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Personal point of view

Tubular aggregates in skeletal muscle: Just a special type of protein aggregates?

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Abstract

Tubular aggregates are inclusions, usually found in type II muscle fibers and in males, consisting of regular arrays of tubules derived from the sarcoplasmic reticulum. Tubular aggregates are associated with a wide variety of muscle disorders, including poorly defined "tubular aggregate myopathies" characterized by weakness and/or myalgia and/or cramps, and are also present in different mouse models, including normal aging muscles. The mechanism(s) responsible for inducing the formation of these structures have not been identified, because of the slow time course of their development *in vivo*, several months in mice. However, identical structures are formed in a few hours in rat muscles kept *in vitro* in hypoxic medium. Here I suggest that tubular aggregates result from reshaping of sarcoplasmic reticulum caused by misfolding and aggregation of membrane proteins and thus represent a special type of "protein aggregates" due to altered proteostasis.

Keywords: Tubular aggregates; Skeletal muscle; Myopathy; Sarcoplasmic reticulum; Protein aggregates; Proteostasis

1. Introduction

Tubular aggregates (TAs) were first clearly described and characterized by Engel et al. [1], in human muscle biopsies. By electron microscopy TAs may display different forms, the most typical being straight single-walled or double-walled tubules, either empty or containing dense material, regularly organized in tightly packed aggregates displaying a para-crystalline order (Fig. 1A). By light microscopy, they appear as bright red inclusions with modified Gomori trichrome stain, and react intensely for NADH tetrazolium reductase, but not for succinate dehydrogenase (Fig. 1B and C). It is now well established that these structures derive from the sarcoplasmic reticulum (SR), however their significance is still enigmatic. Here, I briefly review the occurrence and distribution of TAs in human and mouse skeletal muscle and discuss possible mechanisms for their formation.

2. TAs in human skeletal muscle

Several large surveys examined the frequency and distribution of TAs in human muscle biopsies by histochemistry and electron microscopy. The first survey reported that 24 out of more than 1500 biopsied patients had variable number of fibers with histochemically typical TAs [1]. All affected patients were males, although about equal numbers of females and males were biopsied, and TAs were found only in type II fibers. The most abundant TAs were seen in patients with hypo- and hyper-kalemic periodic paralysis, though only a minority of these patients had TAs in their biopsies, one patient with porphyria cutanea tarda and some otherwise normal individuals who had chronically taken large amounts of drugs. Another survey reported that 15 out of about 1500 muscle biopsy specimens contained TAs [2]. Again, all patients were males

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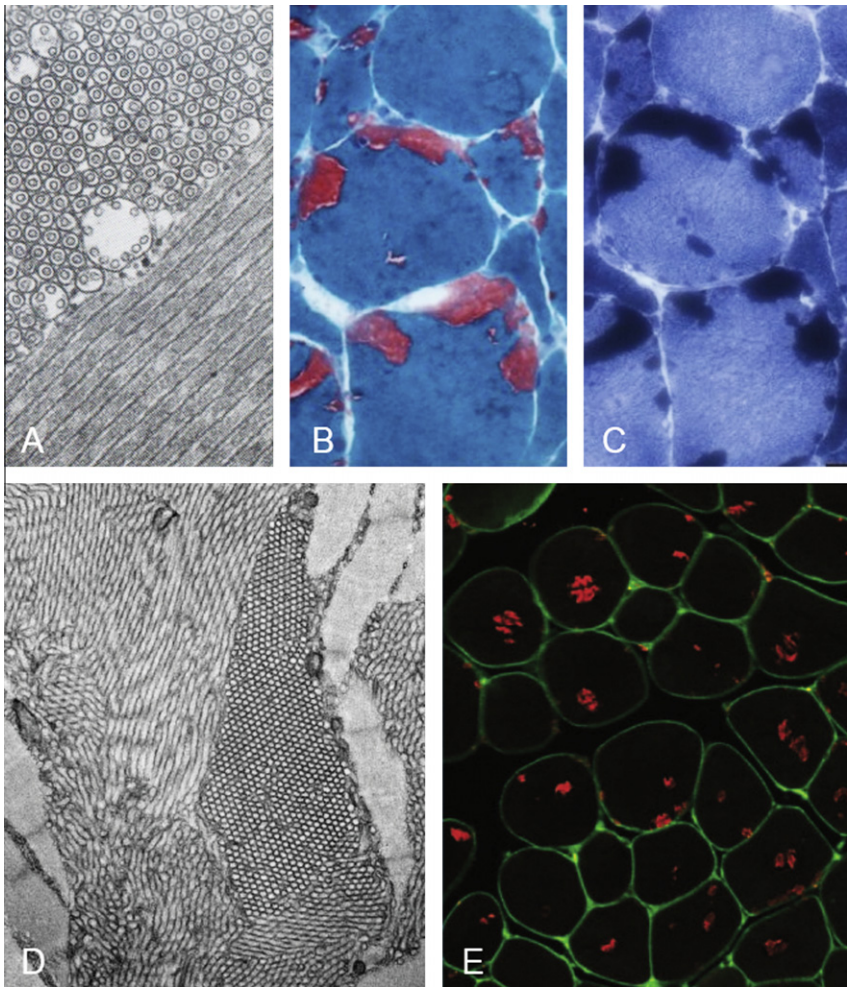

Fig. 1. Tubular aggregates visualized in human skeletal muscle by electron microscopy (A), and by light microscopy using modified Gomori trichromic stain (bright red inclusions in B) and histochemical staining for NADH tetrazolium reductase (dark blue inclusions in C). (D, E) TAs detected in muscle fibers from caveolin-2 null mice by electron microscopy (D) and by SERCA-specific antibodies (red inclusions in E, plasma membrane labeled by caveolin-3-specific antibodies). (A) from [1]; (B, C): from [63]; (D, E): from [16].

and had different diagnoses: hypokalemic periodic paralysis (2 cases); hyperkalemic periodic paralysis (1); myotonia congenita (1); inflammatory myopathies (3). The remaining 8 patients had a syndrome characterized predominantly by myalgia with or without cramps, a condition now often referred to as "tubular aggregate myopathy" because of the absence of any other histopathological abnormality or symptomatology indicating a specific disorder. In a third survey, TAs were identified in 19 out 3000 patients, 17 of them been males, and were present only in type II fibers [3]. Some of these patients had specific disorders, including peripheral neuropathy, amyotrophic lateral sclerosis, systemic lupus erythematosus or congenital myopathy, but seven of them had myalgia as the only clinical symptom. In a more recent survey of 15 cases with TAs on muscle biopsy, TAs were associated with myotonia (1), myotonic dystrophy (1), neuropathy (1), phosphoglycerate mutase (PGAM) deficiency (2) or, more frequently, with muscle weakness (7) [4]. The association of PGAM deficiency with TAs is rather frequent, 5 out 15 cases in a recent study [5], and is often accompanied by exercise-induced cramps and myoglobinuria. Interestingly, other glycogenoses, such as myophosphorylase or phosphofructokinase deficiency, or other defects of terminal glycolysis, such as phosphoglycerate kinase or lactic dehydrogenase deficiency, have never been associated with TAs.

The wide variety of clinical syndromes associated with TAs has been illustrated in a recent workshop, in which data from different centers were presented [6]. In all of these surveys, and in several other single case reports not quoted here, TAs were generally found only in type II muscle fibers and most reported cases were males. However, both type I and type II fibers and both genders were equally involved in some rare dominantly inherited tubular aggregate myopathies [7–9], as well as in some congenital myasthenic syndromes characterized by a limb-girdle