EDITORIAL

Novel Therapeutic Approaches and Targets for the Treatment of Cardiovascular and Immunological Diseases

Giacomo Campi[#], Valentina Mercurio[#], Dario Fabiani, Martina Grieco, Michele Russo and Carlo G. Tocchetti

[#]GC and VM share first authorship.

Department of Translational Medical Sciences, Federico II University, Naples, Italy

Carlo G. Tocchetti

Along with the increasing prevalence of cardiovascular and immunological disorders, in a continuously-ageing population, our understanding of the precise mechanisms that regulate cellular complex biochemical environments is increasing. Cellular networks, pathways and biochemical codes are being deciphered, shedding lights on novel therapeutic routes. In this context, inflammation and dysregulated immune system represent a true cellular model that links the pathophysiology of cardiovascular disease and the fine tuning of all the mechanisms that orchestrate the cellular systems. This Special Issue is composed of important contributions on the topic.

The first manuscript addresses an important immunological disease, such as Common variable immunodeficiency (CVID), the most frequent symptomatic antibody deficiency in adults, in which the humoral immune impairment exposes patients to a wide spectrum of clinical manifestation, including recurrent infections. Interestingly, patients with CVID can present with inflammatory, autoimmune disease, hematologic disease and cancers. Varricchi and collaborators [1] present interesting results from 58 patients diagnosed with CVID and treated with regular immunoglobulin replacement therapy who underwent gastrointestinal endoscopic examination for the evaluation of gastroduodenal manifestations of their CVID. Histopathologic findings revealed a high prevalence of chronic inflammatory gastrointestinal disorders (chronic gastritis, chronic duodenitis, increasing intraepitelial lymphocytes, and the absence of plasma cells) that are not responsive to the immunoglobulin replacement therapy. This observation points out that in CVID patients there is a more complex immune dysregulation rather than a true humoral immunity deficiency. Indeed, these patients could represent a real *in vivo* model to deeply study immune system activation, autoimmunity and inflammation. In this context, in the second article, dr Pecoraro and colleagues [2] explored the ability of a simple screening test, the Calculated Gobulin (CG), to be effective in the early detection of antibody deficiency, in order to reduce diagnostic delays as well as the healthcare costs of specific immunoglobulin dosage. The CG derives from the difference between total protein and albumin, and a ROC curve analysis-derived cut-off of 19 g/l was able to detected patients with IgG lower than 600 mg/dl with a sensitivity of 70% and a specificity of 75%.

Inflammation plays a major role also in the manuscript authored by Pasqua and coworkers [3], that addresses mechanisms of hypertension, the most prevalent cardiovascular disorder. Here, the authors describe in details the role of NLRP (nucleotide binding oligomerization domain Leucine-rich repeat) in the pathophysiology of arterial hypertension. NLRPs are members of pattern recognition receptors (PRR) that have the ability to activate immune cells detecting PAMPs (pattern associated molecular patterns) and DAMPs (damage associated molecular patterns). In the context of the danger-model of hypertension, priming hypertensive stimuli could promote the activation of the NLRP3-inflammosome that maintains a low-grade of sterile inflammation in a vicious circle that sustains hypertension itself, thus leading to organ damages.

Despite the role of Chemokines in inflammation has been extensively underscored, Sara Paccosi and Astrid Parenti [4] dissect the role of chemokine pathways in modulating vascular growth mechanisms. In particular, the family of CC-Chemokines directly interacts with vascular cells, endothelial cells, vascular smooth muscular cells (VSMC), fibroblasts, platelets, erythrocytes, and glomerular renal cells in a leukocyte independent-way, being involved in compensatory vascular remodeling such as angiogenesis, atherosclerosis, arteriogenesis. For example, the CCL-2/CCR2 axis plays an important role in restenosis and plaque formation, with a direct effect on VSMC proliferation. The authors focused on Atypical Chemokine Receptors Families (ACKRs), chemokine receptors that were found to have an important scavenger function in regulating chemokine trafficking, and could be considered an interesting potential therapeutic target.

Finally, two complementary and extensive reviews point out the crucial role of the endothelial progenitor cells (EPCs), a subunit of mononuclear cells (MNCs), in the angiogenesis and remodeling processes, with a special focus as potential therapeutic targets. Guerra and collaborators [5] investigate the precise role of the circulating EPCs in the remodeling mechanism involved in pulmonary vascular diseases. Pulmonary arterial hypertension (PAH) is characterized by circulating progenitor recruitment, enhanced angiogenesis and endothelial cell dysfunction that lead to increasing vascular resistances. Manipulating the VEGF (vascular endotelial grow factor) signaling pathway to stimulate endothelial vascular growth seems to be a promising strategy to counteract pulmonary remodeling in PAH [6, 7] and to induce therapeutic angiogenesis in ischemic patients to reju-

1873-4316/18 $58.00+.00

venate the angiogenic activity. The exhaustive review of Moccia and coworkers [8] illustrates how the Ca^{2+} toolkit, the "signalosome" that regulates the intracellular Ca^{2+} concentration, drives proliferation, tube formation and neovessel formation, in the ECFCs cells, a subset of EPCs that possesses high intrinsic clonal potential. All the signaling components (channels, transporters, pumps and receptors) of the Ca^{2+}toolkit can be tuned and genetically manipulated to improve the vascular regenerative potential. This systematic review offers a complete survey of the signaling cascade that from VEGF and Stromal cell-derived factor-1a (SDF-1a) leads to oscillation of intracellular Ca^{2+} concentrations in peripheral blood and umbilical cord blood-derived ECFCs, triggering store operated Ca^{2+}entry (SOCE). Arachidonic-acid and nicotine acid adenine dinucleotide phosphate (NAAP) could stimulate Ca^{2+} release from the endolysosomal compartment and activate ECFC proliferation, supported by TRP vanilloid receptors.

In conclusion, all the manuscripts of this Special Issue offer different views of the complex mechanisms that regulate inflammation and cardiovascular diseases, from basic science to clinical works, focusing on the special approach that regenerative medicine and genetic manipulation have opened. These observations should open new routes in the knowledge of different conditions and new promising therapeutic targets.

FUNDING

CGT received funding from a Federico II University-Ricerca di Ateneo grant.

REFERENCES

[1] Varricchi, G.; Pecoraro, A.; Crescenzi, L.; Marone, G.; Travaglino, A.; D'Armiento, F.P.; Genovese, A.; Spadaro, G. Gastroduodenal disorders in patients with CVID undergoing immunoglobulin therapy. *Curr. Pharm. Biotechnol*., **2018**, *19*(9), 721-728.

[2] Pecoraro, A.; Jolles, S.; Crescenzi, L.; Varricchi, G.; Marone, G.; Savoia, M.; Genovese, A.; Spadaro, G. Validation of calculated globulin (CG) as a screening test for antibody deficiency in an Italian University Hospital. *Curr. Pharm. Biotechnol*., **2018**, *19*(9), 715-720.

[3] Pasqua, T.; Pagliaro, P.; Rocca, C.; Angelone, T.; Penna, C. role of nlrp-3 inflammasome in hypertension: A potential therapeutic target. *Curr. Pharm. Biotechnol*., **2018**, *19*(9), 700-707.

[4] Paccosi, S.; Parenti, A. Leukocyte-independent effects of CC-chemokines on vascular remodeling. *Curr. Pharm. Biotechnol*., **2018**, *19*(9), 729-741.

[5] Guerra, G.; Perrotta, F.; Testa, G. Circulating endothelial progenitor cells biology and regenerative medicine in pulmonary vascular diseases. *Curr. Pharm. Biotechnol*., **2018**, *19*(9), 700-707.

[6] Mercurio, V.; Palazzuoli, A.; Correale, M.; Lombardi, C.; Passantino, A.; Ravera, A.; Ruocco, G.; Sciatti, E.; Triggiani, M.; Lagioia, R.; Scrutinio, D.; Tocchetti, C.G.; Nodari, S. Right heart dysfunction: From pathophysiologic insights to therapeutic options: A translational overview. *J. Cardiovasc. Med*. (Hagerstown)., **2018**, Jul 25. doi: 10.2459/JCM.0000000000000700. [Epub ahead of print]

[7] Mercurio, V.; Bianco, A.; Campi, G.; Cuomo, A.; Diab, N.; Mancini, A.; Parrella, P.; Petretta, M.; Hassoun, P.; Bonaduce, D. New drugs, therapeutic strategies, and future direction for the treatment of pulmonary arterial hypertension. *Curr. Med. Chem*., **2018**, Jan 31. doi: 10.2174/0929867325666180201095743. [Epub ahead of print]

[8] Moccia, F.; Berra-Romani, R.; Rosti, V. Manipulating Intracellular Ca^{2+} signals to stimulate therapeutic angiogenesis in cardiovascular disorders. *Curr. Pharm. Biotechnol.,* **2018**, *19*(9), 686-699.

Carlo G. Tocchetti, MD, PhD, FHFA
Guest Editor : Current Pharmaceutical Biotechnology
Dipartimento di Scienze Mediche Traslazionali
Universita' degli Studi di Napoli Federico II
Napoli, Italy
Tel: +39-081-746-2242
Fax: +39-081-746-2246
E-mail: carlogabriele.tocchetti@unina.it