Advances in Clinical Medicine 临床医学进展, 2023, 13(11), 17420-17427
Published Online November 2023 in Hans. https://www.hanspub.org/journal/acm
https://doi.org/10.12677/acm.2023.13112440

Hans汉斯

MIF在慢性肾脏病患者中发生心血管事件的相关性

李思莹，刘　珍

新疆医科大学第一附属医院肾脏病中心，新疆　乌鲁木齐

收稿日期：2023年10月8日；录用日期：2023年11月3日；发布日期：2023年11月8日

摘　要

慢性肾脏病(CKD)现在被认为是心血管疾病(CVD)的独立危险因素。而慢性肾脏病发生心血管事件的机制主要包括：肾素－血管紧张素－醛固酮系统异常激活(RAAS)、氧化应激、炎症反应、组织纤维化、贫血、自主神经系统功能紊乱、尿毒症毒素、代谢紊乱等。对于慢性肾脏病患者并发心血管事件，巨噬细胞迁移抑制因子(MIF)在其中扮演什么角色仍然没有统一的结论。MIF仍是目前研究的热点炎症因子。

关键词

慢性肾脏病，心血管疾病，综述，MIF

The Correlation between MIF and Cardiovascular Events in Patients with Chronic Kidney Disease

Siying Li, Zhen Liu

Kidney Disease Center of The First Affiliated Hospital of Xinjiang Medical University, Urumqi Xinjiang

Received: Oct. 8th, 2023; accepted: Nov. 3rd, 2023; published: Nov. 8th, 2023

Abstract

Chronic kidney disease (CKD) is now considered an independent risk factor for cardiovascular disease (CVD). The mechanisms of cardiovascular events in chronic kidney disease mainly include: abnormal activation of the renin angiotensin aldosterone system (RAAS), oxidative stress, inflammatory response, tissue fibrosis, anemia, dysfunction of the autonomic nervous system, uremic

文章引用: 李思莹, 刘珍. MIF 在慢性肾脏病患者中发生心血管事件的相关性[J]. 临床医学进展, 2023, 13(11): 17420-17427. DOI: 10.12677/acm.2023.13112440

toxins, metabolic disorders, etc. There is still no unified conclusion on the role of macrophage migration inhibitory factor (MIF) in cardiovascular events in patients with chronic kidney disease. MIF is still a hot research topic for inflammatory factors.

Keywords

Chronic Kidney Disease, Cardiovascular Disease, Overview, MIF

1. 引言

近 10 年来，全球范围内，慢性肾脏病(CKD)的患病率呈持续增长的趋势。根据卫生计量与评估研究所的数据，2016 年，在 15 至 49 岁的男性中，由 CKD 造成的全球负担占全球死亡人数的 1.94%，而这一数字在低收入国家要高得多[1]。而 CKD 作为心血管疾病的独立危险因素，同时心血管事件是 CKD 患者过早死亡的主要原因，甚至在其进展为终末期肾病之前，CVD 进展率是人群的两倍[2]。作为炎症作用的热门因子巨噬细胞迁移抑制因子(MIF)，目前针对其在 CKD 患者中并发心血管事件展开了多项研究，其中包括 Magdy Algowhary 等人通过对 90 名心衰患者，及 60 名相匹配的对照组，采用 PCR-RFLP 方法证明了 MIF 可能导致心衰的可能性[3]；陈怡仁等人通过 Na 和 Ca 增加肺静脉心律失常，通过 CaMKII 信号传导的 ROS 激活实现失调，从而使 MIF 在其中推动炎症期间房颤的可能发生[4]；而慢性肾脏病就是以慢性炎症、氧化应激为特征的疾病，而通过实验证明 CKD 患者的循环血清 MIF 显著升高[5]，故为慢性肾脏病患者发生房颤提供证据；杨一宁等人通过招募 1176 名冠状动脉疾病患者和 1120 名对照，发现 MIF 基因中 rs755622 的 CC 基因型是冠状动脉疾病的易感因素[6]；刘彦等人通过将慢性肾衰竭患者分为 CKD 组、腹膜透析组及血液透析组，分别测量血清 MIF 及左心室质量指数(LVMI)，得出了慢性肾衰竭患者血清 MIF 明显高于健康对照组，而相应的左心室肥厚的患者的水平也显著升高[7]等等，揭示了 MIF 在 CKD 患者中发生心力衰竭、房颤、冠状动脉性心脏病及左心室肥厚的联系。因此，我将对 MIF 在 CKD 并发相关心血管事件的主要发病机制，包括氧化应激、炎症反应、组织纤维化做一综述。

【介绍】

MIF 在多种细胞类型中表达，如淋巴细胞、单核细胞/巨噬细胞、树突状细胞、中性粒细胞、成纤维细胞、心肌细胞、神经元、生殖组织、脂肪细胞和激素分泌细胞[8]-[17]。MIF 与不同的自身免疫和炎症疾病有关，包括败血症、类风湿性关节炎、肾小球肾炎、多发性硬化、动脉粥样硬化、经典皮肤迟发型超敏反应和急性呼吸窘迫综合征以及癌症[15] [18] [19] [20] [21] [22]。

2. CKD 合并心血管事件的相关性

CKD 是指各种原因引起的肾脏结构或功能异常 ≥ 3 个月，包括出现肾脏损伤标志(白蛋白、尿沉渣异常、肾小管相关病变、组织学检查异常及影像学检查异常)或肾移植病史，伴或不伴肾小球滤过率(GFR)下降；或不明原因的 GFR 下降(<60 ml/min) ≥ 3 个月。国际公认的慢性肾脏病分期按 GFR 将慢性肾脏病的分期及建议将慢性肾脏病分为 1~5 期。1 期：GFR ≥ 90 (ml/min·1.73 m^2)；2 期：GFR 范围在 60~89 (ml/min·1.73 m^2)；3a 期：GFR 范围在 45~59 (ml/min·1.73 m^2)；3b 期：GFR 范围在：30~44 (ml/min·1.73 m^2)；

4 期：GFR 范围在 15~29 (ml/min·1.73 m^2)；5 期：GFR < 15 (ml/min·1.73 m^2)或透析。根据美国卫生计量与评估研究所的数据显示：2016 年，在 15 至 49 岁的男性中，由 CKD 造成的全球负担占全球死亡人数的 1.94%，而这一数值在低收入国家要高得多[1]。2012 年张露霞等研究发现 CKD 在我国成年人中的患病率为 10.8% [23]。而 CKD 合并心血管疾风险增加之间存在密切的关系，CKD 作为心血管疾病的独立危险因素，同时心血管事件是 CKD 患者过早死亡的主要原因，甚至在其进展为终末期肾病之前，CVD 进展率是人群的两倍[2]。大型队列研究表明，在校正了抑制的 CVD 危险因素、CVD 事件史和蛋白尿后，CVD (急性冠状动脉综合征[ACS]、中风、心力衰竭和心源性猝死)和 CKD 之间存在强烈而独立的关联。在 eGFR 为 45~59 ml/min/1.73 m^2 的患者中，风险增加了 43%，而在 eGFR < 5 ml/min/173 m^2 的人群中，风险则增加了 343% [24]。尽管 GFR 类别 G5 (GFR 15 ml/min/1.73 m^2)的人发生 CVD 事件的风险最高，但由于这些类别的患病率更高，GFR 类别 G3a-G3b (GFR 30~59 ml/min/173 m^2)人群中会发生更多事件[25]。这些事件发生在 CKD 患者的较年轻年龄，表明 CKD 加速了 CVD [26]。CKD 与心血管疾病有很多共同的危险因素，包括年龄、高血压、电解质紊乱、代谢综合征、分子信号通路等等[27] [28]。同时，两者的发病机制也存在着相同点，例如：氧化应激、炎症反应、自主神经功能紊乱、组织纤维化、代谢综合征、血流动力学紊乱等。而 MIF 在上述发病机制中发挥着重要的作用。

3. MIF 在 CKD 合并 CVD 中氧化应激的作用

氧化应激在 CKD 及 CVD 中均扮演着重要的角色；有关 MIF 的实验中证明了，MIF 在急性心肌缺血的体内和体外，氧化应激刺激心肌细胞分泌 MIF [29] [30] [31]；氧化应激的增加与 CKD 的进展阶段呈正相关[29] [32] [33]；研究证明，在 CKD 患者中血管紧张素 II 可以通过 GRK2 调控产生 MIF [34]。MIF 可通过 CD74/CD44 MIF 受体复合物激活 AMP 激活蛋白激酶(MAPK)信号通路[35]，进而调节 PI3K/Akt/Src 信号级联转导[36] [37] [38]，而 PI3K/Akt 信号通路可以刺激一氧化氮(NO)的产生，进一步在心肌细胞中发挥着作用氧化应激反应。氧化应激的增加是动脉粥样硬化的关键特征之一，这导致内皮损伤/功能障碍、NO 和 NF-κB 相关信号转导紊乱以及低密度脂蛋白(LDL)的氧化修饰[39]。脂质代谢紊乱是慢性肾脏病中常见的合并症，1997 年 Miyazaki 等人首次将 MIF 的局部合成与脂质诱导损伤的发病机制联系起来研究[40]，这项研究表明了：高胆固醇血症导致肾小球内细胞 MIF 表达上调，这可能是脂质诱导肾损伤发展过程中的单核巨细胞募集和聚集的重要机制；同时，MIF 可能在促进巨噬细胞聚集和随后脂质沉积部位动脉粥样硬化病变的发展中发挥着关键作用[40]。例如：Christin Krammer 等人通过比较 30 周、42 周及 48 周小鼠的 MIF 基因检测，发现 MIF 缺陷小鼠在 30/24 周龄和 42/36 周龄组中表现出动脉粥样硬化病变减少；同时也发现了 MIF 缺乏可促进年轻但未成年小鼠的病变巨噬细胞和 T 细胞计数，确定了 MIF 和衰老依赖性变化，主要与脂质合成和代谢，脂质储存和棕色脂肪细胞分化及免疫力和动脉粥样硬化相关的富集基因有关[41]。有实验通过 MIF 以一种衍生物 MIF (cycl10)，在体外和体内/体外抑制例关键的炎症和致动脉粥样硬化 MIF 的活性，间接表明了 MIF 在动脉粥样硬化功能中起着关键作用[42]；李文强等人通过颈动脉斑块患者 MIF-173G/C 位点基因，得出 MIF 基因-173G/C 位点多态性与颈动脉硬化密切相关，携带 C 基因是颈动脉粥样硬化斑块形成的危险因素，也证明可了 MIF 在动脉粥样硬化中发挥着重要的作用。而脂质的过氧化作用导致的动脉粥样硬化在心血管疾病中发挥着重要的作用。

4. MIF 在 CKD 合并 CVD 中炎症反应作用

炎症反应在 CKD 患者 CVD 事件的发生中起着至关重要的作用。微炎症是只慢性、持续性、低度存在的炎症，而非病原微生物感染的结果[43]。在肾脏中，血管紧张素 II (AngII)现在被认为是一种调节肾细胞反应的细胞因子，并参与肾脏疾病的几个过程，包括细胞损伤及炎症[44]。而 MIF 由一些肾小球上

皮细胞和大约一半的皮质小管表达[45] [46]，而表达的 MIF 与肾功能障碍、组织学损伤和白细胞浸润显著相关[47]。Brown 等人得出结论“受损肾脏内 MIF 产生的增加可以通过尿液 MIF 浓度的增加来反应”[48]。CD74 在多种组织损伤疾病中表达增加，如心脏缺血－再灌注损伤，阿尔兹海默症、动脉粥样硬化斑块、毒素诱导的肝纤维化和广泛的恶性细胞[49]-[57]，CD74 可作为 AngII 与 MIF 的连接蛋白，在许多细胞类型中独立于 MHC II 类表达[58]，即血管紧张素 II I 型受体，同时也是巨噬细胞迁移抑制因子(MIF)的高亲和力受体[59]。AngII 可以激活核因子 κB (NF-κB)，进而刺激 MIF 的产生[60] [61]，而 CD74 与 CD44 的结合形成复合物后与 MIF 结合，可以导致多条细胞内信号通路，如细胞外信号调节酶(ERK) 1 和 2 的激活、PI3K-Akt 信号转导级联、NFjB 和 AMP 激活蛋白激酶(AMPK)的激活[59]从而促进炎症反应。而炎症是导致心血管病理过程的一个主要危险因素，MIF 通过调控的 NF-κB 调节基因包括多种炎性细胞因子，如白介素-1 (IL-1)、IL-6、TNF-α 及干扰素-γ (IFN-γ) [39]参与心血管事件的发生和发展，并且 IL-1 和 TNF-α 激活 NF-κB 从而形成反馈回路。锌是人体健康的必需营养素，具有抗氧化应激和抗炎作用[62]，膳食锌缺乏或细胞内锌缺乏已表明会导致培养细胞、动物模型和人类中 NF-κB 和 NF-κ 调节性炎性细胞因子的表达的激活[63] [64]，补充锌可能通过抑制 IκB 的磷酸化和降解来抑制 NF-κB 活化和 NF-κ。一些研究表明 CKD 患者锌平衡为负[65] [66]。这可能是由于肠道吸收减少、食物摄入量减少、尿毒症性、生物利用度和/或缺失增加，如通过面部、尿液或血液透析等[67]。缺锌还与 CVD 事件相关的各种危险因素相关，如高血压、血脂异常、2 型糖尿病、炎症和氧化应激[67]。锌已被证明可以阻断缺氧刺激的 HIF-1α 核异位，随后破坏 HIF-1 异二聚体，并诱导 HIF-1α 蛋白酶体降解[68]。另一方面，锌预处理可以诱导肾细胞中 HIF 基因的表达，包括 HIF-1α *[69]*。

5. MIF 在 CKD 合并 CVD 中纤维化作用

在 CKD 中，足细胞的丢失及其 ECM 替代(称为肾小球硬化)、肾小管细胞损伤和随后的肾小管间质纤维化会导致肾单位丢[70] [71]。这些过程导致实质组织被 ECM 替代，细胞外基质(ECM)是纤维化的病理标志，并伴随着不可逆的损伤[72]。TGF-β 是一种由肾脏中所有的细胞类型产生的强大的纤维化生长因子，其诱导纤维化的机制包括增强成纤维化细胞增殖和肌成纤维细胞转分化、ECM 蛋白合成以及通过诱导蛋白酶抑制剂抑制 MMP 活性来保存基质[73]。TGF-β 通过激活结缔组织生长因子刺激细胞增殖和 ECM 积累[74]，TGF-β 通过 Smad2/3H 和 p38 丝裂原激活蛋白(MAP)激酶信号传导诱导 EMT。除了成纤维作用外，TGF-β 还导致肾小管上皮细胞凋亡和炎性细胞聚集。巨噬细胞的数量与衰老的主要标志[75] [76] [77] [78]。MIF 可能通过 TGF-β1/Smads 信号通路抑制纤维化。成纤维细胞生长因子 23 (FGF23)的重要水平在慢性肾脏病(CKD)中升高，并与左心室肥厚、心力衰竭和死亡密切相关[79]。CKD 中 FGF23 的慢性升高与心力衰竭和死亡的发展独立相关[80]-[85]。

6. 结论

MIF 可以通过多种途径参与 CKD 基础上并发心血管事件，其中促进的机制比较复杂，且机制之间相互影响，共同促进。对 MIF 在 CKD 合并 CKD 患者的病理生理机制有助于进一步筛选早期 CKD 患者并发心血管事件的发生及发展。通过对 MIF 在其病理生理机制的研究，为 CKD 合并血管患者提供治疗方案的可能性。

参考文献

[1] Obrador, G.T., Levin, A., *et al*. (2019) CKD Hotspots: Challenges and Areas of Opportunity. *Seminars in Nephrology*, **39**, 308-314. https://doi.org/10.1016/j.semnephrol.2019.02.009

[2] Formentini, I., Bobadilla, M., Haefliger, C., *et al*. (2012) Current Drug Development Challenges in Chronic Kidney

Disease (CKD)—Identification of Individualized Determinants of Renal Progression and Premature Cardiovascular Disease (CVD). *Nephrology Dialysis Transplantation*, **27**, iii81-iii88. https://doi.org/10.1093/ndt/gfs270

[3] El-Mahdy, R.I., *et al*. (2021) Functional Variants in the Promoter Region of Macrophage Migration Inhibitory Factor rs755622 Gene (MIF G173C) among Patients with Heart Failure: Association with Echocardiographic Indices and Disease Severity. *Heart & Lung*: *The Journal of Critical Care*, **50**, 92-100. https://doi.org/10.1016/j.hrtlng.2020.07.015

[4] Chin, C.G., Chen, Y.C., Lin, Y.K., *et al*. (2022) Effect of Macrophage Migration Inhibitory Factor on Pulmonary Vein Arrhythmogenesis through Late Sodium Current. *Europace*, **25**, 698-706. https://doi.org/10.1093/europace/euac152

[5] Bruchfeld, A., Carrero, J.J., Qureshi, A.R., *et al*. (2009) Elevated Serum Macrophage Migration Inhibitory Factor (MIF) Concentrations in Chronic Kidney Disease (CKD) Are Associated with Markers of Oxidative Stress and Endothelial Activation. *Molecular Medicine*, **15**, 70-75. https://doi.org/10.2119/molmed.2008.00109

[6] Luo, J.Y., Fang, B.B., Du, G.L., *et al*. (2021) Association between MIF Gene Promoter rs755622 and Susceptibility to Coronary Artery Disease and Inflammatory Cytokines in the Chinese Han Population. *Scientific Reports*, **11**, Article No. 8050. https://doi.org/10.1038/s41598-021-87580-6

[7] Liu, Y., Zhang, X., Liu, G., *et al*. (2016) Expressions of Macrophage Migration Inhibitory Factor in Patients with Chronic Kidney Disease. *Nigerian Journal of Clinical Practice*, **19**, 778-783. https://doi.org/10.4103/1119-3077.183239

[8] Bernhagen, J., Calandra, T., Mitchell, R.A., *et al*. (1993) MIF Is a Pituitary-Derived Cytokine That Potentiates Lethal Endotoxaemia. *Nature*, **365**, 756-759. https://doi.org/10.1038/365756a0

[9] Aeberli, D., Yang, Y., Mansell, A., *et al*. (2006) Endogenous Macrophage Migration Inhibitory Factor Modulates Glucocorticoid Sensitivity in Macrophages via Effects on MAP Kinase Phosphatase-1 and p38 MAP Kinase. *FEBS Letters*, **580**, 974-981. https://doi.org/10.1016/j.febslet.2006.01.027

[10] Calandra, T. and Roger, T. (2003) Macrophage Migration Inhibitory Factor: A Regulator of Innate Immunity. *Nature Reviews Immunology*, **3**, 791-800. https://doi.org/10.1038/nri1200

[11] Bacher, M., Meinhardt, A., Lan, H.Y., *et al*. (1998) MIF Expression in the Rat Brain: Implications for Neuronal Function. *Molecular Medicine* (*Cambridge*, *Mass*.), **4**, 217-230. https://doi.org/10.1007/BF03401919

[12] Bernhagen, J., Calandra, T., Cerami, A., *et al*. (1994) Macrophage Migration Inhibitory Factor Is a Neuroendocrine Mediator of Endotoxaemia. *Trends in Microbiology*, **2**, 198-201. https://doi.org/10.1016/0966-842X(94)90111-H

[13] Nishio, Y., Minami, A., Kato, H., *et al*. (1999) Identification of Macrophage Migration Inhibitory Factor (MIF) in Rat Peripheral Nerves: Its Possible Involvement in Nerve Regeneration. *Biochimica et Biophysica Acta* (*BBA*)—*Molecular Basis of Disease*, **1453**, 74-82. https://doi.org/10.1016/S0925-4439(98)00086-6

[14] Wada, S., Fujimoto, S., Mizue, Y., *et al*. (1997) Macrophage Migration Inhibitory Factor in the Human Ovary: Presence in the Follicular Fluids and Production by Granulosa Cells. *IUBMB Life*, **41**, 805-814. https://doi.org/10.1080/15216549700201841

[15] Meyer-Siegler, K.L., Vera, P.L., Iczkowski, K.A., *et al*. (2007) Macrophage Migration Inhibitory Factor (MIF) Gene Polymorphisms Are Associated with Increased Prostate Cancer Incidence. *Genes & Immunity*, **8**, 646-652. https://doi.org/10.1038/sj.gene.6364427

[16] Wistow, G.J., Shaughnessy, M.P., Lee, D.C., *et al*. (1993) A Macrophage Migration Inhibitory Factor Is Expressed in the Differentiating Cells of the Eye Lens. *Proceedings of the National Academy of Sciences*, **90**, 1272-1275. https://doi.org/10.1073/pnas.90.4.1272

[17] Waeber, G., Calandra, T., Roduit, R., *et al*. (1997) Insulin Secretion Is Regulated by the Glucose-Dependent Production of Islet β Cell Macrophage Migration Inhibitory Factor. *Proceedings of the National Academy of Sciences*, **94**, 4782-4787. https://doi.org/10.1073/pnas.94.9.4782

[18] Bernhagen, J., Bacher, M., Calandra, T., *et al*. (1996) An Essential Role for Macrophage Migration Inhibitory Factor in the Tuberculin Delayed-Type Hypersensitivity Reaction. *The Journal of Experimental Medicine*, **183**, 277-282. https://doi.org/10.1084/jem.183.1.277

[19] Schober, A., Bernhagen, J. and Weber, C. (2008) Chemokine-Like Functions of MIF in Atherosclerosis. *Journal of Molecular Medicine*, **86**, 761-770. https://doi.org/10.1007/s00109-008-0334-2

[20] Denkinger, C., Metz, C., Fingerle-Rowson, G., *et al*. (2004) Macrophage Migration Inhibitory Factor and Its Role in Autoimmune Diseases. *Archivum Immunologiae et Therapiae Experimentalis*, **52**, 389-400.

[21] Pan, J.H., Lindholt, J.S., Sukhova, G.K., *et al*. (2003) Macrophage Migration Inhibitory Factor Is Associated with Aneurysmal Expansion. *Journal of Vascular Surgery*, **37**, 628-635. https://doi.org/10.1067/mva.2003.74

[22] Donnelly, S.C., Haslett, C., Reid, P.T., *et al*. (1997) Regulatory Role for Macrophage Migration Inhibitory Factor in Acute Respiratory Distress Syndrome. *Nature Medicine*, **3**, 320-323. https://doi.org/10.1038/nm0397-320

[23] Zhang, L., Wang, F., Wang, L., 等. 中国慢性肾脏病的流行病学调查: 横断面研究[J]. 中华肾病研究电子杂志, 2012(2): 127.

[24] Parfrey, P.S., Foley, R.N., Harnett, J.D., *et al*. (1996) Outcome and Risk Factors for Left Ventricular Disorders in Chronic Uraemia. *Nephrology*, *Dialysis*, *Transplantation*, **11**, 1277-1285. https://doi.org/10.1093/ndt/11.7.1277

[25] Hallan, S.I., Dahl, K., Oien, C.M., *et al*. (2006) Screening Strategies for Chronic Kidney Disease in the General Population: Follow-Up of Cross Sectional Health Survey. *BMJ*: *British Medical Journal*, **333**, Article No. 1047. https://doi.org/10.1136/bmj.39001.657755.BE

[26] Kelsey, R. (2012) Chronic Kidney Disease: A Risk Factor for Stroke and Bleeding in Patients with Atrial Fibrillation. *Nature Reviews Nephrology*, **8**, 551-551. https://doi.org/10.1038/nrneph.2012.168

[27] 陈牧, 李毅刚. 生物标志物与心房颤动卒中风险分层[J]. 中国心脏起搏与心电生理杂志, 2014, 28(2): 161-163.

[28] Xu, G.S., Luo, K.P., Liu, H.X., *et al*. (2015) The Progress of Inflammation and Oxidative Stress in Patients with Chronic Kidney Disease. *Renal Failure*, **37**, 45-49.

[29] Yu, C.M., *et al*. (2001) Elevation of Plasma Level of Macrophage Migration Inhibitory Factor in Patients with Acute Myocardial Infarction. *The American Journal of Cardiology*, **88**, 774-777. https://doi.org/10.1016/S0002-9149(01)01850-1

[30] Yu, C.M., Lai, K.W.H., Chen, Y.X., *et al*. (2003) Expression of Macrophage Migration Inhibitory Factor in Acute Ischemic Myocardial Injury. *Journal of Histochemistry & Cytochemistry*, **51**, 625-631. https://doi.org/10.1177/002215540305100508

[31] Takahashi, M. (2001) Macrophage Migration Inhibitory Factor as a Redox-Sensitive Cytokine in Cardiac Myocytes. *Cardiovascular Research*, **52**, 438-445. https://doi.org/10.1016/S0008-6363(01)00408-4

[32] Lopez, A.D., Mathers, C.D., Ezzati, M., *et al*. (2006) Global and Regional Burden of Disease and Risk Factors, 2001: Systematic Analysis of Population Health Data. *The Lancet* (*London*, *England*), **367**, 1747-1757. https://doi.org/10.1016/S0140-6736(06)68770-9

[33] Petrovsky, N., Socha, L., Silva, D., *et al*. (2003) Macrophage Migration Inhibitory Factor Exhibits a Pronounced Circadian Rhythm Relevant to Its Role as a Glucocorticoid Counter-Regulator. *Immunology and Cell Biology*, **81**, 137-143. https://doi.org/10.1046/j.0818-9641.2002.01148.x

[34] 郑猛, 单志新, 林秋雄, 等. GRK2 调控血管紧张素 II 诱导产生 MIF[C]//第七届海峡两岸心血管科学研讨会论文集. 中国病理生理学会, 中国药理学会, 中国生理学会, 台湾急诊医学会, 香港大学心脏血管研究所, 中华医学会心血管专业委员会. 2009: 57.

[35] Tilstam, P.V., Qi, D., Leng, L., *et al*. (2017) MIF Family Cytokines in Cardiovascular Diseases and Prospects for Precision-Based Therapeutics. *Expert Opinion on Therapeutic Targets*, **21**, 671-683. https://doi.org/10.1080/14728222.2017.1336227

[36] Shi, X., Leng, L., Wang, T., *et al*. (2006) CD44 Is the Signaling Component of the Macrophage Migration Inhibitory Factor-CD74 Receptor Complex. *Immunity*, **25**, 595-606. https://doi.org/10.1016/j.immuni.2006.08.020

[37] Lue, H., Thiele, M., Franz, J., *et al*. (2007) Macrophage Migration Inhibitory Factor (MIF) Promotes Cell Survival by Activation of the Akt Pathway and Role for CSN5/JAB1 in the Control of Autocrine MIF Activity. *Oncogene*, **26**, 5046-5059. https://doi.org/10.1038/sj.onc.1210318

[38] Leng, L., Metz, C.N., Fang, Y., *et al*. (2003) MIF Signal Transduction Initiated by Binding to CD74. *Journal of Experimental Medicine*, **197**, 1467-1476. https://doi.org/10.1084/jem.20030286

[39] Choi, S., Liu, X., Pan, Z., *et al*. (2018) Zinc Deficiency and Cellular Oxidative Stress: Prognostic Implications in Cardiovascular Diseases. *Acta Pharmacologica Sinica*, **39**, 1120-1132. https://doi.org/10.1038/aps.2018.25

[40] Miyazaki, K., Isbel, N.M., Lan, H.Y., *et al*. (1997) Up-Regulation of Macrophage Colony-Stimulating Factor (M-CSF) and Migration Inhibitory Factor (MIF) Expression and Monocyte Recruitment during Lipid-Induced Glomerular Injury in the Exogenous Hypercholesterolaemic (ExHC) Rat. *Clinical and Experimental Immunology*, **108**, 318-323. https://doi.org/10.1046/j.1365-2249.1997.3671260.x

[41] Christine, K., Bishan, Y., Sabrina, R., *et al*. (2023) Pathways Linking Aging and Atheroprotection in Mif-Deficient Atherosclerotic Mice. *FASEB Journal*: *Official Publication of the Federation of American Societies for Experimental Biology*, **37**, e22752. https://doi.org/10.1096/fj.202200056R

[42] Krammer, C., Kontos, C., Dewor, M., *et al*. (2021) A MIF-Derived Cyclopeptide that Inhibits MIF Binding and Atherogenic Signaling via the Chemokine Receptor CXCR2. *Chembiochem*, **22**, 1012-1019. https://doi.org/10.1002/cbic.202000574

[43] Liu, X.Q., Jiang, T.T., Wang, M.Y., *et al*. (2022) Using Machine Learning to Evaluate the Role of Microinflammation in Cardiovascular Events in Patients with Chronic Kidney Disease. *Frontiers in Immunology*, **12**, Article ID: 796383. https://doi.org/10.3389/fimmu.2021.796383

[44] Ruiz-Ortega, M., Rupérez, M., Esteban, V., *et al*. (2006) Angiotensin II: A Key Factor in the Inflammatory and Fibrotic Response in Kidney Diseases. *Nephrology Dialysis Transplantation*, **21**, 16-20. https://doi.org/10.1093/ndt/gfi265

[45] Lan, H.Y., Mu, W., Yang, N., *et al*. (1996) De Novo Renal Expression of Macrophage Migration Inhibitory Factor during the Development of Rat Crescentic Glomerulonephritis. *The American Journal of Pathology*, **149**, 1119-1127.

[46] Lan, H.Y., Yang, N., Brown, F.G., *et al*. (1998) Macrophage Migration Inhibitory Factor Expression in Human Renal Allograft Rejection. *Transplantation*, **66**, 1465-1471. https://doi.org/10.1097/00007890-199812150-00009

[47] Lan, H.Y., Yang, N., Nikolic-Paterson, D.J., *et al*. (2000) Expression of Macrophage Migration Inhibitory Factor in Human Glomerulonephritis. *Kidney International*, **57**, 499-509. https://doi.org/10.1046/j.1523-1755.2000.00869.x

[48] Brown, F.G., Nikolic-Paterson, D.J., Hill, P.A., *et al*. (2002) Urine Macrophage Migration Inhibitory Factor Reflects the Severity of Renal Injury in Human Glomerulonephritis. *Journal of the American Society of Nephrology*, **13**, S7-S13. https://doi.org/10.1681/ASN.V13suppl_1s7

[49] Burton, J.D., Ely, S., Reddy, P.K., *et al*. (2004) CD74 Is Expressed by Multiple Myeloma and Is a Promising Target for Therapy. *Clinical Cancer Research*: *An Official Journal of the American Association for Cancer Research*, **10**, 6606-6611. https://doi.org/10.1158/1078-0432.CCR-04-0182

[50] Otterstrom, C., Soltermann, A., Opitz, I., *et al*. (2014) CD74: A New Prognostic Factor for Patients with Malignant Pleural Mesothelioma. *British Journal of Cancer*, **110**, 2040-2046. https://doi.org/10.1038/bjc.2014.117

[51] Datta, M.W., Shahsafaei, A., Nadler, L.M., *et al*. (2000) Expression of MHC Class II-Associated Invariant Chain (Ii;CD74) in Thymic Epithelial Neoplasms. *Applied Immunohistochemistry & Molecular Morphology*: *AIMM*, **8**, 210-215. https://doi.org/10.1097/00129039-200009000-00007

[52] Beswick, E.J., Das, S., Pinchuk, I.V., *et al*. (2005) *Helicobacter pylori*-Induced IL-8 Production by Gastric Epithelial Cells Up-Regulates CD74 Expression. *Journal of Immunology* (*Baltimore*, *Md*.: 1950), **175**, 171-176. https://doi.org/10.4049/jimmunol.175.1.171

[53] Martín-Ventura, J.L., Madrigal-Matute, J., Muñoz-Garcia, B., *et al*. (2009) Increased CD74 Expression in Human Atherosclerotic Plaques: Contribution to Inflammatory Responses in Vascular Cells. *Cardiovascular Research*, **83**, 586-594. https://doi.org/10.1093/cvr/cvp141

[54] Heinrichs, D., Knauel, M., Offermanns, C., *et al*. (2011) Macrophage Migration Inhibitory Factor (MIF) Exerts Antifibrotic Effects in Experimental Liver Fibrosis via CD74. *Proceedings of the National Academy of Sciences of the United States of America*, **108**, 17444-17449. https://doi.org/10.1073/pnas.1107023108

[55] Miller, E.J., Li, J., Leng, L., *et al*. (2008) Macrophage Migration Inhibitory Factor Stimulates AMP-Activated Protein Kinase in the Ischaemic Heart. *Nature*, **451**, 578-582. https://doi.org/10.1038/nature06504

[56] Sanchez-Niño, M.D., Sanz, A.B., Ruiz-Andres, O., *et al*. (2013) MIF, CD74 and Other Partners in Kidney Disease: Tales of a Promiscuous Couple. *Cytokine & Growth Factor Reviews*, **24**, 23-40. https://doi.org/10.1016/j.cytogfr.2012.08.001

[57] Lawrance, I.C., Fiocchi, C. and Chakravarti, S. (2001) Ulcerative Colitis and Crohn's Disease: Distinctive Gene Expression Profiles and Novel Susceptibility Candidate Genes. *Human Molecular Genetics*, **10**, 445-456. https://doi.org/10.1093/hmg/10.5.445

[58] Momburg, F., Koch, N., Möller, P., *et al*. (1986) Differential Expression of Ia and Ia-Associated Invariant Chain in Mouse Tissues after *in Vivo* Treatment with IFN-Gamma. *Journal of Immunology* (*Baltimore*, *Md*.: 1950), **136**, 940-948. https://doi.org/10.4049/jimmunol.136.3.940

[59] Su, H., Na, N., Zhang, X., *et al*. (2017) The Biological Function and Significance of CD74 in Immune Diseases. *Inflammation Research*, **66**, 209-216. https://doi.org/10.1007/s00011-016-0995-1

[60] Esteban, V., Ruperez, M., Sánchez-López, E., *et al*. (2005) Angiotensin IV Activates the Nuclear Transcription Factor-kappaB and Related Proinflammatory Genes in Vascular Smooth Muscle Cells. *Circulation Research*, **96**, 965-973. https://doi.org/10.1161/01.RES.0000166326.91395.74

[61] Kim, J., Montagnani, M., Koh, K.K., *et al*. (2006) Reciprocal Relationships between Insulin Resistance and Endothelial Dysfunction: Molecular and Pathophysiological Mechanisms. *Circulation*, **113**, 1888-1904. https://doi.org/10.1161/CIRCULATIONAHA.105.563213

[62] Prasad, A.S. (2008) Clinical, Immunological, Anti-Inflammatory and Antioxidant Roles of Zinc. *Experimental Gerontology*, **43**, 370-377. https://doi.org/10.1016/j.exger.2007.10.013

[63] Beattie, J.H., Gordon, M.J., Duthie, S.J., *et al*. (2012) Suboptimal Dietary Zinc Intake Promotes Vascular Inflammation and Atherogenesis in a Mouse Model of Atherosclerosis. *Molecular Nutrition & Food Researc*h, **56**, 965-973. https://doi.org/10.1002/mnfr.201100776

[64] Wong, C.P. and Ho, E. (2012) Zinc and Its Role in Age-Related Inflammation and Immune Dysfunction. *Molecular Nutrition & Food Research*, **56**, 77-87. https://doi.org/10.1002/mnfr.201100511

[65] Cardozo, L.F.M.F. and Mafra, D. (2020) Don't Forget the Zinc. *Nephrology Dialysis Transplantation*, **35**, 1094-1098. https://doi.org/10.1093/ndt/gfaa045

[66] Mahajan, S.K., Bowersox, E.M., Rye, D.L., *et al*. (1989) Factors Underlying Abnormal Zinc Metabolism in Uremia. *Kidney International*. *Supplement*, **27**, S269-S273.

[67] Nakatani, S., Mori, K., Shoji, T., *et al*. (2021) Association of Zinc Deficiency with Development of CVD Events in Patients with CKD. *Nutrients*, **13**, Article No. 1680. https://doi.org/10.3390/nu13051680

[68] Nardinocchi, L., Pantisano, V., Puca, R., *et al*. (2010) Zinc Downregulates HIF-1α and Inhibits Its Activity in Tumor Cells *in Vitro* and *in Vivo*. *PLOS ONE*, **5**, e15048. https://doi.org/10.1371/journal.pone.0015048

[69] Rao, K., Sethi, K., Ischia, J., *et al*. (2017) Protective Effect of Zinc Preconditioning against Renal Ischemia Reperfusion Injury Is Dose Dependent. *PLOS ONE*, **12**, e0180028. https://doi.org/10.1371/journal.pone.0180028

[70] Meng, X.M., Nikolic-Paterson, D.J. and Lan, H.Y. (2014) Inflammatory Processes in Renal Fibrosis. *Nature Reviews. Nephrology*, **10**, 493-503. https://doi.org/10.1038/nrneph.2014.114

[71] Hodgkins, K.S. and Schnaper, H.W. (2012) Tubulointerstitial Injury and the Progression of Chronic Kidney Disease. *Pediatric Nephrology* (*Berlin*, *Germany*), **27**, 901-909. https://doi.org/10.1007/s00467-011-1992-9

[72] Ruiz-Ortega, M., Rayego-Mateos, S., Lamas, S., *et al*. (2020) Targeting the Progression of Chronic Kidney Disease. *Nature Reviews Nephrology*, **16**, 269-288. https://doi.org/10.1038/s41581-019-0248-y

[73] Biernacka, A. and Frangogiannis, N.G. (2011) Aging and Cardiac Fibrosis. *Aging and Disease*, **2**, 158-173.

[74] Lawson, J., Elliott, J., Wheeler-Jones, C., *et al*. (2015) Renal Fibrosis in Feline Chronic Kidney Disease: Known Mediators and Mechanisms of Injury. *The Veterinary Journal*, **203**, 18-26. https://doi.org/10.1016/j.tvjl.2014.10.009

[75] Lim, J.H., Kim, E.N., Kim, M.Y., *et al*. (2012) Age-Associated Molecular Changes in the Kidney in Aged Mice. *Oxidative Medicine and Cellular Longevity*, **2012**, Article ID: 171383. https://doi.org/10.1155/2012/171383

[76] Gagliano, N., Arosio, B., Santambrogio, D., *et al*. (2000) Age-Dependent Expression of Fibrosis-Related Genes and Collagen Deposition in Rat Kidney Cortex. *The Journals of Gerontology*. *Series A*, *Biological Sciences and Medical Sciences*, **55**, B365-B372. https://doi.org/10.1093/gerona/55.8.B365

[77] Denic, A., Glassock, R.J. and Rule, A.D. (2016) Structural and Functional Changes with the Aging Kidney. *Advances in Chronic Kidney Disease*, **23**, 19-28. https://doi.org/10.1053/j.ackd.2015.08.004

[78] Maric, C., Sandberg, K. and Hinojosa-Laborde, C. (2004) Glomerulosclerosis and Tubulointerstitial Fibrosis Are Attenuated with 17beta-Estradiol in the Aging Dahl Salt Sensitive Rat. *Journal of the American Society of Nephrology*: *JASN*, **15**, 1546-1556. https://doi.org/10.1097/01.ASN.0000128219.65330.EA

[79] Mehta, R., Cai, X., Lee, J., *et al*. (2016) Association of Fibroblast Growth Factor 23 with Atrial Fibrillation in Chronic Kidney Disease, from the Chronic Renal Insufficiency Cohort Study. *JAMA Cardiology*, **1**, 548-556. https://doi.org/10.1001/jamacardio.2016.1445

[80] Seiler, S., Reichart, B., Roth, D., *et al*. (2011) FGF-23 Associates with Death, Cardiovascular Events, and Initiation of Chronic Dialysis. *Journal of the American Society of Nephrology*: *JASN*, **22**, 1913-1922. https://doi.org/10.1681/ASN.2010121224

[81] Gutiérrez, O.M., Januzzi, J.L., Isakova, T., *et al*. (2009) Fibroblast Growth Factor 23 and Left Ventricular Hypertrophy in Chronic Kidney Disease. *Circulation*, **119**, 2545-2552. https://doi.org/10.1161/CIRCULATIONAHA.108.844506

[82] Gutiérrez, O.M., Mannstadt, M., Isakova, T., *et al*. (2008) Fibroblast Growth Factor 23 and Mortality among Patients Undergoing Hemodialysis. *The New England Journal of Medicine*, **359**, 584-592. https://doi.org/10.1056/NEJMoa0706130

[83] Isakova, T., Xie, H., Yang, W., *et al*. (2011) Fibroblast Growth Factor 23 and Risks of Mortality and End-Stage Renal Disease in Patients with Chronic Kidney Disease. *JAMA*, **305**, 2432-2439. https://doi.org/10.1001/jama.2011.826

[84] Scialla, J.J., Xie, H., Rahman, M., *et al*. (2014) Fibroblast Growth Factor-23 and Cardiovascular Events in CKD. *Journal of the American Society of Nephrology*: *JASN*, **25**, 349-360. https://doi.org/10.1681/ASN.2013050465

[85] Scialla, J.J., Astor, B.C., Isakova, T., *et al*. (2013) Mineral Metabolites and CKD Progression in African Americans. *Journal of the American Society of Nephrology*: *JASN*, **24**, 125-135. https://doi.org/10.1681/ASN.2012070713