Cardioimmunology of arrhythmias: the role of autoimmune and inflammatory cardiac channelopathies

Pietro Enea Lazzerini, Franco Laghi-Pasini, Mohamed Boutjdir and Pier Leopoldo Capecchi

We have read with great interest the excellent review on cardioimmunology by Filip K. Swirski & Matthias Nahrendorf (Cardioimmunology: the immune system in cardiac homeostasis and disease. *Nat. Rev. Immunol.* 18, 733–744 (2018))[1]. The authors extensively discussed the role of immune cells in normal and diseased heart, specifically in myocardial infarction, myocarditis and endocarditis, heart failure and rhythm disorders[1]. Regarding rhythm disorders, they speculated that the immune system could contribute to arrhythmias through two mechanisms — a crosstalk between immune cells and fibroblasts and/or myocytes, leading to insulating fibrosis, or a direct participation of leukocytes (macrophages) in the electrical regulation of conducting cells, by interacting through connexin 43 (CX43)-containing gap junctions[1].

However, the authors substantially disregarded a third important mechanism of arrhythmias in this new field of immuno-cardiac electrophysiology. In fact, accumulating data indicate that the immune system can promote cardiac arrhythmias by means of autoantibodies and/or inflammatory cytokines that directly affect the function of specific ion channels on the surface of cardiomyocytes[2–4].

Several autoantibodies have been described that target cardiac Ca^{2+}, K^+ or Na^+ channels and that have arrhythmogenic effects in the absence of evident histological changes in the heart; these are known as autoimmune cardiac channelopathies[2,4]. Indeed, it is well recognized that anti-Sjögren's-syndrome-related antigen A (anti-SSA) antibodies (also known as anti-Ro/SSA antibodies) can cross react with the pore region of both L-type Ca^{2+} channels ($Ca_V1.2$ and $Ca_V1.3$) and T-type Ca^{2+} channels ($Ca_V3.1$ and $Ca_V3.2$). By inhibiting the related Ca^{2+} currents, these antibodies promote conduction disturbances, such as sinus bradycardia and atrioventricular (AV) block[5,6] (FIG. 1a). Similar clinical consequences were also shown for autoantibodies recognizing the extracellular loop of domain

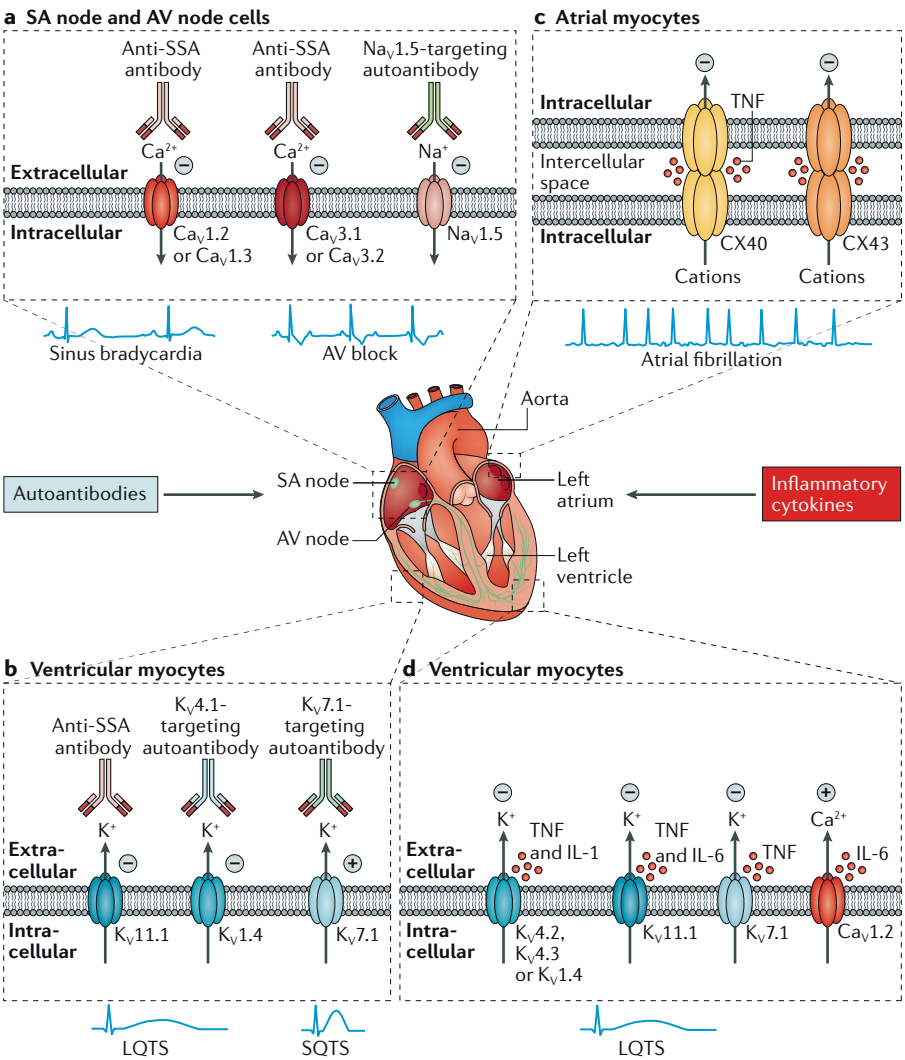

Fig. 1 | **Autoimmune and inflammatory cardiac channelopathies and arrhythmias: molecular basis.** Autoantibodies and inflammatory cytokines can modulate the function of cardiac ion channels and promote arrhythmias. **a** | Bradyarrhythmias and conduction disturbances can be induced by anti-Sjögren's-syndrome-related antigen A (anti-SSA) antibodies (also known as anti-Ro/SSA antibodies), which target the L-type and/or T-type Ca^{2+} channels and inhibit the related currents, or by autoantibodies targeting the $Na_V1.5$ Na^+ channel, which inhibit the Na^+ current, in cells of the sinoatrial (SA) node and atrioventricular (AV) node. **b** | Long-QT syndrome (LQTS) can be induced by anti-SSA antibodies, which target the $K_V11.1$ K^+ channel (also known as hERG) and inhibit the rapidly activating repolarizing component of the delayed rectifier K^+ current, or by autoantibodies targeting the $K_V1.4$ K^+ channel, which might inhibit the transient outward K^+ current in ventricular myocytes. Short-QT syndrome (SQTS) can be induced by autoantibodies targeting the $K_V7.1$ K^+ channel, which increase the slowly activating repolarizing component of the delayed rectifier K^+ current in ventricular myocytes. **c** | Atrial fibrillation can be induced by tumour necrosis factor (TNF), which impairs the expression and/or distribution of connexin 40 (CX40) and CX43 and inhibits the function of gap junctions in atrial myocytes. **d** | LQTS can be induced by TNF, which targets $K_V4.2$, $K_V4.3$, $K_V11.1$ and $K_V7.1$ K^+ channels and inhibits the respective currents; by IL-1, which inhibits the transient outward K^+ current; or by IL-6, which targets the L-type Ca^{2+}channel ($Ca_V1.2$) and increases the L-type Ca^{2+} current, in ventricular myocytes. For simplicity, IL-6 and TNF receptors are not shown in panel d.

I S5–S6 of the $Na_V1.5$ Na^+ channel[7]. These antibodies, which can be detected in patients with idiopathic AV block, inhibit Na^+ currents and induce conduction disturbances in experimental models[7].

Other autoantibodies that target ion channels can affect the action potential duration (APD) of ventricular myocytes, leading to long-QT syndrome (LQTS) or short-QT syndrome (SQTS) and associated malignant arrhythmias[3]. LQTS can be induced by anti-SSA antibodies, which inhibit the rapidly activating repolarizing K^+ current by targeting the extracellular pore loop of the $K_V11.1$ K^+ channel (also known as hERG)[8,9], as well as by autoantibodies targeting $K_V1.4$ K^+ channels, possibly through blockade of the transient outward K^+ current[10]. Conversely, agonist-like autoantibodies targeting $K_V7.1$ K^+ channels that enhance the slowly activating repolarizing K^+ current were associated with SQTS[11] (FIG. 1b).

Moreover, inflammatory cytokines — in particular, tumour necrosis factor (TNF), IL-1 and IL-6 — can be arrhythmogenic by directly affecting the function of cardiac ion channels; these are known as inflammatory cardiac channelopathies[4]. Specifically, it has been shown that TNF induces dysfunction of gap junctions in atrial myocytes through impaired expression and/or distribution of CX40 and CX43 and that these changes promote atrial fibrillation by favouring a slow and heterogeneous conduction in the atria[12] (FIG. 1c). In addition, cytokines can favour the development of LQTS by decreasing specific cardiac K^+ currents and/or increasing L-type Ca^{2+} currents[3,4]. TNF inhibits transient outward, rapidly activating repolarizing and slowly activating repolarizing K^+ currents as a result of the downregulation of channel expression and/or alterations in channel-gating kinetics, which are also associated with prolongation of the APD and/or QT interval[4,13]. Similar effects are mediated by IL-1, which reduces the transient outward K^+ current[14], and by IL-6, which enhances the L-type Ca^{2+} current through $Ca_V1.2$ phosphorylation[15] and inhibits the rapidly activating repolarizing K^+ current through a pathway involving the IL-6 receptor and Janus kinase[16] (FIG. 1d).

In terms of translational medicine, emphasizing the role of autoimmune and inflammatory cardiac channelopathies in arrhythmogenesis may lead to innovative anti-arrhythmic therapies based on the targeted modulation of the immune–inflammatory system, such as cytokine-targeting monoclonal antibodies or short decoy peptides that divert autoantibodies from their binding sites on ion channels.

There is a reply to this letter by Swirski, F. K. & Nahrendorf, M. *Nat. Rev. Immunol.* https://doi.org/10.1038/s41577-018-0099-y (2018).

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Competing interests
The authors declare no competing interests.