Poster P.10.84

TRANSLATING MOLECULAR PATHOLOGY INTO A THERAPEUTIC STRATEGY IN SCA38, A NEWLY IDENTIFIED FORM OF SPINOCEREBELLAR ATAXIA.

Di Gregorio E.[1], Manes M.[2], Hoxha E.[3], Ferrero M.[1], Tripathy D.[4], Di Campli A.[5], Pavinato L.[1], Costanzi C.[2], Giorgio E.[1], Pozzi E.[1], Mitro N.[6], Basso M.[4], Sallese M.[7], Caruso D.[6], Tempia F.[3], Brusco A.*[1], Borroni B.[2]

[1]University of Torino, Dept. Medical Sciences ~ Torino ~ Italy, [2]University of Brescia, Dept. of Clinical and Experimental Sciences, ~ Brescia ~ Italy, [3]Neuroscience Institute Cavalieri Ottolenghi ~ Orbassano (TO) ~ Italy, [4]University of Trento, Centre for Integrative Biology ~ Trento ~ Italy, [5]Institute of Protein Biochemistry (IBP), Italian National Research Council (CNR) ~ Napoli ~ Italy, [6]University of Milan, Dept. of Pharmacological and Biomolecular Sciences, ~ Milano ~ Italy, [7]University 'G. d'Annunzio, Dept. of Medical, Oral and Biotechnological Sciences, ~ Chieti ~ Italy

Spinocerebellar ataxias (SCA) are rare autosomal dominant, genetically heterogeneous, neurological disorders phenotypically mainly characterized by gait ataxia with cerebellar atrophy.
In 2014, we described spinocerebellar ataxia type 38 (SCA38) as associated with missense variants in the ELOVL5 gene. This gene encodes for an elongase, which is deputed to the synthesis of very long chain fatty acids, specifically DHA and EPA which are decreased in patients' serum.
Our research had two major aims: the study of SCA38 pathogenic mechanisms in cellular models and Elovl5 knockout (ko) mice, and the efficacy evaluation of DHA in an off-label trial in humans.
In SCA38 cellular models, we showed that mutant ELOVL5-pGly230Val - the main missense pathogenic variant found in three of the four described SCA38 families - is mislocalized from the ER to the Golgi. This causes the enlargement of Golgi and alters the ER-to-Golgi transport. We also showed that the mutant ELOVL5-pGly230Val is likely misfolded and degraded by proteasome. It activates the ER-stress response pathway, overall behaving as a gain-of-function variant.
In the animal ko model, deficits in the principal functions of cerebellar Purkinje cells are absent. On the other hand, the impairment of action potential conduction along central and peripheral nerve fibers points to a more extensive deficit in myelination, confirmed by ultrastructural analysis of myelin sheaths, which resulted less compact. The lipidomic analysis highlighted a strong shift of phospholipids composition, from the long chain and polyunsaturated fatty acids, which are predominant in wild type mice, to shorter and more saturated ones, more abundant in Elovl5 knock out animals. Overall, these results suggest that the reconstitution of the normal pattern of polyunsaturated fatty acids should rescue the ultrastructural and functional deficits of myelin. This will be a starting point to refine the therapy based on the administration of fatty acids deficient in the animal model as well as in SCA38 patients.
Our project indeed explored the use of DHA in patients with SCA38. In a double-blind, randomised, placebo-controlled study followed by a short-term and long-term open label phase, we demonstrated that oral DHA is a safe and effective treatment for SCA38 patients, claiming that it is the eligible therapy for SCA38. Based on our observation, we speculated that DHA is even beneficial in the presymptomatic stage of the disease to delay disease onset and slow the progression of symptoms. Suggested dosage was 600-1000 mg twice a day.
Our data overall show that the pathogenesis of SCA38 is likely a mix of loss-of-function and gain-of-function pathogenic mechanisms. Interestingly, both these pathways point to a similar treatment with DHA, which can compensate the loss, and induce a downregulation of the ELOVL5 expression.

Dal meccanismo patogenetico alla terapica in SCA38, una nuova forma di atassia spinocerebellare.
Le atassie spinocerebellari (SCA) includono più di 30 diversi sottotipi di malattie del sistema nervoso

centrale e colpiscono 1 persona su 30.000. Abbiamo identificato il gene che, se mutato, è causa della SCA38, una rara forma di atassia spinocerebellare associata a neuropatia. Il gene, chiamato ELOVL5, codifica per un enzima coinvolto nella sintesi di molecole note come acidi grassi omega-3, e la sua alterazione causa una riduzione degli omega-3 nel siero dei pazienti SCA38. Questo dato ha suggerito che integrare la dieta con specifici omega-3 potesse migliorare i sintomi nei pazienti.
Abbiamo pertanto condotto uno studio in doppio cieco, randomizzato, controllato con placebo, seguito da una fase in aperto, e abbiamo dimostrato che il DHA è un trattamento privo di effetti collaterali ed efficace per la SCA38, determinando un miglioramento clinico e del metabolismo cerebellare, sia a breve che a lungo termine.
Il progetto ci ha permesso di comprendere i meccanismi patogenetici in SCA38 che si sono confermati essere sia da acquisto (produzione di una proteina dalla conformazione anomala) che da perdita di funzione (alterata localizzazione cellulare nell'apparato di Golgi). Questi dati si combinano con i risultati ottenuti nel modello murino in cui manca Elovl5, dove è stato dimostrato che l'assenza del gene è sufficiente per causare una riduzione di volume del cervelletto, deficit motori e un difetto dei segnali nervosi che viaggiano lungo le fibre nervose. Questi deficit sono associati a difetti della mielina, la guaina isolante delle fibre nervose, attribuibili alla disorganizzazione del profilo lipidico. Questi risultati evidenziano l'importanza di ristabilire in SCA38 la corretta composizione dei lipidi, mediante trattamenti basati sulla dieta.

Di Gregorio E, Borroni B, Giorgio E, Lacerenza D, Ferrero M, Lo Buono N, Ragusa N, Mancini C, Gaussen M, Calcia A, Mitro N, Hoxha E, Mura I, Coviello DA, Moon Y-A, Tesson C, Vaula G, Couarch P, Orsi L, Duregon E, Papotti MG, Deleuze J-F, Imbert J, Costanzi C, Padovani A, Giunti P, Maillet-Vioud M, Durr A, Brice A, Tempia F, Funaro A, Boccone L, Caruso D, Stevanin G, Brusco A. ELOVL5 mutations cause Spinocerebellar Ataxia 38. Am J Hum Genet. Aug 7;95(2):209-17, 2014. doi: 10.1016/j.ajhg.2014.07.001

Borroni B, Di Gregorio E, Orsi L, Vaula G, Costanzi C, Tempia F, Mitro N, Caruso D, Manes M, Pinessi L, Padovani A, Brusco A, Boccone L. Clinical and neuroradiological features of Spinocerebellar Ataxia 38 (SCA38). Parkinsonism and related disorders Jul;28:80-86, 2016.

Manes M, Alberici A, Di Gregorio E, Boccone L, Premi E, Mitro N, Pasolini MP, Pani C, Paghera B, Perani D, Orsi L, Costanzi C, Ferrero M, Zoppo A, Tempia F, Caruso D, Padovani A, Brusco A, Borroni B. DHA is a beneficial replacement treatment for Spinocerebellar Ataxia 38 (SCA38). Annals of Neurology Oct;82(4):615-621, 2017. doi: 10.1002/ana.25059. Epub 2017 Oct 22.

Hoxha E, Gabriele RMC, Balbo I, Ravera F, Masante L, Zambelli V, Albergo C, Mitro N, Caruso D, Di Gregorio E, Brusco A, Borroni B, Tempia F. Motor deficits and cerebellar atrophy in Elovl5 knock out mice. Frontiers in Cellular Neuroscience, 11:343, 1-11, 2017. 10.3389/fncel.2017.00343.

Manes M, Alberici A, Di Gregorio E, Boccone L, Premi E, Mitro N, Pasolini MP, Pani C, Paghera B, Orsi L, Costanzi C, Ferrero M, Tempia F, Caruso D, Padovani A, Brusco A, Borroni B. Long-term efficacy of Docosahexaenoic acid (DHA) for Spinocerebellar Ataxia 38 (SCA38) treatment: an open label extension study. Parkinsonism Relat Disord. 2019 Jun;63:191-194.

Coordinator: Barbara Borroni
Partners: Alfredo Brusco. Donatella Caruso, Loredana Boccone, Filippo Tempia

Telethon Project (nr):

GGP14225

Disease Name:

Spinocerebellar Ataxia 38 (SCA38)

Keywords:

ataxia, therapy, pathogenic mechanism