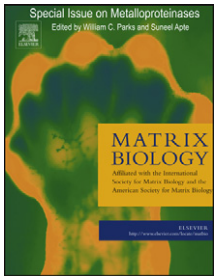
Review



Role of gelatinases in pathological and physiological processes involving the dystrophin–glycoprotein complex

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Abstract

Dystrophin is a cytosolic protein belonging to a membrane-spanning glycoprotein complex, called dystrophin–glycoprotein complex (DGC) that is expressed in many tissues, especially in skeletal muscle and in the nervous system. The DGC connects the cytoskeleton to the extracellular matrix and, although none of the proteins of the DGC displays kinase or phosphatase activity, it is involved in many signal transduction pathways. Mutations in some components of the DGC are linked to many forms of inherited muscular dystrophies. In particular, a mutation in the dystrophin gene, leading to a complete loss of the protein, provokes one of the most prominent muscular dystrophies, the Duchenne muscular dystrophy, which affects 1 out of 3500 newborn males. What is observed in these circumstances, is a dramatic alteration of the expression levels of a multitude of metalloproteinases (MMPs), a family of extracellular Zn^{2+}-dependent endopeptidases, in particular of MMP-2 and MMP-9, also called gelatinases. Indeed, the enzymatic activity of MMP-2 and MMP-9 on dystroglycan, an important member of the DGC, plays a significant role also in physiological processes taking place in the central and peripheral nervous system. This mini-review discusses the role of MMP-2 and MMP-9, in physiological as well as pathological processes involving members of the DGC.

Introduction

Dystrophin is a cytosolic protein associated to a glycoprotein complex, the dystrophin–glycoprotein complex (DGC), composed by the intracellular α and β-syntrophin, α-dystrobrevin and neuronal nitric oxide synthase (nNOS), the transmembrane β-dystroglycan, α-, β-, γ- and δ-sarcoglycan and sarcospan, and the extracellular α-dystroglycan [1,2]. The DGC is expressed in a wide variety of tissues, especially in skeletal muscle and in the nervous system, and provides a strong contribution to the sarcolemma stability. The DGC represents an important link between the cytoskeleton and the extracellular matrix, in several respects. It is directly and indirectly involved in different signal transduction pathways. As an example, nNOS, an enzyme activated by muscle contraction, produces nitric oxide from L-arginine, which in turn triggers the production of cGMP catalyzed by the guanylyl cyclase; the second messenger cGMP stimulates vasodilatation favoring the blood influx into the contracting muscle [3–5]. Furthermore, some DGC members, including dystrobrevin [6], syntrophins [7] and β-dystroglycan [8], serve as platforms to recruit phosphatases and kinases involved in signal transduction pathways. In addition to their indirect involvement in signal transduction pathways, the two dystroglycan subunits, α- and β, which represent the DGC inner core, interact in a non-covalent fashion through the C-terminal domain of α-dystroglycan and the β-dystroglycan ectodomain [9], playing a key role in maintaining the connection

between the cytoskeleton and the extracellular matrix through formation of a multitude of interactions [10].

This network of interactions contributes to the plasma membrane stability in normal conditions, on the other hand, the connection between the cytosol and the extracellular matrix needs to be interrupted when tissue remodeling takes place. In such circumstances, an overexpression of some matrix–metalloproteinases (MMPs) is often observed. These proteins belong to a family of Zn^{2+}-dependent extracellular endopeptidases involved in many physiological (such as morphogenesis, development, cell migration, proliferation and adhesion) as well as pathological processes, such as cancer, neurodegeneration, inflammation and muscular dystrophy [11].

Although dystrophin has recently been proposed as a new target of MMP-2 during ischemic injury [12] and a decrease in γ-sarcoglycan levels has been shown to correlate with an increase of MMP-2 activity, in an animal model of right ventricular failure [13], dystroglycan remains the only ascertained and direct DGC target of MMP-2 and MMP-9. In vitro, the two gelatinases disrupt the recombinant β-dystroglycan ectodomain by two distinct molecular mechanisms. MMP-9 induces a first cleavage leaving an intact C-terminal region of about 30 amino acids and an N-terminal region that is further processed [14], whereas MMP-2 produces multiple early cleavages on the entire protein [15] (see Fig. 1). MMP-2 has lately also been found to exert a significant proteolytic activity on native and recombinant α-dystroglycan in vitro [16].

Dystroglycan degradation is driven by gelatinases in physiological conditions

The ectodomain of β-dystroglycan represents the Achille's heel of the DGC. The possibility of a proteolytic breakdown, likely to take place at the ectodomain of β-dystroglycan, was first postulated after observing the electrophoretic behavior of a 30 kDa β-dystroglycan fragment in carcinoma cell lines [17].

The first direct evidence of an enzymatic activity driven by an MMP on dystroglycan comes from a study of Yamada and colleagues who found a truncated form of β-dystroglycan, devoid of part of its ectodomain and therefore unable to maintain its link with α-dystroglycan, in healthy tissues, such as peripheral nerve, kidney, lung and smooth muscle. In the same study the authors indicated the metalloproteinases MMP-2/MMP-14 and MMP-9, as the main players involved in the production of this 30 kDa β-dystroglycan fragment [18].

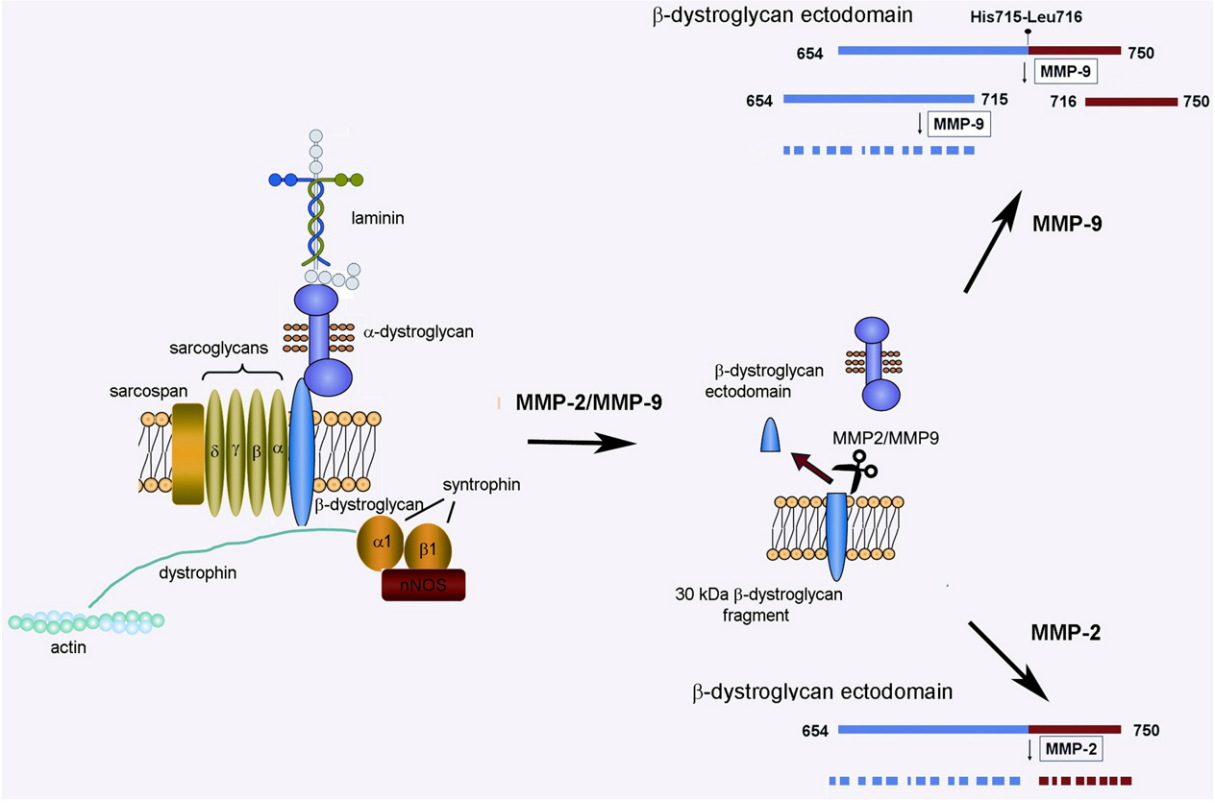

Fig. 1. *Scheme of the DGC and β-dystroglycan degradation driven by gelatinases.* In vitro, MMP-9 catalyzes a first cleavage within the β-dystroglycan ectodomain producing an intact C-terminal region of about 30 amino acids and an N-terminal region that is further processed [14], while MMP-2 induces multiple cleavages on the entire ectodomain [15].