中文摘要

川崎病 (KD) 和兒童多系統發炎綜合症 (MIS-C) 是高度相似的兒科綜合徵，其特徵為血管病變、心臟和全身免疫病理學。值得注意的是，包括心肌炎和冠狀動脈瘤（CAA）在內的心臟病使患者因心肌梗塞而死亡的風險增加。鑑於 KD 和 MIS-C 的分子機制重疊，可以透過控制這兩種疾病的關鍵調節因子來靶向它們。然而，關鍵的致病驅動因素在很大程度上尚不清楚。我們整合了不同階段的 KD 和 MIS-C 以及其他兒科疾病的 PBMC 單細胞轉錄組的多隊列真實臨床數據。我們研究了 KD 和 MIS-C 心血管疾病發展的分子機制，並透過進一步獨立的轉錄組數據隊列驗證了關鍵發現。透過一系列生物資訊學和化學資訊學方法，我們確定了新的病理驅動因素，並提出了針對 KD 和 MIS-C 的小分子藥物。我們的研究結果揭示了 KD 和 MIS-C 中 $CD177^+$ 中性粒細胞的擴張和過度激活，這可能介導脈管系統歸巢機制（透過 CD31 和 PDPN）。有趣的是，$CD177^+$中性粒細胞明顯激活了心血管疾病相關的免疫特徵，過度激活了其效應子通路，並發揮了在介導全身性發炎和不受限制的分子損傷中具有核心功能的分子。疾病基因網路圖譜揭示了 $CD177^+$ 嗜中性球與冠狀動脈和心肌疾病的關聯。從轉錄角度來看，這些異常的中性粒細胞活動可能是由 KD 和 MIS-C 中共享中性粒細胞表達程序 (SNEP) 的 SPI1 依賴性調節網絡驅動的，該網絡與臨床嚴重程度、治療和恢復相關。透過高維加權基因共表達網絡分析，我們確定了 S100A12 和 TSPO 是 KD 和 MIS-C 免疫病理學中 $CD177^+$ 中性粒細胞過度激活的主要靶標，並確定了 FDA 批准的藥物，這些藥物可以開發為單一治療策略來減弱兩者疾病。我們的研究結果表明，$CD177^+$中性粒細胞透過參與分子損傷的效應路徑的過度活化及其異常的脈管系統歸巢效應，在 KD 和 MIS-C 血管、心臟和全身免疫病理學中發揮關鍵作用。作為 KD 和 MIS-C 免疫發病機制的關鍵分子驅動因素，S100A12 或 TSPO 標靶可能被開發成新的治療策略。

關鍵字：川崎病，兒童多系統發炎綜合徵，嗜中性球，冠狀動脈瘤，心肌炎，CD177，scRNA-seq

ABSTRACT

Kawasaki disease (KD) and multisystem inflammatory syndrome in children (MIS-C) are highly similar pediatric syndromes characterized by vasculopathic, cardiac, and systemic immunopathologies. Notably, the cardiac pathologies, including myocarditis and coronary artery aneurysm (CAA), predispose patients to increased risk of mortality through myocardial infarction. Given the overlapping molecular mechanisms of KD and MIS-C, they can be targeted via a key regulator controlling both diseases. However, the key pathogenic drivers are largely undefined. We integrated multi-cohort real-world clinical data of PBMC single-cell transcriptomes of KD and MIS-C at various stages, as well as other pediatric diseases. We investigated the molecular mechanisms underlying KD and MIS-C cardiovascular disease development and validated the key findings through further independent cohorts of transcriptomics data. Through a series of bioinformatics and cheminformatics approaches, we identified novel pathological drivers and proposed small molecule drugs against KD and MIS-C. Our findings reveal the expansion and hyperactivation of $CD177^+$ neutrophils in KD and MIS-C which may mediate a vasculature homing mechanism (through CD31 and PDPN). Intriguingly, $CD177^+$ neutrophils distinctly activated cardiovascular disease-associated immune signatures, overactivated its effector repertoire pathways, and exerted molecules with central functions in mediating systemic inflammation and unrestricted molecular damages. Disease-gene network mapping revealed the connection of $CD177^+$ neutrophils with coronary and myocardial disorders. Transcriptionally, these aberrant neutrophilic activities could be driven by a SPI1-dependent regulatory network of shared neutrophil expression program (SNEP) in KD and MIS-C, that is associated with clinical severity, treatment, and recovery. Through high-dimensional weighted gene co-expression network analysis, we identified S100A12 and TSPO as primary targets involved in $CD177^+$ neutrophil hyperactivation in KD and MIS-C immunopathologies and identified FDA-approved drugs that can be developed as a single therapeutic strategy to attenuate both diseases. Our findings suggest the pivotal role of $CD177^+$ neutrophils in KD and MIS-C vascular, cardiac, and systemic immunopathologies via the hyperactivation of effector pathways involved in molecular damage and its aberrant vasculature homing effect. As key molecular drivers central to KD and MIS-C immunopathogenesis, S100A12 or TSPO targeting may be developed into novel therapeutic strategies.

Keywords: Kawasaki disease, multisystem inflammatory syndrome in children, neutrophil, coronary artery aneurysm, myocarditis, CD177, scRNA-seq