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Response of circulating miRNAs to acute exercise: A systematic Review and Meta-Analysis

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Introduction: Extra-cellular or cell-free microRNAs (cf-miRNAs) are circulating miRNA molecules found in most biological fluids including blood, urine and saliva[1]. While our understanding of their specific role and relevance in circulation is limited, specific cf-miRNAs display high levels of regulation in numerous pathological[2] and physiological conditions, including exercise[3]. Over the last decade, the field of exercise physiology has taken a specific interest at investigating the cf-miRNA response to exercise to establish whether plasma and serum cf-miRNAs may constitute valid markers of adaptation to exercise and, more broadly, of human health. Cf-miRNA research is increasingly common but is poorly reproducible. The aim of the systematic review was to examine the current literature regarding the cf-miRNA response to an acute bout of exercise and to interpret it in the light of the known limitations of the field.
Methods: This systematic review was conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020). Eight cf-miRs were included in the meta-analysis. We focused on three specific timepoints post an acute bout of exercise (immediately post, 1-2 hr post and 24 hr post). A correlated and hierarchical effects mixed effects meta-analysis was performed[4] and was followed by cluster-robust estimate using the "sandwich" estimator to account for any misspecification of the model[5]. The fixed effects were the fold-change compared to baseline at each time point and the influence of exercise modality (endurance or resistance) on cf-miRNA levels. The random effects were of a nested model structure, where observations within the same cohort were dependent and observations from different cohorts were independent. Finally, we ran an exploratory machine-learning-based approach to try and capture relevant moderators that could be influencing effect size.
Results: Cf-miR-1 and cf-miR-133b levels increased 1-2 hr and 24 hr post exercise, and cf-miR-133a levels increased immediately, 1-2 hr and 24 hr post exercise. Cf-miR -146, -206, -21, -126, -206, -208, -210, -221 and -222 did not change with an acute bout of exercise. Interestingly, differential responses between an acute endurance and resistance bout were observed for -1, -133a and -221. Exploratory moderator analysis determined that exercise modality and sampling timepoint were significant variables moderating the levels of cf-miR-1, cf-miR-133a, cf-miR-133b and cf-miR-206 in response to exercise. Interestingly, cf-miR-206 did not display differences in response to exercise in the meta-analysis however, after accounting for methodological methods in the exploratory moderator analysis, this indicated that cf-miR-206 did indeed change in response to an exercise bout. Whether assessment of haemolysis and or a spike-in control were used to normalise differences in miRNA input during RNA extraction were also ranked as influential moderators of cf-miR -1 and -133a.
Discussion: Collectively, results from the meta-analysis reveal temporal and modality specific cf-miR responses to an acute exercise bout. Further, we found that differences in the use of quality controls checks can increase between-study variation. We recommend these methodological checks should become the 'norm' in c-miRNA studies as they will increase reproducibility and contribute to untangle the role and regulation of cf-miRNA response following exercise.

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