Revista Portuguesa de Cardiologia 40 (2021) 849–851

Revista Portuguesa de
Cardiologia
Portuguese Journal of Cardiology
www.revportcardiol.org

EDITORIAL COMMENT

Immune cell subsets as a marker of development of heart failure: The application of bioinformatics tools

Subtipos de células imunitárias como marcador prognóstico na insuficiência cardíaca: a aplicação de ferramentas bioinformáticas

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Available online 11 October 2021

Survivors of an acute myocardial infarction (MI) are at risk of developing symptomatic heart failure (HF) or sudden cardiac death. HF complicating MI is common, affecting up to one quarter of post-MI patients, and may be present on admission or develop during hospitalization. In this setting, HF incidence is closely linked with myocardial ischemic time and most interventions have been directed toward improving revascularization timing and rates. Although extensive efforts have been made to identify effective therapies to ameliorate the prognosis of these patients in recent decades, there is still a strong relationship between the degree of post-MI HF and mortality. In view of the increasing prevalence of HF, it is urgent to find accurate screening and predictive methods after MI. Clinical risk factors, such as age, gender, hypertension or diabetes, are valuable but are limited in their predictive ability. In recent years, new biochemical markers, genetic variants, molecular imaging and even remote monitoring have helped the medical community to identify patients at particular risk of developing HF after an MI.[1]

The increase in number and complexity of biological datasets has led to the replacement of traditional biostatistics by the implementation of machine learning algorithms and artificial intelligence approaches applied to biology. This is one application of bioinformatics, a multidisciplinary field that brings together biology, statistics and computational science, in order to provide methods and tools that enable investigators to understand complex biological data. One of the biological tools that provide large sets of data is the microarray. A microarray is a laboratory technique used to detect the expression of thousands of genes at the same time. Not surprisingly, the analysis, interpretation and visualization of such large datasets cannot be performed by traditional statistical tools. With the exponential increase in the generation and accessibility of high-throughput data, there is a constant need to generate new tools and software

DOI of original article: https://doi.org/10.1016/j.repc.2020.12.011
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https://doi.org/10.1016/j.repc.2021.09.005

that enable researchers and data analysts to extract as much as possible from a single dataset. CIBERSORT[2] is an analytical tool which can estimate the abundance of 22 immune cell types using gene expression data. Such a tool, in association with the vast amount of gene expression data available in public repositories such as the Gene Expression Omnibus (GEO, https://www.ncbi.nlm.nih.gov/geo/) and ArrayExpress (https://www.ebi.ac.uk/arrayexpress/), gives a new perspective to old data, providing novel insights and promoting the reuse of datasets. One example of CIBERSORT's usefulness is in determining the presence of infiltrated immune cells in microarrays applied to cancer tissues. For all the above reasons, the search for new markers of development of HF is of great importance, as is the application of bioinformatics tools to previously published data.

In their study published in the current issue of the *Journal*,[3] Zhou and Yu used the CIBERSORT tool to identify predictors of post-MI HF, giving new life to a dataset originally published in 2015.[4] The authors began by assessing the general composition of the 436 samples, of which 46 were from healthy controls, and the correlations between cell types. They then used the predefined groups, composed of control samples (n=46) and patients at various timepoints after an index MI (first day, n=111; 4-6 days, n=101; one month, n=95; and six months, n=83), to assess the dynamics of the proportions of immune cells over time. They report an increase in neutrophils and monocytes after MI that faded over time. Conversely, they found a decrease in some T cell subsets and natural killer cells during the index MI admission, followed by an increase at the subsequent timepoints. After their broad characterization of the evolution of immune cell distribution after MI, the authors focused their attention on a subset of samples derived from 17 patients, nine who developed HF after MI compared with eight without HF after MI, in order to find a immune cell signature that would enable HF development after MI to be predicted. They found that on the first day after MI there was an increase in neutrophils and a decrease in naïve $CD4^+$ T cells in patients who eventually developed HF during follow-up, compared with patients who did not develop HF. Finally, the authors analyzed differentially expressed genes (DEGs) in 111 post-MI patients, comparing patients with low and high neutrophil counts and low and high naïve $CD4^+$ T cell counts, and stratifying samples by median values of neutrophils and naïve $CD4^+$ T cells. They identified two DEGs, interleukin 1 receptor 2 (*IL1R2*) and leucine-rich repeat neuronal protein 3 (*LRRN3*), as molecular candidates.

Increased inflammation plays a central role in the pathophysiology of cardiovascular disease, and MI is no exception, as recent evidence has highlighted.[5] The inflammatory process is complex and involves numerous players, including leukocytes, monocytes, lymphocytes, platelets and cellular mediators such as cytokines, chemokines and adhesion molecules. The neutrophil-to-lymphocyte ratio, an indicator of systemic inflammation, was found to be a predictive parameter for hospitalization of MI patients[6] and several immunomodulatory therapies have been shown in recent years to impact post-MI cardiovascular events.[7,8] Making use of a bioinformatics approach in different datasets, Zhao and colleagues identified and confirmed the *IL-1R2*, *IRAK* and *THBD* genes as prognostic markers of HF after MI.[9] Interleukin (IL)-1R2 is a decoy receptor that competes for IL-1 with IL1R1, inhibiting IL-1 signaling. This receptor has a role in the pathophysiology of autoimmune diseases, and has been proposed as a therapeutic agent.[10] Regarding *LRRN3*, this gene has high expression levels in humans, mainly in the adrenal glands, brain and testes. In the brain, *LRRN3* has been associated with neuroblastoma[11] and autism,[12] but its role in cardiac tissue remains unknown.

The study by Zhou et al.[3] was constructed using a complex dataset that enabled the authors to cover several issues related to HF in post-MI patients. However, the authors could have validated their results by applying different methods of immune cell estimation, such as those included in the R package Immunedeconv.[13] Other factors, such as protein-protein and drug-gene interactions or the druggability of the DEGs, could have been explored in the present study. Despite the limitations noted above, the authors were very careful in choosing the dataset, which enabled them to assess the evolution of the immune cell content in the peripheral blood of MI patients and controls, to find two cell types altered in MI patients who developed HF, and to identify two molecular candidates.

Lastly, it is important to note the reuse of previously published data, which is only possible due to growing acceptance of the importance of the FAIR (findable, accessible, interoperable and reusable) guiding principles and Open Science guidelines.

Funding

This work was funded by National Funds via FCT (Foundation for Science and Technology) through Strategic Project UIDB/04539/2020 and UIDP/04539/2020 (CIBB), and through Research Project POCI-01-0145-FEDER-032414.

Conflicts of interest

The authors have no conflicts of interest to declare.

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