Nagara et al., 1980; Yajima and Suzuki, 1979). This argues to factors in addition to mitochondria in the pathogenesis of Menkes disease neurodegeneration.

The emphasis on the neuropathology of Menkes disease has focused on the neurodegeneration associated with this disorder. However, it is important to emphasize that Menkes brains in humans or mice possess Purkinje cell heterotopy, abnormal neuroblast migration, and altered neuronal arborization (El Meskini et al., 2007; Hirano et al., 1977; Niciu et al., 2006; Purpura et al., 1976) (Fig. 1). These defects precede neuronal cell death (El Meskini et al., 2007; Kodama et al., 2012; Niciu et al., 2006). The cellular basis of these structural abnormalities observed in Purkinje cells points to defective developmental mechanisms

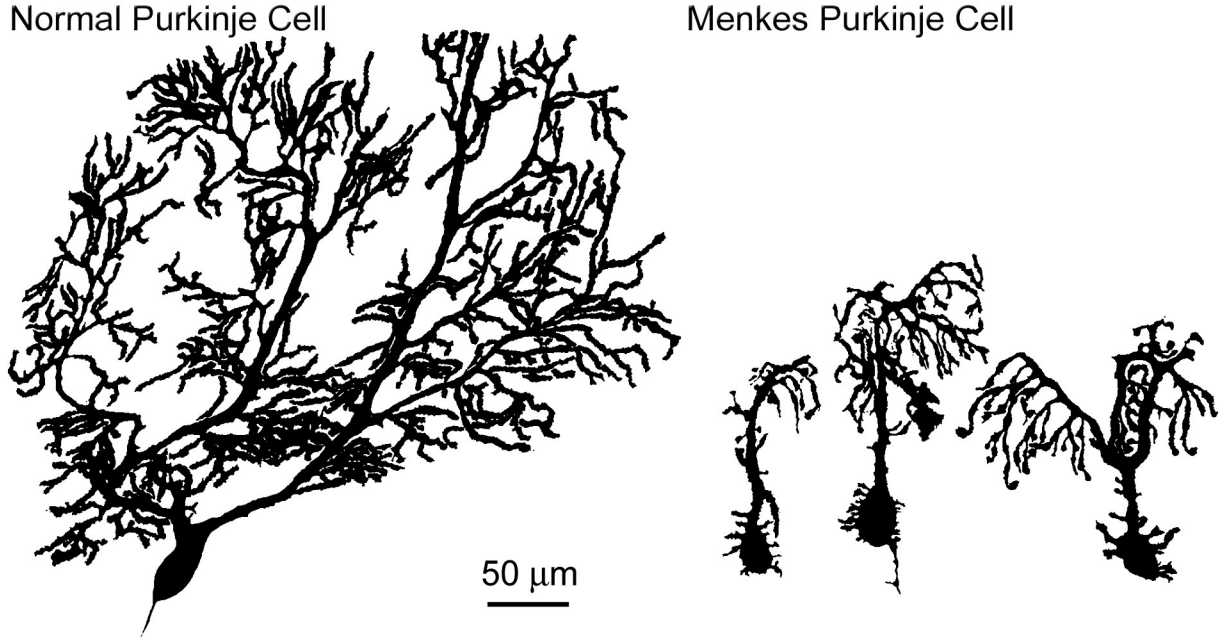

Fig. 1. Branching abnormalities of cerebellar cortex Purkinje cells. Human tissue was processed with Golgi stain. Panels depict camera lucida drawings of Purkinje cells. Note the dendritic systems of Purkinje cells in Menkes disease are atrophic and lack organized tertiary branches.
Modified from Purpura et al., 1976.

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