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Review

Anti-troponin antibodies following myocardial infarction

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ABSTRACT

Recent improvements in medical and surgical coronary revascularization techniques have significantly improved outcomes for patients with acute myocardial infarction (MI). However, large infarctions are often followed by a poorly understood process of pathological ventricular remodelling, which fails to return the heart to its premorbid state. Although it remains incompletely understood, there is increasing interest in the role of the immune system in this process. One hypothesis is that released cardiac proteins become the focus of an immune response that results in the formation of functionally significant autoantibodies. This review summarizes the current literature, both human and animal, relating to the formation and clinical relevance of anti-troponin antibodies (ATAs) in patients with MI.

Contents

Introduction

There has been increasing interest in the role of anti-cardiac autoantibodies as mediators of heart disease over the past two decades [1–5]. In the context of infection with cardiotropic viruses [6], bacteria [7–10], and protozoa [11], the pathophysiological mechanism underpinning autoantibody formation has been well elucidated. However, the potential role of structural heart damage, such as myocardial infarction (MI), in precipitating the formation of anti-cardiac autoantibodies, remains incompletely understood.

Given that cardiomyocytes are incapable of significant regeneration, post-MI repair occurs via a sophisticated, yet poorly understood, process of ventricular remodelling. Both humoral and

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cell mediated immune mechanisms, directed against a number of cardiac antigens – including troponin [12–15], myosin [3], actin [16,17], tissue transglutaminase [18] and endothelial cells [19,20] – have been implicated in the pathophysiology of this process [21]. Anti-myosin antibodies (AMAs) have a sound experimental evidence base, which has provided a plausible mechanistic explanation for the potential role of these antibodies in mediating cardiac dysfunction in MI patients. This review critically appraises the literature, both human and animal, relating to the formation and functional significance of anti-troponin antibodies (ATAs) in patients with MI. Given that cardiac troponin C is not specific for cardiac tissue, antibodies against this isoform have been excluded from the discussion.

Anti-troponin antibodies

Troponin is a heterotrimetric protein complex involved in the regulation of excitation–contraction coupling in striated muscle [22]. It is composed of three distinct gene products, which are arranged in a 1:1:1 stoichiometric ratio along the thin filament [23,24]. Troponin T (cTnT), the largest of the three subunits, secures the troponin complex to the myofibrillar thin filament via its interaction with tropomyosin. Troponin I (cTnI), the inhibitory subunit, prevents actin–myosin interaction during muscle relaxation. Troponin C (cTnC), the smallest subunit, binds calcium to initiate a muscle contraction (Fig. 1a) [23,24]. Although isoforms of cTnI and cTnT can be found in skeletal muscle [25,26], they are structurally different to the myocardial forms and do not cross-react with modern troponin assays [27,28]. Troponin C is not specific for cardiac tissue [29,30].

Anti-troponin I antibodies (ATIAs) have been observed in healthy individuals [14,31–35] (Table 1). They have also been described in animal models of dilated cardiomyopathy (DCM) [36–38] and myocarditis [39,40] (Table 2), and patients with DCM [14,33,36], ischaemic cardiomyopathy (ICM) [14,31,36], hypertrophic cardiomyopathy [36] (Table 3) and MI [12–15] (Table 3). The prevalence of ATIA among healthy patients varies between 0–12.7% (median 6.7%) (Table 1). In otherwise healthy people, the explanation for, and significance of, circulating ATIAs remains undetermined. It is possible that these antibodies reflect exposure to troponin following 'silent infarcts' or non-ischaemic cardiac damage among some of the study subjects. However, the study populations are poorly characterized in the literature, and the plausibility of this hypothesis remains difficult to determine.

Following MI, the proportion of patients developing ATIA at follow-up ranges between 7.5–10.9% (median 9.3%) (Table 3)

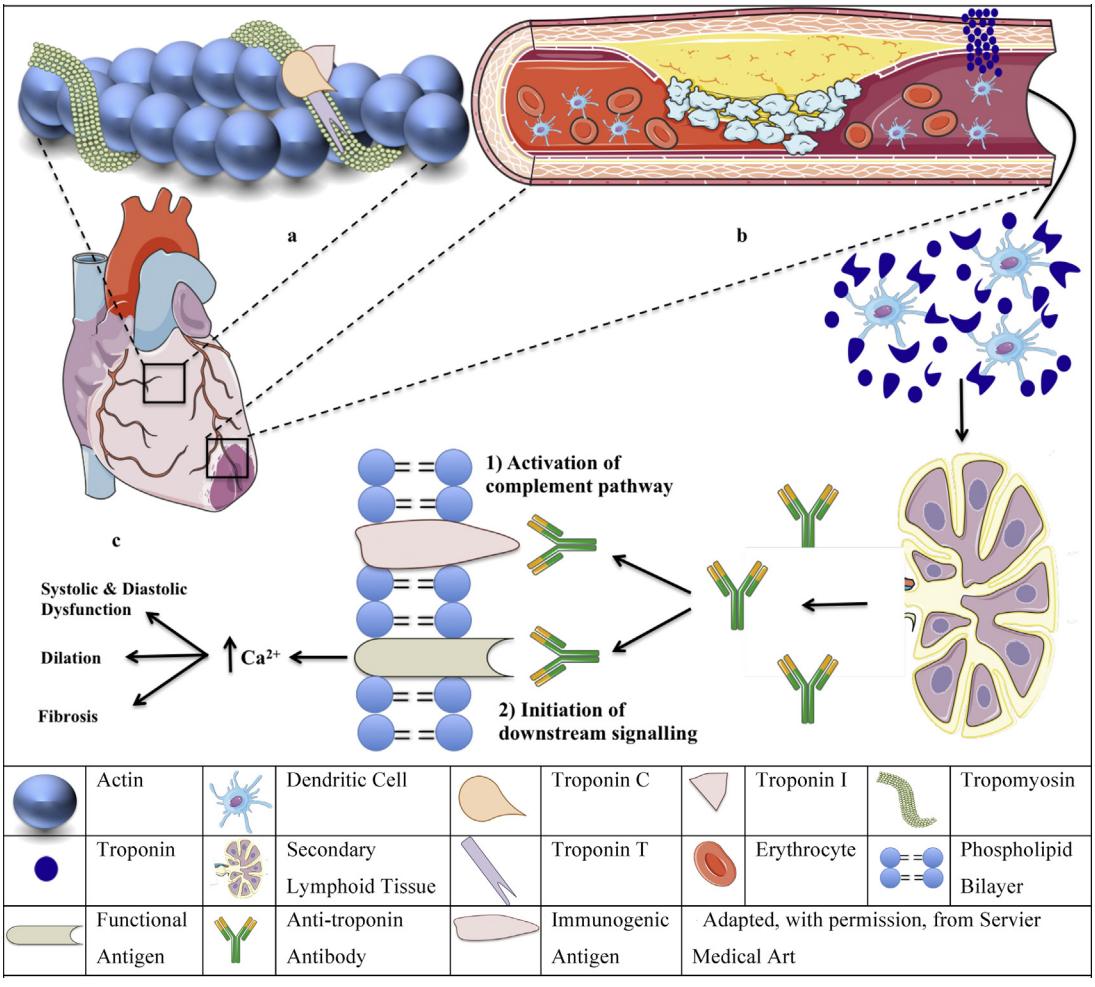

Fig. 1. (a) Cardiac troponin complex: troponin T anchors the complex to the underlying thin filament via tropomyosin. Troponin C and I regulate muscle contraction. (b) Formation of ATAs following MI: MI results in the spillage of troponin into the bloodstream. Free, unbound troponin, and troponin processed by antigen presenting cells, travel to secondary lymphoid tissue. In susceptible individuals, troponin may then be presented to autoreactive T-cells. Activated T-cells are capable of stimulating complementary B-cells to mature and produce ATAs. (c) Potential mechanism of ATA mediated myocardial damage: two potential mechanisms. (1) ATAs recognize and attach to a surface protein, which subsequently initiates complement mediated cellular damage. (2) ATAs modulate intracellular calcium concentration, via signal transduction, after binding with a surface protein.

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