Available online at www.sciencedirect.com

SciVerse ScienceDirect

Neuromuscular Disorders 23 (2013) 867–870

www.elsevier.com/locate/nmd

Personal Point of View

Increased levels of expression of dystroglycan may protect the heart

Andrea Brancaccio *

Istituto di Chimica del Riconoscimento Molecolare (CNR), c/o Istituto di Biochimica e Biochimica Clinica, Università Cattolica del Sacro Cuore, Largo F. Vito 1, 00168 Roma, Italy

Abstract

Dystroglycan is a major adhesion complex composed of two subunits, α and β, that undergoes extensive post-translational modifications. In particular, its α subunit is heavily decorated with sugars, influencing its basement membrane binding properties. An altered glycosylation of α-dystroglycan is at the molecular basis of muscular dystrophies defined as secondary dystroglycanopathies, that depend on malfunctioning of the enzymes in the glycosylation pathway. An increased level of transcription of the dystroglycan gene may be crucial for obtaining sufficient amounts of dystroglycan precursor substrate required for the production of the heavily glycosylated and fully functional α-dystroglycan molecule. Even slight differences in these transcriptional levels may exert a protective or pathogenetic effect, as discussed for the unique case of primary dystroglycanopathy so far identified (T192M), where the heart tissues are not affected by the pathology. Moreover, the N-terminal fragment of α-dystroglycan is also proposed to have a regulatory role in the glycosylation/maturation process.

1. Higher levels of pre-DG/α-DG may protect cardiac tissue: the case of T192M primary dystroglycanopathy

Dystroglycan (DG) is a widely distributed transmembrane complex composed of two subunits: α-DG, a highly glycosylated peripheral membrane protein, and β-DG, a transmembrane protein. Through the establishment of multiple complexes, DG serves the crucial role of connecting the basement membrane to the internal cytoskeleton [1]. In particular, in skeletal muscle the complex is deeply involved in muscle stability, and thus in muscular dystrophy and in a series of phenotypes, all showing defects in the glycosylation of DG that have been identified and referred to as secondary dystroglycanopathies [2]. These depend on genetic abnormalities of a series of glycosyltransferases, or putative glycosyltransferases, involved in the decoration of α-DG in several tissues (see Figs. 1 and 2).

In patients affected by severe αDG-related muscular conditions, although α-DG is widely expressed and distributed, some tissues, in particular those from heart, seem to be completely spared from any pathologic consequences.

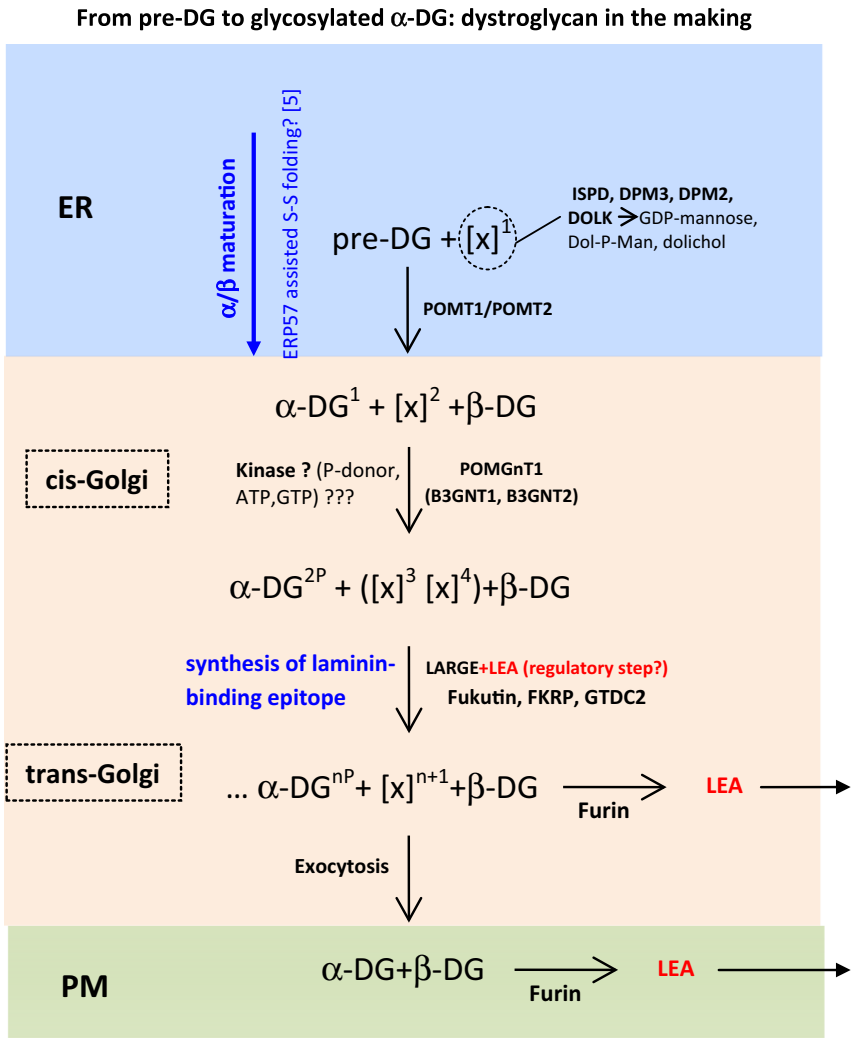
Although there is an increasing number of reports on cardiac complications observed in POMT1, FKRP, FKTN and DOL patients [8], in general skeletal muscle, brain and the eye are the most seriously affected districts in several forms of dystroglycanopathy. In fact, some of the most severe congenital cases were often referred to as muscle eye brain diseases (reinforcing the notion of the absence of a cardiac involvement at least in this subgroup of cases).

That said, the dystroglycan T192M homozygous mutation described by Hara and colleagues is particularly interesting [9], not only since it represents the first example of primary dystroglycanopathy reported so far, but also since the cardiac tissue seems to be absolutely normal.

Apparently, this 16-year old female patient who was initially described by Dincer and colleagues, did not show any sign of cardiomyopathy [10]. This has been confirmed by the extensive biochemical analysis carried out by Hara and colleagues on the T190M mouse model

* Fax: +39 06 3053598.
E-mail address: andrea.brancaccio@icrm.cnr.it

0960-8966/$ - see front matter © 2013 Elsevier B.V. All rights reserved.
http://dx.doi.org/10.1016/j.nmd.2013.06.371



[x]1: mannose (Man).
[x]2: acetylglucosamine (Glc NAc), acetylgalactosamine (GalNAc) as well as acetylglucosamine (Glc NAc), galactose and N-acetylneuraminic acid (i.e. sialic acid) forming a trisaccharide or tetrasaccharide with the initial mannose [3].
[x]3: xilose (Xyl).
[x]4: glucuronic acid (GlcA).
ER: Endoplasmic Reticulum.
PM: Plasma Membrane.

Fig. 1. The multi-enzymatic cascade underlying the post-translational modification of α-DG core protein implies that a plethora of known or suspected glycosyltransferases catalyzes the decoration of the mucin-like domain of α-DG. Several chaperones, proteases and kinases are likely to contribute to the maturation process. An oversimplified consecutive reaction scheme based on a series of bimolecular steps may be envisaged for describing the overall reaction, in which the substrates are i) unglycosylated pre-DG and its progressively glycosylated products and ii) all the UDP-precursors [x] carrying the required sugar blocks, starting from the first mannose unit. In α-DG^{2P}, mannose is phosphorylated at its hydroxyl group in position C6 in the Golgi and LARGE catalyzes a post-posphoryl phosphodiester ramification from this position [3]. LEA (LARGE Enhancing Antigen) represents the N-terminal region of α-DG detached ultimately by furin proteolysis in the trans-Golgi, between positions R312-Q313 [4]: such region is herein proposed to play a LARGE-binding regulatory role (see text). (See above-mentioned references for further information).

that they have generated and that shows similar clinical signs to the human patient. In fact, unlike the case of skeletal muscle or brain, laminin can easily recognize and bind the cardiac T190M α-DG in an overlay assay. In addition, the cardiac α-DG is perfectly detected by the IIH6 antibody that targets the carbohydrate moieties introduced by like-acetylglucosaminyltransferase (LARGE) and by the other enzymes in the cascade (see Fig. 1) [7], which represents the most used molecular probe revealing the presence of a functional α-DG.

At a first glance, this interesting observation cannot be easily accounted for. In skeletal muscle and brain the α-DG core protein is present but it is largely