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

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

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We have read with great interest the excellent review on Cardioimmunology, by Swirski & Nahrendorf.[1] The authors extensively discussed the role of immune-cells in normal and diseased heart, specifically in myocardial infarction, myocarditis/endocarditis, heart failure, and rhythm disorders.[1] Regarding the latter topic on rhythm disorders, they speculated that the immune system could contribute to arrhythmias via two fundamental routes, i.e. a cross-talk between immune-cells and fibroblasts/myocytes leading to insulating fibrosis, or a direct participation of leukocytes (macropahages) in electrical regulation of conducting cells, by interacting through connexin 43(Cx43)-containing gap-junctions.[1]

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

Several autoantibodies have been described which target cardiac calcium(Ca^{++}), potassium(K^+), or sodium(Na^+) channels and exert arrhythmogenic effects regardless of evident histologic changes in the heart(*autoimmune channelopathies*).[2,4] Indeed, it is well recognized that anti-Ro/SSA antibodies can cross-react with the pore region of both L-type($Ca_v1.2/1.3$) and T-type($Ca_v3.1/3.2$) Ca^{++}-channels, and by inhibiting related I_{CaL} and I_{CaT} currents promote conduction disturbances, such as sinus bradycardia/atrio-ventricular(AV) block.[5,6] Similar clinical consequences were also demonstrated for autoantibodies recognizing the extracellular loop of domain I S5-S6 of the Na^+-channel($Na_v1.5$).[7] These antibodies, detected in patients with idiopathic AV-block, inhibit I_{Na} and induce conduction disturbances in experimental models[7](Figure 1A).

Other anti-ion channels autoantibodies can affect action potential duration(APD) of ventricular myocytes, leading to long-QT syndrome(LQTS) or short-QT syndrome(SQTS) and associated malignant arrhythmias.[2] LQTS can be induced by anti-Ro/SSA antibodies, which inhibit the I_{Kr} current by targeting the extracellular pore loop of the $K_v11.1$ K^+-channel(hERG),[8,9] and anti-$K_v1.4$ K^+-channel autoantibodies, possibly via a blockade of the related I_{to} current.[10] Conversely, agonist-

like anti-Kv7.1 K^+-channel autoantibodies enhancing the I_{Ks} current were associated with SQTS[11](Figure 1B).

Moreover, also inflammatory cytokines, particularly TNFα, IL-1 and IL-6, can be *per se* arrhythmogenic by directly affecting cardiac ion-channels function(*inflammatory channelopathies*).[4] Specifically, it has been demonstrated that TNFα induces gap-junction channel dysfunction in atrial myocytes via impaired atrial connexin(Cx)40 and Cx43 expression and/or distribution, and that these changes promote atrial fibrillation by favouring a slow and heterogeneous conduction in the atria[12](Figure 1C). In addition, cytokines can favour LQTS development by decreasing specific cardiac K^+-currents and/or increasing I_{CaL}.[3,4] TNFα inhibits I_{to}, I_{Kr}, and I_{Ks}, as a result of a down-regulation of channel expression and/or alterations in channel-gating kinetics, also associating to APD/QT-interval prolongation.[4,13] Similar effects are exerted by IL-1, by reducing I_{to},[14] and IL-6, via $Ca_v1.2$ phosphorylation leading to I_{CaL} enhancement[15](Figure 1D).

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

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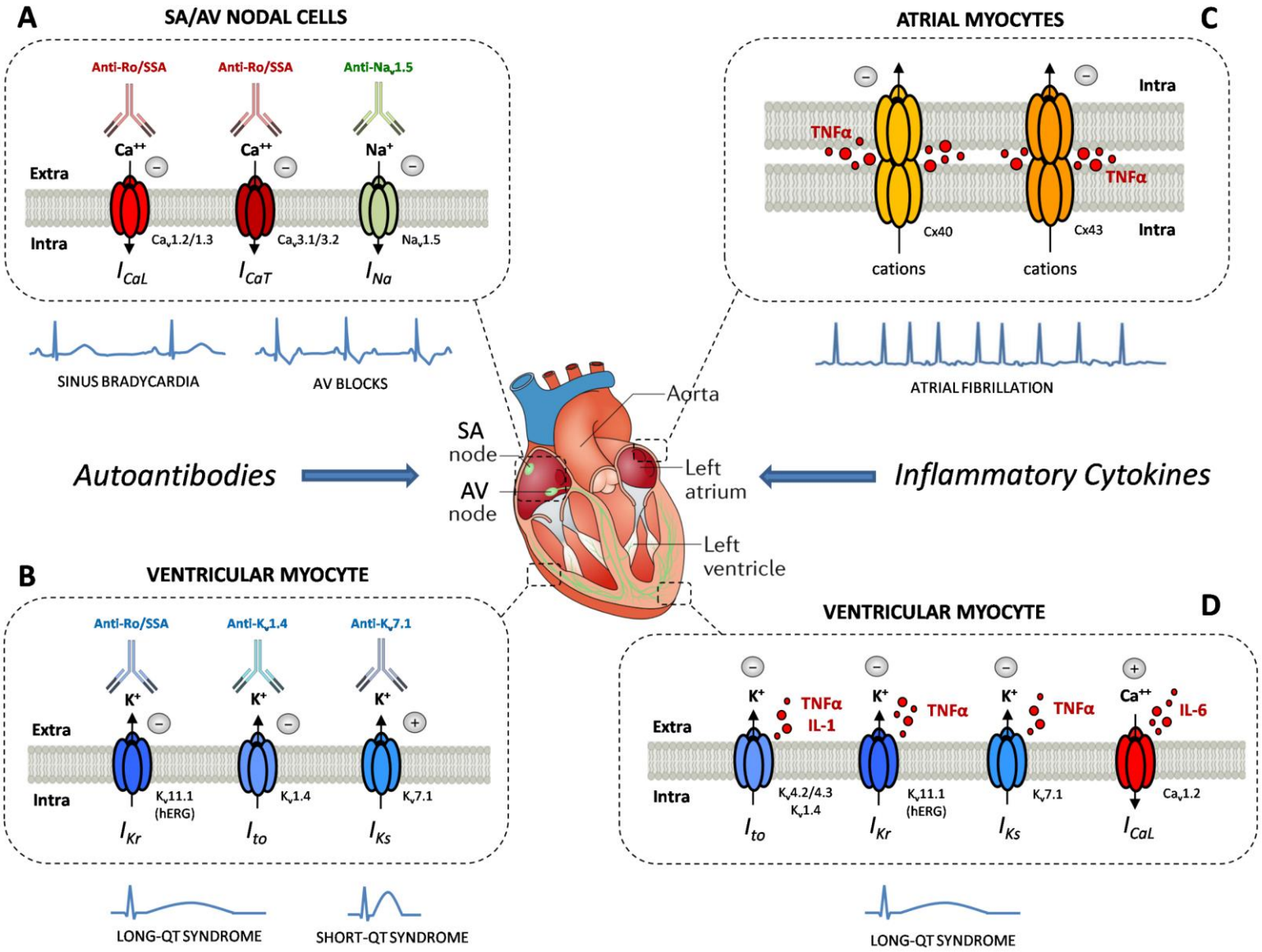
LEGEND TO FIGURE

Figure 1. Autoimmune and inflammatory cardiac channelopathies and arrhythmias: molecular basis. Autoantibodies and inflammatory cytokines can modulate cardiac ion channels function and promote arrhythmias. **A** | Bradyarrhythmias and conduction disturbances can be induced by anti-Ro/SSA autoantibodies which target the L-type and/or T-type calcium (Ca^{++}) channels and inhibit the related currents (I_{CaL} and I_{CaT}), or by anti-$Na_v1.5$ channel autoantibodies which inhibit sodium (Na^+) current (I_{Na}), in sino-atrial (SA)/atrio-ventricular (AV) nodal cells. **B** | Long-QT syndrome (LQTS) can be induced by anti-Ro/SSA autoantibodies which target the human ether-à-go-go-related gene (hERG) potassium (K^+) channel and inhibit the rapid component of the delayed rectifier K^+ current (I_{Kr}), or by anti-Kv1.4-K^+ channel autoantibodies which might inhibit the transient outward K^+ current (I_{to}), in ventricular myocytes. Short-QT syndrome (SQTS) can be induced by anti-$K_v7.1$-K^+ channel which increase the slow component of the delayed rectifier K^+ current (I_{Ks}) in ventricular myocytes. **C** | Atrial fibrillation can be induced by tumour necrosis factor-α (TNFα) which impairs connexin (Cx)40 and Cx43 expression/distribution and inhibit gap-junction channels function in atrial myocytes. **D** | LQTS can be induced by TNFα which targets $K_v4.2/4.3$, hERG and $K_v7.1$-K^+ channels, and inhibits the respective currents I_{to}, I_{Kr}, and I_{Ks}; by interleukin-1 (IL-1) which inhibits I_{to}; or by interleukin-6 (IL-6) which targets the L-type Ca^{++} channel and increases I_{CaL}, in ventricular myocytes.


A
SA/AV NODAL CELLS
Anti-Ro/SSA
Anti-Ro/SSA
Anti-Nav1.5
Ca++
Ca++
Na+
Extra
Intra
Cav1.2/1.3
Cav3.1/3.2
Nav1.5
ICaL
ICaT
INa
SINUS BRADYCARDIA
AV BLOCKS
C
ATRIAL MYOCYTES
Intra
TNFα
TNFα
Cx40
Cx43
Intra
cations
cations
ATRIAL FIBRILLATION
Autoantibodies
Inflammatory Cytokines
Aorta
SA node
AV node
Left atrium
Left ventricle
B
VENTRICULAR MYOCYTE
Anti-Ro/SSA
Anti-Kv1.4
Anti-Kv7.1
K+
K+
K+
Extra
Intra
Kv11.1 (hERG)
Kv1.4
Kv7.1
IKr
Ito
IKs
LONG-QT SYNDROME
SHORT-QT SYNDROME
D
VENTRICULAR MYOCYTE
K+
TNFα
IL-1
K+
TNFα
K+
TNFα
Ca++
IL-6
Extra
Intra
Kv4.2/4.3
Kv1.4
Kv11.1 (hERG)
Kv7.1
Cav1.2
Ito
IKr
IKs
ICaL
LONG-QT SYNDROME