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**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.<sup>1</sup> 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.<sup>1</sup> 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 (macrophages) in electrical regulation of conducting cells, by interacting through connexin 43(Cx43)-containing gap-junctions.<sup>1</sup>

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.<sup>2-4</sup>

Several autoantibodies have been described which target cardiac calcium( $\text{Ca}^{++}$ ), potassium( $\text{K}^+$ ), or sodium( $\text{Na}^+$ ) channels and exert arrhythmogenic effects regardless of evident histologic changes in the heart(*autoimmune channelopathies*).<sup>2-4</sup> Indeed, it is well recognized that anti-Ro/SSA antibodies can cross-react with the pore region of both L-type( $\text{Ca}_v1.2/1.3$ ) and T-type( $\text{Ca}_v3.1/3.2$ )  $\text{Ca}^{++}$ -channels, and by inhibiting related  $\text{I}_{\text{CaL}}$  and  $\text{I}_{\text{CaT}}$  currents promote conduction disturbances, such as sinus bradycardia/atrio-ventricular(AV) block.<sup>5,6</sup> Similar clinical consequences were also demonstrated for autoantibodies recognizing the extracellular loop of domain I S5-S6 of the  $\text{Na}^+$ -channel( $\text{Na}_v1.5$ ).<sup>7</sup> These antibodies, detected in patients with idiopathic AV-block, inhibit  $\text{I}_{\text{Na}}$  and induce conduction disturbances in experimental models<sup>7</sup>(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.<sup>2</sup> LQTS can be induced by anti-Ro/SSA antibodies, which inhibit the  $\text{I}_{\text{Kr}}$  current by targeting the extracellular pore loop of the  $\text{K}_v11.1$   $\text{K}^+$ -channel(hERG),<sup>8,9</sup> and anti- $\text{K}_v1.4$   $\text{K}^+$ -channel autoantibodies, possibly via a blockade of the related  $\text{I}_{\text{to}}$  current.<sup>10</sup> Conversely, agonist-

like anti-Kv7.1 K<sup>+</sup>-channel autoantibodies enhancing the I<sub>Ks</sub> current were associated with SQTs<sup>11</sup>(Figure 1B).

Moreover, also inflammatory cytokines, particularly TNF $\alpha$ , IL-1 and IL-6, can be *per se* arrhythmogenic by directly affecting cardiac ion-channels function(*inflammatory channelopathies*).<sup>4</sup> Specifically, it has been demonstrated that TNF $\alpha$  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<sup>12</sup>(Figure 1C). In addition, cytokines can favour LQTS development by decreasing specific cardiac K<sup>+</sup>-currents and/or increasing I<sub>CaL</sub>.<sup>3,4</sup> TNF $\alpha$  inhibits I<sub>to</sub>, I<sub>Kr</sub>, and I<sub>Ks</sub>, as a result of a down-regulation of channel expression and/or alterations in channel-gating kinetics, also associating to APD/QT-interval prolongation.<sup>4,13</sup> Similar effects are exerted by IL-1, by reducing I<sub>to</sub>,<sup>14</sup> and IL-6, via Ca<sub>v</sub>1.2 phosphorylation leading to I<sub>CaL</sub> enhancement<sup>15</sup>(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 ( $\text{Ca}^{++}$ ) channels and inhibit the related currents ( $I_{\text{CaL}}$  and  $I_{\text{CaT}}$ ), or by anti- $\text{Na}_v1.5$  channel autoantibodies which inhibit sodium ( $\text{Na}^+$ ) current ( $I_{\text{Na}}$ ), 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 ( $\text{K}^+$ ) channel and inhibit the rapid component of the delayed rectifier  $\text{K}^+$  current ( $I_{\text{Kr}}$ ), or by anti- $\text{K}_v1.4$ - $\text{K}^+$  channel autoantibodies which might inhibit the transient outward  $\text{K}^+$  current ( $I_{\text{to}}$ ), in ventricular myocytes. Short-QT syndrome (SQTS) can be induced by anti- $\text{K}_v7.1$ - $\text{K}^+$  channel which increase the slow component of the delayed rectifier  $\text{K}^+$  current ( $I_{\text{Ks}}$ ) in ventricular myocytes. **C** | Atrial fibrillation can be induced by tumour necrosis factor- $\alpha$  ( $\text{TNF}\alpha$ ) which impairs connexin (Cx)40 and Cx43 expression/distribution and inhibit gap-junction channels function in atrial myocytes. **D** | LQTS can be induced by  $\text{TNF}\alpha$  which targets  $\text{K}_v4.2/4.3$ , hERG and  $\text{K}_v7.1$ - $\text{K}^+$  channels, and inhibits the respective currents  $I_{\text{to}}$ ,  $I_{\text{Kr}}$ , and  $I_{\text{Ks}}$ ; by interleukin-1 (IL-1) which inhibits  $I_{\text{to}}$ ; or by interleukin-6 (IL-6) which targets the L-type  $\text{Ca}^{++}$  channel and increases  $I_{\text{CaL}}$ , in ventricular myocytes.



