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Commentary

Blood speaks: Personalised medicine profiling for heart failure patients

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Heterogeneity in patient populations caused by factors such as age, genetic background, and clinical condition confound prognostication efforts toward treatment efficacy of coronary artery bypass grafting (CABG) surgery. The conundrum of patient heterogeneity has been approached by advances in personalised medicine to develop tailored therapies. Recent biomedical studies search for patient-specific biomarker signatures to effectively predict postoperative results. In this article of *EBioMedicine,* Wolfien et al. propose a diagnostic strategy to predict the response of CABG surgery patients in terms of myocardial repair induced by bone marrow stem cells (BMSC) [1]. Predictive analyses in such a scenario would provide much needed information to identify those individuals most likely to benefit from BMSC treatment with patient-specific diagnostic characteristics.

Over the past decade a substantial amount of effort has been expended upon BMSCs transplantation with concomitant CABG surgery with the goal of leveraging synergistic paracrine, angiogenic and, anti-inflammatory effect of the cells to promote recovery. Collective results demonstrate autologous CD133^{+} BMSC transplantation combined with CABG surgery is a safe cellular intervention strategy, albeit with highly debated efficacy. Despite outcome variability, recent randomised multicenter trials with large patient populations such as phase II IMPACT-CABG [2], phase III PERFECT [3] and phase II/III COMPARE CPM-RMI [4] reported significant improvement in left ventricle ejection fraction (LVEF) in CD133^{+}BMSC recipients compared to the placebo group (CABG only). Meta-analyses accumulating large patient cohorts in randomised controlled trials (RCTs) confirmed an overall improvement in LVEF in response to BMSC treatment [5,6]. Confoundingly, clinically relevant improvement of LV function as well as non-responsiveness were both reported in BMSC/CABG recipients and the placebo/CABG group. Regardless of treatment, approximately 40% of patients were not responsive to the therapy [5]. Inconsistent outcomes for individuals treated in each clinical trial stems from the inherent heterogeneity of patient groups due to patient-specific variation in response to BMSC treatment. Preliminary studies suggest circulating cytokines, lipoprotein and BNP as possible biomarkers influencing the

outcome of CABG surgery. Having a comprehensive preoperative signature predictive of postoperative response upon BMSC/CABG therapy would be of tremendous value for improving efficacy of treatment.

Through a combination of machine learning (ML) clustering together with gene expression and co-expression analyses, Wolfien et al. provide a detailed characterization of peripheral blood in 23 patients from the PERFECT clinical trial undergoing CABG surgery in addition to BMSC transplantation or placebo treatment [3]. Findings reveal a particular transcriptome profile signature characteristic of responders (Rs) and non-responders (NRs). Specifically, *SH2B3* was found as a biomarker correlating to CABG/BMSC treatment outcome. SH2B3/LNK is involved in hematopoiesis and inflammation partially through regulating c-Kit/SCF signaling pathway and plays a role in heart disease as well as post-MI cardiac repair in both human and rodents [7,8]. Relevance of SH2B3/LNK adaptor protein to cardiac repair upon myocardial infarction (MI) was additionally evaluated in *Sh2b3* deficient mouse models. Thus, findings presented by Wolfien et al. highlight SH2B3/LNK as a potential therapeutic target in myocardial repair to be confirmed with further future investigation in human patients.

ML clustering analysis is emerging as a predictive measure in cancer and heart disease research. The novel aspect of the approach presented by Gustav Steinhoff's group is incorporation of ML as a preemptive assessment of patient outcome upon BMSC/CABG surgery. The independent ML-based biomarker/feature selection analysis demonstrated *PLCG1, LPCAT2, AP1B1, AFAP1, GRB2, KLF8, MARK3* and serum proteins Erythropoietin and VEGF as the top discriminating factors of Rs vs. NRs. Overall, these findings were consistent with angiogenesis-related biomarker signature in Rs vs. NRs peripheral blood [3]. This collective of markers provides a roadmap for candidate genes to follow in independent patient cohorts to predict patient outcome. However, these bioinformatic findings also raise multiple new questions requiring additional experimental assessment including: 1) what are the exact roles of these markers in developing biological characteristics of hematopoietic stem cells (HSCs); 2) is there a potential molecular and functional interplay between them and SH2B3/LNK; 3) how does this presumably complex gene circuit correlate with patient response to the treatment?

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The integrative ML-based top feature selection algorithm reported by Wolfien et al. resulted in 96% prediction/classification accuracy that was improved compared to 80% in a previous report [3]. The relatively limited population (n = 23) prompted further validation in 14 additional patients which diminished predictive accuracy to 85%. The decline in prediction accuracy highlights limitations due to small numbers of patients, emphasizing the necessity for larger patient cohorts in future research. Findings are limited to a small focus population of patients facing CABG surgery, leaving unanswered the clinical significance when broadened to a much larger population of heart disease patients not in need for a revascularization surgery.

Overall, the correlative study by Wolfien et al. proposes a potential preoperative signature to prognosticate postoperative response in patients undergoing BMSC/CABG surgery. The correlation between the characteristics of HSCs and recovery of patients from BMSC/CABG therapy has valuable application for clinical use to identify patients with predicted non-responsive signature (NRs) and eliminate them from the BMSC/CABG procedure to avoid unnecessary patient suffering. The differential gene expression analysis performed in the present study led to the identification of a R/NR signature including 161 genes. The broad size of the gene signature limits applicability of transcriptome profiling in the clinical setting as a routine diagnostic screen. However, these findings provide a solid basis for future investigation to develop and adopt a simplified panel of genes to predict treatment outcome and to facilitate identifying responders and non-responders in clinical settings. The strategic approach of combining transcriptome profiling with precise patient phenotyping by protein expression analysis in conjunction with ML-based feature selection provides potentially valuable insight toward advancing personalized medicine in conjunction with cell-based therapy. Future directions will need to refine profile characteristics of R vs. NR with an eye toward discriminating factors that accurately foreshadow outcomes of BMSC therapy. Conversely, pre-conditioning or modifying cells prior to therapeutic delivery could be employed to enhance efficacy and potentiate outcomes for both R and NR alike [9,10].

Authors' contribution

F. Firouzi and M.A. Sussman wrote the commentary.

Declaration of Competing Interest

F. Firouzi has nothing to disclose. M.A. Sussman has nothing to disclose.

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