antihypertensive, lipid-lowering and, although not always, aspirin.⁽⁸⁾

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NEW BLOOD

Cardiorenal Syndrome: immune system as an intriguing connector between Heart and Kidney

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Since 1836 when Robert Bright first described the relationship between heart and kidneys, the scientific community has dedicated itself to better understanding the mechanisms involved in the kidney–heart axis, known in recent decades as cardiorenal syndrome (CRS)^[1]. CRS can be classified into 5 different types,

where types 1 and 2 are defined by acute or chronic cardiac alterations that lead to renal dysfunction, types 3 and 4 defined by acute or chronic renal alterations responsible for later cardiac alterations, and finally type 5, characterized by concomitant dysfunctions of the kidneys and heart due to systemic alterations such as

sepsis or diabetes^[2]. CRS type 3 affects a large amount of the population and is defined by an acute renal alteration capable of generating important cardiac alterations^[3]. The acute kidney injury (AKI) increases from 5% to 30-50% in all patients hospitalized in intensive care units and is present in ~43% of all deaths related to cardiovascular diseases^[4]. Ischemia and reperfusion (IR) injury is the main cause of AKI. This is a temporary condition that obstructs the blood flow in the kidney, leading to the release of oxidative stress compounds as well as inflammatory cytokines^[5]. In this sense, our laboratory has been seeking to understand the cellular, molecular and functional mechanisms involved in cardiac alterations induced by AKI in an IR model in mice.

The AKI induced by the IR model leads to an inflammatory process that seems to be important to the development of heart dysfunction. One of the main focuses of our group was to evaluate the role of innate immunity, represented by Toll-Like receptors (TLRs), in cardiac

tropism modulated by acute kidney injury. First, we demonstrate that IR model are able to induce an acute systemic inflammation (until 8 days of reperfusion) followed by a concentric cardiac hypertrophy (after 15 days of reperfusion) not accompanied by fibrosis. Besides, TLRs 2 and 4 are essential for cardiac hypertrophy development observed in IR model^[6]. In addition to cardiac hypertrophy and acute inflammation, it was possible to observe important electrical changes demonstrated to an increase on action potential duration (APD) and QTc interval^[7].

The increased number of pro-arrhythmogenic events stimulated us to investigate the role of some inflammatory cytokines that were shown to be altered in this experimental model. Thus, we studied the role of NLRP3 inflammasome and IL-1b on arrhythmogenic events and we demonstrated, for the first time, that the inflammatory cytokine IL-1b plays a crucial role in cardiac arrhythmia induced by acute kidney injury once knockout models and pharmacological interventions were able to prevent arrhythmogenic events^[7]. Besides, other studies by our group have shown that the Renin-Angiotensin-Aldosterone System (RAAS) and the Sympathetic Nervous System (SNS) are important mediators of the kidney-heart axis since cardiac inflammatory events induced by renal IR, caused by the simultaneous upregulation of the SNS and RAAS in the heart, possibly support the mechanism involved in the development of cardiorenal syndrome^[8]. Furthermore, it was possible to demonstrate that the IR model mimicking CRS3 presents

a specific tissue and time regulation regarding the redox balance, which suggests possible forms of therapeutic interventions^[9].

Although some of the mediators of the conversation between kidneys and heart are known, much remains to be explored regarding the mechanisms involved in each type of CRS. Some of them we are currently studying as the participation of mitochondria dysfunction, modulation of lymphocytes and macrophages populations, accumulation of uremic toxins and extracellular vesicles content.

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