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A novel paradigm for therapeutic basis of advanced heart failure—assessment by gene therapy

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Abstract

The precise mechanism(s) of the progression of advanced heart failure (HF) should be determined to establish strategies for its treatment or prevention. Based on pathological, molecular, and physiological findings in 3 animal models and human cases, we propose a novel scheme that a vicious cycle formed by increased sarcolemma (SL) permeability, preferential activation of calpain over calpastatin, and translocation and cleavage of dystrophin (Dys) commonly lead to advanced HF. The aim of this article was to assess our recent paradigm that disruption of myocardial Dys is a final common pathway to advanced HF, irrespective of its hereditary or acquired origin (Toyo-oka et al., PNAS, 2004) [Toyo-oka, T., Kawada, T., Nakata, J., Xie, H., Urabe, M., Masui, F., & et al. (2004). Translocation and cleavage of myocardial dystrophin as a common pathway to advanced heart failure: a scheme for the progression of cardiac dysfunction. *Proc Natl Acad Sci U S A* 101, 7381–7385], but not intended to provide a comprehensive overview of the various factors that may be involved in the course of HF in different clinical settings. In addition, each component of Dys-associated proteins (DAP) was heterogeneously degraded in vivo and in vitro, i.e. Dys and α-sarcoglycan (SG) were markedly destroyed using isolated calpain 2, while δ-SG was not degraded at all. The up-regulation of calpain 2 was confirmed through previously published data that remain insufficient for precise evaluation, supporting our new scheme that the activation of calpain(s) is involved in the steady process of Dys cleavage. In addition, somatic gene therapy (Kawada et al., PNAS, 2002) [Kawada, T., Nakazawa, M., Nakauchi, S., Yamazaki, K., Shimamoto, R., Urabe, M., & et al. (2002). Rescue of hereditary form of dilated cardiomyopathy by rAAV-mediated somatic gene therapy: amelioration of morphological findings, sarcolemmal permeability, cardiac performances, and the prognosis of TO-2 hamsters. *Proc Natl Acad Sci U S A* 99, 901–906] is discussed as a potential option to ameliorate the physiological/metabolic indices and to improve the prognosis.

Keywords: Dystrophin (Dys); δ-Sarcoglycan (SG); Gene therapy; Heart failure (HF); Proteolysis; Calpains

Abbreviations: A-kinase, cyclic adenosine monophosphate (cAMP)-dependent protein kinase; AMI, acute myocardial infarction; DAP, dystrophin-associated proteins; DCM, dilated cardiomyopathy; DG, dystroglycan; Dys, dystrophin; EB, Evans blue; HCM, hypertrophic cardiomyopathy; HF, heart failure; Isp, isoproterenol; KAF, kinase-activating factor; LVP, left ventricular pressure; NAM, natural actomyosin; OMI, old myocardial infarction; rAAV, recombinant adeno-associated virus; SG, sarcoglycan; SL, sarcolemma; TN, troponin.

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1. Introduction

Heart failure (HF) is one of the leading causes of premature death and poor quality of life. Community-based epidemiological studies have provided much-needed information on the demography of HF, requiring insight into its influence on public health. In most patients, chronic HF is accompanied by a range of concomitant disorders that contribute to the cause of the disease and play a key role in its progression and response to treatment (Krum & Gilbert, 2003).

Although several pharmacological agents have improved both the mortality and morbidity of patients with advanced HF (for review, see Jessup & Brozena, 2003), no treatment is available to completely prevent its progression except cardiac transplantation. However, the transplantation encompasses a variety of socioeconomic problems in addition to its medical limitations. End-stage dilated cardiomyopathy (DCM) is the condition that most frequently requires heart transplantation in Japan. The hereditary origin of DCM is estimated to account for ~20% to 30% of all patients with DCM (Michels et al., 1992; Towbin & Bowles, 2002).

2. Dystrophin and dystrophin-associated proteins

Dystrophin (Dys) and Dys-associated proteins (DAP) are located in sarcolemma (SL) of cardiac and skeletal muscles and in plasma membrane of central nervous system or retina (Cox & Kunkel, 1997; Henry & Campbell, 1999). Dys is a rod-like protein that lies beneath the SL and forms part of a system which links actin on the inside of muscle fibers, through DAP to extracellular matrix proteins, laminin α2 (Fig. 1). DAP contain 2 groups of membrane proteins: dystroglycans (DGs) and sarcoglycans (SGs, Cox & Kunkel, 1997; Holt et al., 1998; Henry & Campbell, 1999) that are closely associated with DGs and would support the mechanical resistance to the over-expansion of the SL.

Gene mutations of cardiac F-actin, Dys, each SG and laminin α2 in addition to lamin A/C cause DCM in human cases as the chief symptoms or partial signs (Fadic et al., 1996; Cox & Kunkel, 1997; Olson et al., 1998; Fatkin et al., 1999; Barresi et al., 2000; Tsubata et al., 2000; Politano et al., 2001; Seidman & Seidman, 2001). A gene defect and the corresponding protein disruption in one of the DAP

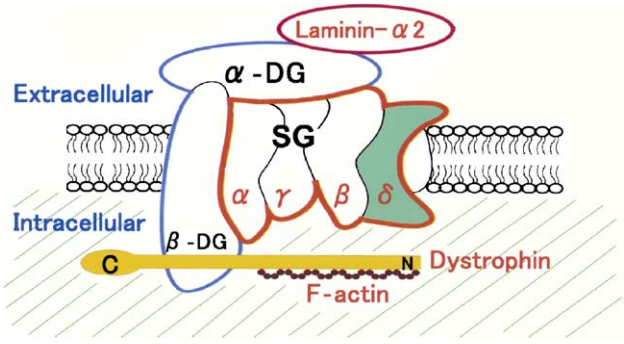

Fig. 1. A potential localization of dystrophin-associated proteins (DAPs). Mutations in DAP, which cause DCM in human cases, are shown in red characters. SG, sarcoglycan; DG, dystroglycan.