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REVIEW ARTICLE

Myelin changes in Alexander disease☆

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Abstract
Introduction: Alexander disease (AxD) is a type of leukodystrophy. Its pathological basis, along with myelin loss, is the appearance of Rosenthal bodies, which are cytoplasmic inclusions in astrocytes. Mutations in the gene coding for glial fibrillary acidic protein (GFAP) have been identified as a genetic basis for AxD. However, the mechanism by which these variants produce the disease is not understood.
Development: The most widespread hypothesis is that AxD develops when a gain-of-function mutation causes an increase in GFAP. However, this mechanism does not explain myelin loss, given that experimental models in which GFAP expression is normal or mutated do not exhibit myelin disorders. This review analyses other possibilities that may explain this alteration, such as epigenetic or inflammatory alterations, presence of NG2 (+) — GFAP (+) cells, or post-translational modifications in GFAP that are unrelated to increased expression.
Conclusions: The different hypotheses analysed here may explain the myelin alteration affecting these patients; several of these mechanisms may co-occur. These theories raise the possibility of designing therapies based on these mechanisms.
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PALABRAS CLAVE
Enfermedad de Alexander;
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Astrocitos

La alteración de la mielina en la enfermedad de Alexander

Resumen
Introducción: La enfermedad de Alexander (AxD) es una leucodistrofia. Su base patológica, junto a la pérdida de mielina, es la aparición de los cuerpos de Rosenthal, que son inclusiones citoplasmáticas en células astrocitarias. Mutaciones en el gen que codifica la GFAP se han identificado como una base genética para AxD. Sin embargo, no se conoce el mecanismo por el cual estas variantes producen la enfermedad.
Desarrollo: La hipótesis más extendida es que AxD se desarrolla por un mecanismo por ganancia de función debido al incremento de GFAP. Sin embargo, este mecanismo no explica la pérdida mielínica, dado que los modelos experimentales que expresan GFAP normal o mutada no generan alteración mielínica. En la presente revisión se analizan otras posibilidades que permitan justificar dicha alteración, como son alteraciones epigenéticas, inflamatorias, la existencia de células NG2 (+)-GFAP (+) o cambios postraslacionales sobre la GFAP al margen de la mayor expresión.
Conclusiones: Las diferentes hipótesis analizadas pueden explicar la alteración de la mielina que aparece en los pacientes y que pueden presentarse asociadas y abren la posibilidad de plantear terapéuticas basadas en estos mecanismos.
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Introduction

Alexander disease (AxD), named after the physician who first described it in 1949,[1] is a leukodystrophy causing the destruction of myelin. In addition to myelin loss, the pathophysiology of the disease involves the formation of Rosenthal fibres,[2] cytoplasmic inclusions within glial cells that have also been observed in some gliomas. These inclusions are formed by glial fibrillary acidic protein (GFAP), α−β crystallin, and heat shock protein 27 (HSP27),[3,4] although other proteins such as vimentin, p62, and plectin have also been reported.[5] From a clinical viewpoint, the disease has three different forms: infantile, juvenile, and adult; the infantile form has the poorest prognosis.[6–8] Mutations in the *GFAP* gene constitute the genetic basis of AxD. These mutations, constituting changes in 32 specific nucleotides, are present in both familial and sporadic cases.[9,10] However, we are yet to determine the mechanism by which these mutations cause GFAP aggregation within astrocytes, the way in which GFAP expressed by astrocytes contributes to symptoms, and especially the mechanism of demyelination. Radiology studies reveal periventricular demyelination[11]; patients with long survival times display extremely severe demyelination, affecting nearly all the white matter.[12]

GFAP, first isolated and described by Eng in 1969,[13] is a component of the intermediate filaments found in astrocytes, together with vimentin and nestin. In addition to playing a structural role in astrocytes, where together with microtubules and microfilaments they form the cytoskeleton, these filaments are also involved in signal transmission. GFAP is also present in other central nervous system (CNS) cells, such as ependymal cells, in non-myelin-producing Schwann cells of the peripheral nervous system, and in enteric glia.

The protein is encoded by a single gene located on 17q21, which contains nine exons. At least 10 isoforms result from alternative splicing of *GFAP* pre-mRNA and the polyadenylation signal.[14–17] GFAP-α (isoform 1) is the predominant isoform in the brain and spinal cord, but it also appears in the peripheral nervous system; it contains the classic 432 residues with full usage of the 9 exons of the *GFAP* gene. GFAP-δ or GFAP-ε (isoform 2) is preferentially expressed by astrocytes from neurogenic niches including the subventricular zone and the hippocampus. GFAP-δ includes the use of an intron before exon 8 and has an alternative C-terminus and 431 residues. GFAP-δ is expressed in reactive astrocytes in diseases such as epilepsy, Alzheimer disease, and gliomas. The remaining isoforms are less frequent, although the association between some of these variants and neurodegenerative diseases has made them a subject of considerable research interest.[18,19]

Myelin is produced by oligodendrocytes in a dynamic process requiring 3 conditions: the presence of oligodendrocyte precursor cells (OPCs) in the demyelinated area, changes in oligodendrocyte form and membranes, and a favourable microenvironment. OPCs are immature oligodendrocytes that remain in the adult brain after embryonic development. They account for 5%-8% of the population of CNS glial cells[20] and contribute to restoration of the myelin sheath, differentiating throughout adulthood. OPCs can express proteins including Olig2 and NG2. Myelin proteins produced and accumulated as a result of demyelination prevent remyelination through the protein kinase C α, Nogo 1, or LINGO1 signalling pathways.[21,22] Semaphorins also play a role in regulating remyelination.[23] Consequently, demyelination in patients with AxD may be explained by mechanisms with at least 4 effects[24]: (1) OPCs not being generated or surviving; (2) absence of stimuli promoting oligodendrocyte maturation; (3) prevention

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