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Editorial

Immunoprofiling and immunoscoring in cor onary artery disease: From vascular research to the bedside?

Coronary artery disease (CAD) accounts as the leading cause of death in Western Countries [1,2]. CAD has been historically associated with different risk factors, classified as non-modifiable and and modifiable risk factors. Family history, age, gender and ethnicity are recognized as non-modifiable risk factors in CAD, while hypercholesterolemia, diabetes mellitus, hypertension, a dietary regimen rich in fat uptake, sedentary lifestyle, and smoking habits, are largely known as modifiable risk factors in CAD [3–5].

From clinical, translational, and basic research points of view, CAD has been mostly considered as a disease mediated by aberrant lipid accumulation, and subsequent injury to the cardiovascular system. However, more recently, apart from this lipid-centric view, the attention of researchers and clinicians has been directed to the contribution of the immune system in the pathogenesis and progression of CAD. Accordingly, it has been clearly demonstrated that pro-inflammatory immune cells represent a relevant host-dependent hallmark in CAD [6]. Advances in basic science research have allowed to establish the crucial role of immune cells in orchestrating all stages of CAD [7]. Currently, strong evidence support that multiple interrelated immune mechanisms interact with metabolic, genetic, and environmental risk factors to initiate, promote, and ultimately activate lesions in the coronary arteries [8–10].

In this issue of the Journal, Kimberley et al. [11] report their findings about profiling immune cells and related subsets/subpopulations in different stages of human coronary artery disease, using a novel multiplex immunohistochemistry (mIHC) technique. The immune profile panel used by the authors allow discrimination of immune cells from both innate and adaptive immunity, providing a complete scenario of the overall immune landscape and of its potential dynamic changes in CAD. Of note, authors are the first to provide a comprehensive and exhaustive immune mapping of cell subtypes across plaque types in coronary arteries.

Attention to the immune landscape in cardiovascular diseases is now emerging as a relevant approach [12–14] (Fig. 1), mirroring the success obtained in cancer biology, with the revolutionary concept of "immunoscore", referred to as quantification of the *in situ* immune infiltrate to classify tumors [15] and immunotherapy, with the goal of using and/or re-educating the immune system of the host organism to eliminate cancers [15].

Kimberley et al. [11] performed the immune mapping of samples of patients with atherosclerotic plaques from the left anterior descending coronary artery, characterized as eccentric, intimal thickening (N = 11), pathological intimal thickening (N = 10), fibroatheroma (N = 9), and fibrous plaque (N = 9). Eccentric intimal thickening was considered normal, and pathological intimal thickening, fibroatheroma, and fibrous plaque were considered diseased coronary arteries. The immune mapping was performed by multiplex immunohistochemistry, to detect several immune cells and related subsets both from innate and adaptive immunity.

While this can be considered a pilot study, due to the relatively small sample size analyzed, it offers relevant and challenging opportunities to translate the concept of the immunoscore also to cardiovascular research and to clinical practice in CVD.

Another challenging idea arising from the results showed by Kimberley et al. [11] is that to parallel/compare the immune contexture of atherosclerotic plaque, with that of the circulating immune counterpart, both in term of innate and of adaptive immunity (Fig. 1). This will allow the application of a liquid-biopsy based method in the context of CAD and other CVDs (Fig. 1).

The mIHC panel generated by Kimberley et al. [11] can be easily applied to blood samples of CAD patients, to be profiled by multicolor flow cytometry, thus generating a tissue and blood panel to map the dynamic changes of plaque, and circulating immune contexture to possibly classify, stratify and/or select CAD patients, based on immune-oriented targets. Once again, by mimicking the immunoscore in cancer, mIHC can be envisaged as a tool to classify subjects as "cold" (poorly immune infiltrating and inflammatory) or "hot" (highly immune infiltrating and pro-inflammatory) CAD patients.

Results provided by this work clearly suggest that the interaction of cardiologists and immunologists can be proposed as a step forward in advancing our knowledge of the pathophysiology of CAD disease, by a cardiovascular-immunology point of view that can be challenging in CAD and well as in the whole complex scenario of cardiovascular diseases, where inflammation account as a shared host-dependent hallmark (Fig. 1).

Finally, the feasibility to apply the knowledge generated by CAD patient immune mapping/immune profiling to design next generation immunotherapy, or "repurposing" old drugs [15,16] aimed at modifying/re-educating the immune system in CAD and other CVDs may no longer be a remote fanciful goal, but something that might become reality in clinical practice in the near future.

Author contributions

All authors listed have made a substantial, direct, and intellectual contribution to the work and approved the final text for publication.

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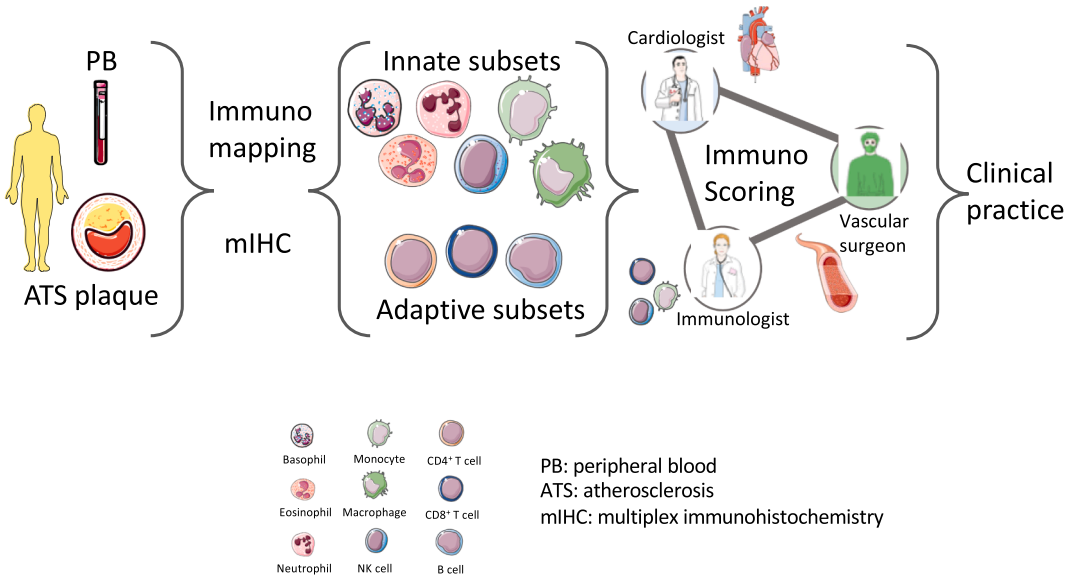

Fig. 1. Proposed flow chart for immune mapping/scoring of CAD patients. The immune mapping of CAD patients will allow the identification of the alterations in term of innate and immune cell subsets presence and distribution in peripheral blood and ATS plaque. This will help to generate a potential tissue-local, possibly paired with circulating immune score to classify and stratify CAD patients based on the inflammatory/immune contexture. Circulating immuno score in CAD patients can be, therefore, envisaged as a novel immunological classifier tool in CAD patients, generated using a minimally invasive and liquid-biopsy based approach. Finally, the feasibility of translating the knowledge generated by application of the immune score and immune mapping in CAD and CVD, strongly require the close interactions between cardiologists, vascular surgeons and immunologists.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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