Advances in Clinical Medicine 临床医学进展, 2022, 12(5), 4154-4165
Published Online May 2022 in Hans. http://www.hanspub.org/journal/acm
https://doi.org/10.12677/acm.2022.125603

Hans汉斯

基于网络药理学探讨黄芩–黄连治疗动脉粥样硬化的作用机制

罗舒文，俞　琦

贵州中医药大学研究生院，贵州　贵阳

收稿日期：2022年4月16日；录用日期：2022年5月11日；发布日期：2022年5月18日

摘　要

动脉粥样硬化是一种以脂质代谢紊乱为特征的心脑血管疾病。由于一线药物的不良反应，临床上迫切需要发现新的药物来治疗动脉粥样硬化。黄芩、黄连是中药中最有前景的治疗药物之一。但黄芩、黄连抗动脉粥样硬化的作用机制尚不清晰。在这项研究中，我们使用网络药理学研究黄芩、黄连与动脉粥样硬化之间的相互作用。首先从TCMSP、GEO数据库中确定了与黄芩、黄连的活性成分、潜在靶点和疾病的差异基因。通过两者取交集，确定了14个黄芩、黄连治疗动脉粥样硬化靶点。然后，利用string数据构建了黄芩、黄连和动脉粥样硬化靶点。最后，通过R包进行GO和KEGG功能富集分析。GO分析表明BP涉及脂多糖的反应、对细菌源性分子的反应、细胞对金属离子的反应等过程。CC涉及侧质膜、膜筏等细胞器。MF涉及泛素蛋白连接酶结合、泛素样蛋白连接酶结合等过程。KEGG结果表明，黄芩、黄连治疗AS的信号通路包括IL-17信号传导途径、TNF信号传导途径、脂质和动脉硬化等过程。本研究最后发现，黄芩、黄连改善动脉粥样硬化的作用机制可能是通过影响KCNH2、SCN5A、PTGS2、SLC6A2、ACHE、BCL2L1、MMP9、JUN、THBD、CXCL2、E2F2、ERBB3、FASN、MAPK1等基因的表达进而调控了IL-17、TNF、AGE-RAGE、NF-κB、血管内皮生长因子等信号传导途径实现的。

关键词

网络药理学，黄芩，黄连，动脉粥样硬化

Exploring the Mechanism of Action of *Scutellaria baicalensis*-Huanglian in the Treatment of Atherosclerosis Based on Network Pharmacology

Shuwen Luo, Qi Yu

Graduate School, Guizhou University of Traditional Chinese Medicine, Guiyang Guizhou

文章引用: 罗舒文, 俞琦. 基于网络药理学探讨黄芩-黄连治疗动脉粥样硬化的作用机制[J]. 临床医学进展, 2022, 12(5): 4154-4165. DOI: 10.12677/acm.2022.125603

Received: Apr. 16th, 2022; accepted: May 11th, 2022; published: May 18th, 2022

Abstract

Atherosclerosis is a cardiovascular disease characterised by disturbances in lipid metabolism. Due to the adverse effects of first-line drugs, there is an urgent clinical need to discover new drugs to treat atherosclerosis. *Scutellaria baicalensis* and Huanglian are among the most promising therapeutic agents in Chinese medicine. However, the mechanism of action of *Scutellaria baicalensis* and Huanglian against atherosclerosis is not clear. In this study, we used network pharmacology to investigate the interaction between *Scutellaria baicalensis* and Huanglian and atherosclerosis. Firstly, differential genes with active ingredients, potential targets and diseases of scutellaria and Huanglian were identified from the TCMSP, GEO database. By taking the intersection of the two, 14 baicalin and scutellaria targets were identified for the treatment of atherosclerosis. Then, baicalin, scutellaria and atherosclerosis targets were constructed using string data. Finally, GO and KEGG were performed by R package for functional enrichment analysis. GO analysis showed that BP involved processes such as response to lipopolysaccharide, response to bacterial-derived molecules, and cellular response to metal ions. CC involved organelles such as lateral plasma membrane and membrane rafts. MF involved processes such as ubiquitin protein ligase binding, ubiquitin-like protein ligase binding, and scaffold protein binding. KEGG results indicated that the signalling pathways of *Scutellaria baicalensis* and Huanglian signaling pathways for the treatment of AS include processes such as IL-17 signaling pathway, TNF signaling pathway, lipid and atherosclerosis. The final finding of this study was that the mechanism of action of *Scutellaria baicalensis* and Huanglian ameliorating atherosclerosis may be achieved through affecting the expression of genes such as KCNH2, SCN5A, PTGS2, SLC6A2, ACHE, BCL2L1, MMP9, JUN, THBD, CXCL2, E2F2, ERBB3, FASN, MAPK1 and thereby regulating the expression of IL-17, TNF, AGE-RAGE, NF-κB, vascular endothelial growth factor and other signaling pathways.

Keywords

Network Pharmacology, *Scutellaria baicalensis*, Huanglian, Atherosclerosis

1. 引言

动脉粥样硬化(AS)是一种以脂质代谢改变、炎症和内皮损伤为主的心脑血管疾病。心血管疾病是全球人口死亡的主要原因，与衰老相关的慢性病患病率逐年增加。根据世界卫生组织(WHO)的一项调查，2016 年有 1790 万人死于心血管疾病，占全球死亡总数的 31% [1]。AS 性载脂斑块是血管阻塞的主要病因，这些斑块堆积在内皮下空间后导致血管壁变窄，使人体的组织器官得不到充足的氧气及营养物质供应[2]。且 AS 在恶化前多呈无症状表现，因此早期发现较为困难。因此，大多数情况下 AS 预后较差，这与高死亡率直接相关[3]。现代研究表明，动脉粥样硬化受多种因素的综合作用。而临床中，对于 AS 的治疗方案多采用他汀类药物、手术等措施，但这些方案不可避免地带来了较多的副作用[4]。

中国传统医学治疗 AS 有独到的见解和优势，中医理论将 AS 归于“胸痹”的范畴。胸痹在古籍中有“热争则卒心痛”、“热上犯心而痛”、“愠愠如满”、“蕴蕴而痛”的论述。在治疗上秦景明、

李中梓等众多医家多重视火热之邪所致胸痹而痛，反复强调寒凉之品的使用。黄芩、黄连是临床中治疗 AS 的常见配伍药材，多用于治疗由心火亢盛所致的胸痹患者，虽取得了较好的疗效但具体作用机制不清[5]。

网络药理学是一种以系统药理学为基础，研究药物与疾病相互作用的新兴学科[6]。在网络药理学中，药物－靶点网络使研究人员探究药物治疗疾病的作用机制更加简洁。疾病靶点可应用于药物设计、药物发现和生物标志物检测领域[7]。心血管疾病和癌症等复杂疾病并不归因于单分子突变或信号通路功能障碍。因此，本研究通过网络药理学，构建“成分－靶点－通路－疾病”多维网络，探索黄芩、黄连治疗 AS 的潜在分子机制，为黄芩、黄连的临床应用以及 AS 相关疾病基础与临床研究提供一定的理论依据。

2. 方法

2.1. 黄芩－黄连有效成分及靶点的收集

采用 TCMSP 数据库及相关文献筛选黄芩、黄连的有效成分及药物靶点。有效成分筛选标准为：OB > 30%，DL > 0.18。

2.2. 动脉粥样硬化疾病靶点的获取

AS 相关基因从高通量基因表达(Gene Expression Omnibus, GEO)数据库(https://www.ncbi.nlm.nih.gov/geo/)中下载 GSE71226 数据集(GPL570 [HG-U133_Plus_2] Affymetrix Human Genome U133 Plus 2.0 Array)，该数据集共包含 3 例动脉粥样硬化样本和 3 例正常对照样本。运用 GEO2R 进行分析，设定 $P < 0.05$，获取差异 mRNA。使用 R 包展示各样本的归一化信号强度及二维分布特征。

2.3.“中药－有效成分－靶点”网络的构建及主要有效成分筛选

将筛选得到的有效成分以及有效作用靶点导入 Cytoscape 3.8.1 软件中，构建“中药-有效成分-靶点”网络并进行拓扑分析。将有效成分按节点度值大小排名，选取度值排名前 5 位的成分作为主要有效成分。

2.4. 蛋白互作网络的构建与分析

将黄芩-黄连治疗 AS 的潜在作用靶点输入 STRING 数据库(https://string-db.org/)，物种设定为“Homo sapiens”，获得蛋白与蛋白之间的相互作用关系，将数据保存为 TSV 格式，利用 Cytoscape 3.8.1 进行可视化处理并借助 cytoHubba 筛选出核心靶点。

2.5. 富集分析

为了研究与潜在目标相关的生物学功能，我们通过“clusterProfiler”R 包进行了基因本体论(GO)和京都基因和基因组百科全书(KEGG)通路富集分析。“clusterProfiler”R 包作为一种用户友好的富集工具，具有基于多种资源的集成基因聚类分析。GO 富集分析从三个维度对基因进行解释和注释，包括细胞成分(CC)、分子功能(MF)和生物过程(BP)分析。KEGG 数据库主要用于通路分析。低于 0.05 的 P 值被认为具有统计学意义。

3. 结果

3.1. 中药化合成分及靶点的获取

黄芩、黄连共有 41 个化合成分，200 个药物靶标。Quercetin、wogonin、baicalein、beta-sitosterol、Stigmasterol、(R)-Canadine、acacetin、oroxylin a、Moslosooflavone。

3.2. 疾病靶点的获取

通过 R 语言对 GEO 数据库中 GSE71226 数据集进行标准化及 PCA 分析(图 1(a)，图 1(b))，观察样本内各基因表达数据的稳定性及空间分布。经差异分析后共得到 1681 个动脉粥样硬化相关靶点，通过 ggplot2 包绘制部分差异基因的火山图和热图进行展示(图 1(c)，图 1(d))。1681 个疾病靶点与 200 个药物靶标取交集后，共获得 14 个差异基因(图 2)。

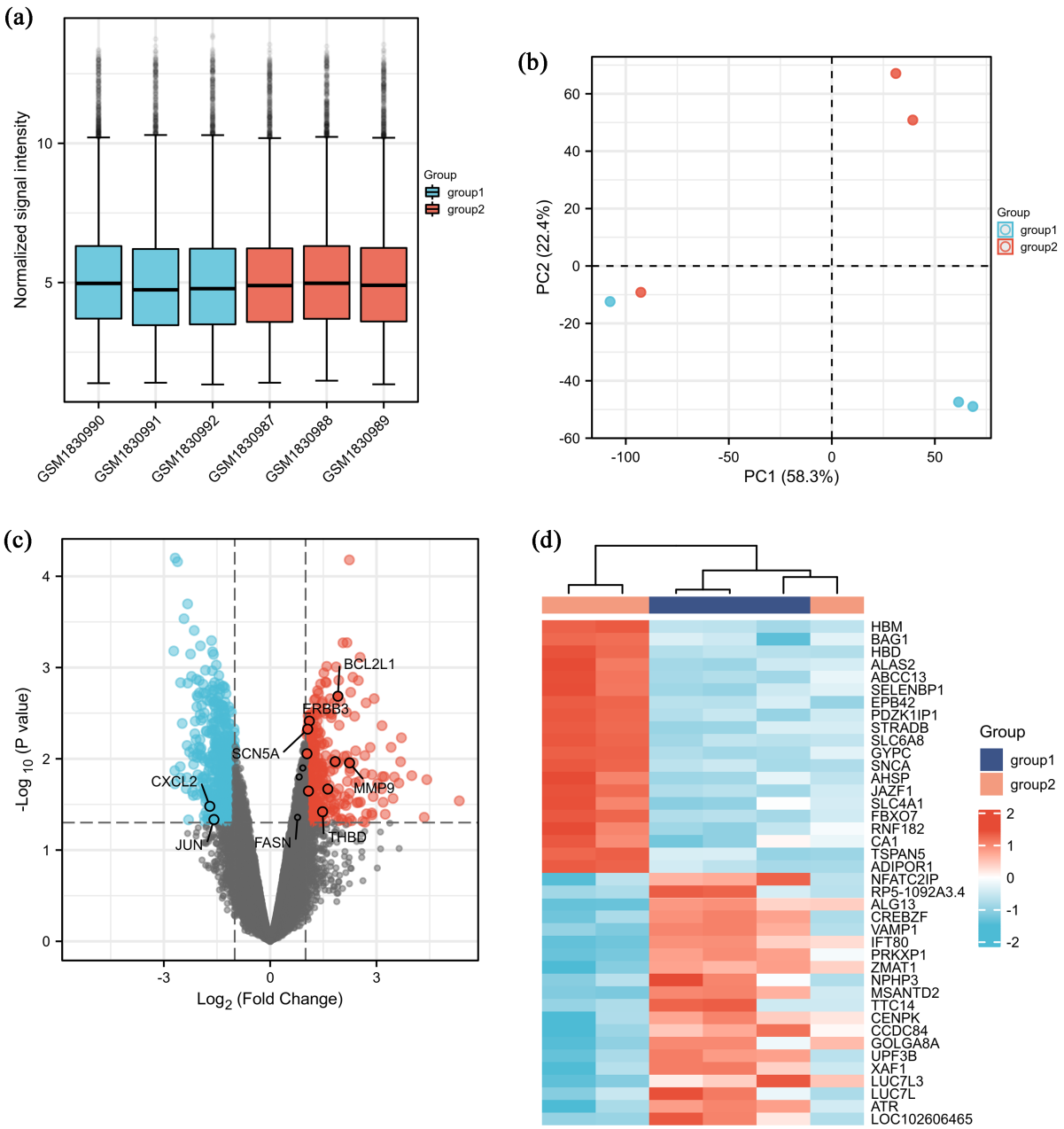

Figure 1. Processing and difference analysis of GEO dataset (a) Boxplot of GEO standardized data distribution; (b) GEO data dimensionality reduction PCA spatial distribution diagram; (c) GEO dataset differential gene volcano plot; (d) GEO dataset differential analysis gene volcano plot

图 1. GEO 数据集的处理及差异分析。(a) GEO 标准化数据分布箱线；(b) GEO 数据降维 PCA 空间分布图；(c) GEO 数据集差异基因火山图；(d) GEO 数据集差异分析基因火山图

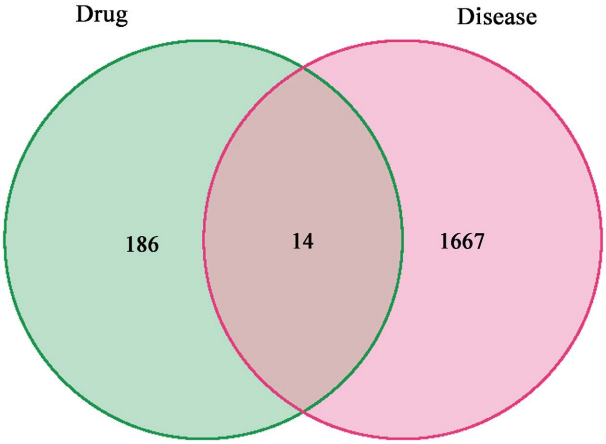

Figure 2. Venn diagram of drug targets and disease targets
图 2. 药物靶点与疾病靶点的韦恩图

3.3.“中药－有效成分－靶点”网络的构建及主要有效成分筛选

使用 Cytoscape 3.8.1，绘制黄芩-黄连有效成分治疗动脉粥样硬化致病基因的网络图(图 3)。AS 致病

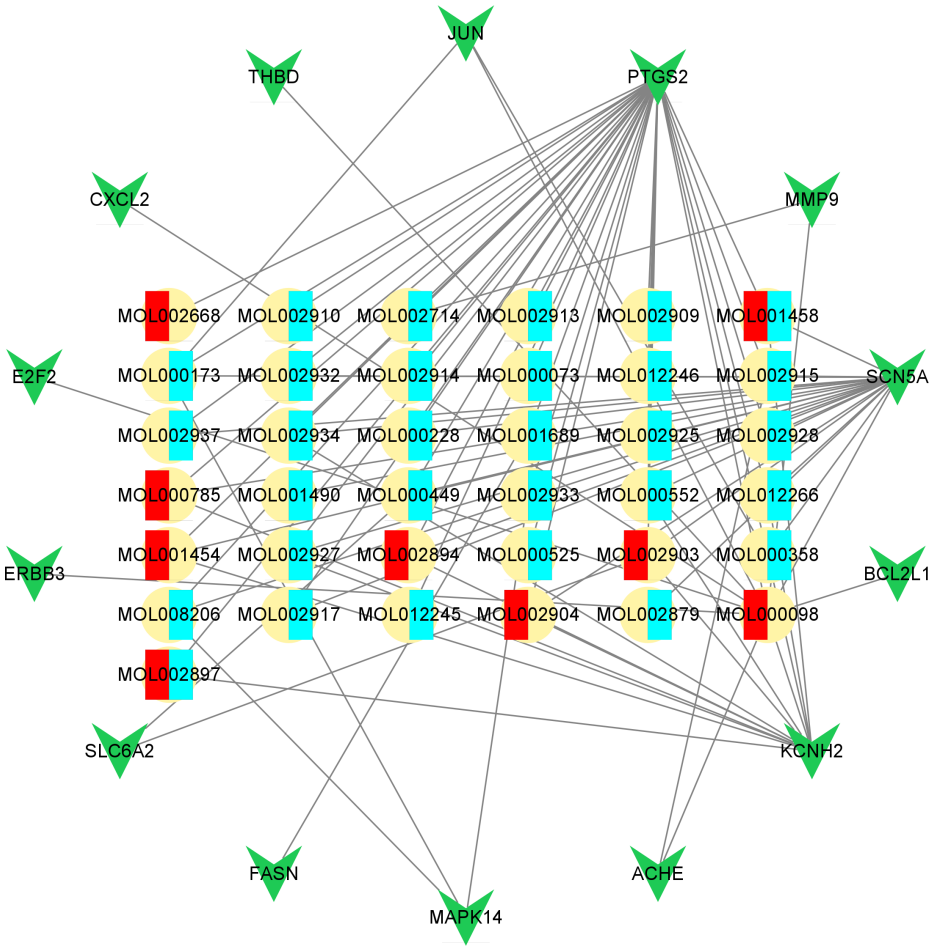

Figure 3. Traditional Chinese medicine-active ingredients-target network diagram
图 3. 中药－有效成分－靶点网络图

基因在外以环状的绿色梭形展示。在内呈矩形分布的为黄连、黄芩的有效成分。其中若矩形中有红色，则代表此化合物是黄连的化合成分之一，若矩形中有浅蓝色，则代表此化合物是黄芩的化合成分之一。

3.4. 蛋白互作网络的构建与分析

PPI 结果显示，KCNH2、SCN5A、PTGS2、SLC6A2、ACHE、BCL2L1、MMP9、JUN、THBD、CXCL2、E2F2、ERBB3、FASN、MAPK14 是黄芩黄连治疗 AS 的潜在靶点(图 4)。

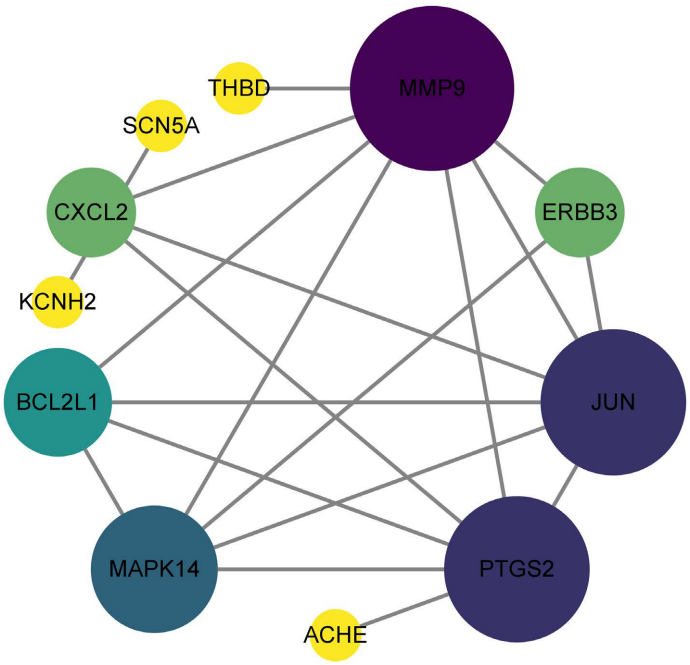

Figure 4. Construction and analysis of PPI protein interaction network
图 4. PPI 蛋白互作网络的构建与分析

3.5. 富集分析

GO 结果显示，BP 涉及脂多糖的反应、对细菌源性分子的反应、细胞对金属离子的反应、线粒体中细胞色素 c 的释放、细胞对无机物的反应、神经炎症反应、棕色脂肪细胞分化的积极调节、肌肉细胞增殖。CC 涉及侧质膜、膜筏、膜微域、RNA 聚合酶 II 转录调节器复合物、电压门控钠通道复合体。MF 涉及泛素蛋白连接酶结合、泛素样蛋白连接酶结合、鹰架蛋白结合、胶原蛋白结合、单价无机阳离子跨膜转运器活性、金属离子跨膜转运体的活性、生长因子结合、钠离子跨膜转运体活性、钠氯共存器活性、BH 结构域结合(图 5)。

KEGG 结果表明，黄芩、黄连治疗 AS 的信号通路包括 IL-17 信号传导途径、TNF 信号传导途径、脂质和动脉硬化、内分泌抵抗、流体剪切应力与动脉粥样硬化、乙型肝炎、NOD 样受体信号传导途径、AGE-RAGE 信号通路在糖尿病并发症中的应用、NF-κB 信号传导途径、C 型凝集素受体信号通路等传导途径(图 6)。

4. 讨论

AS 是一种慢性多因素病变，是多种心脑血管疾病的病理基础，并伴有慢性炎症反应[8]。这些炎症反应会刺激内皮细胞的激活，内皮细胞被激活后会使临近组织中的巨噬细胞、淋巴细胞(T 和 B 细胞)、树突

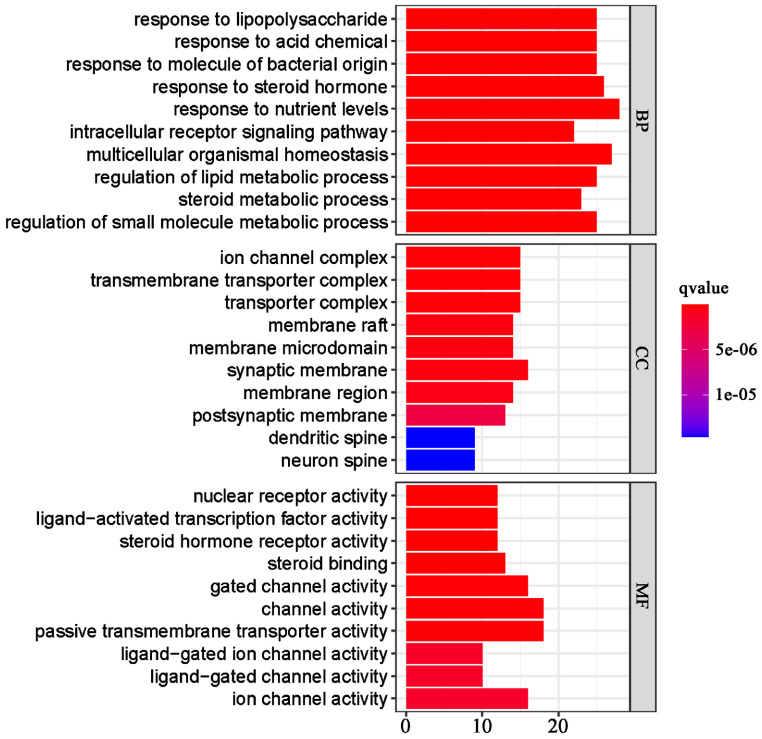

Figure 5. GO analysis bar graph
图 5. GO 分析条形图

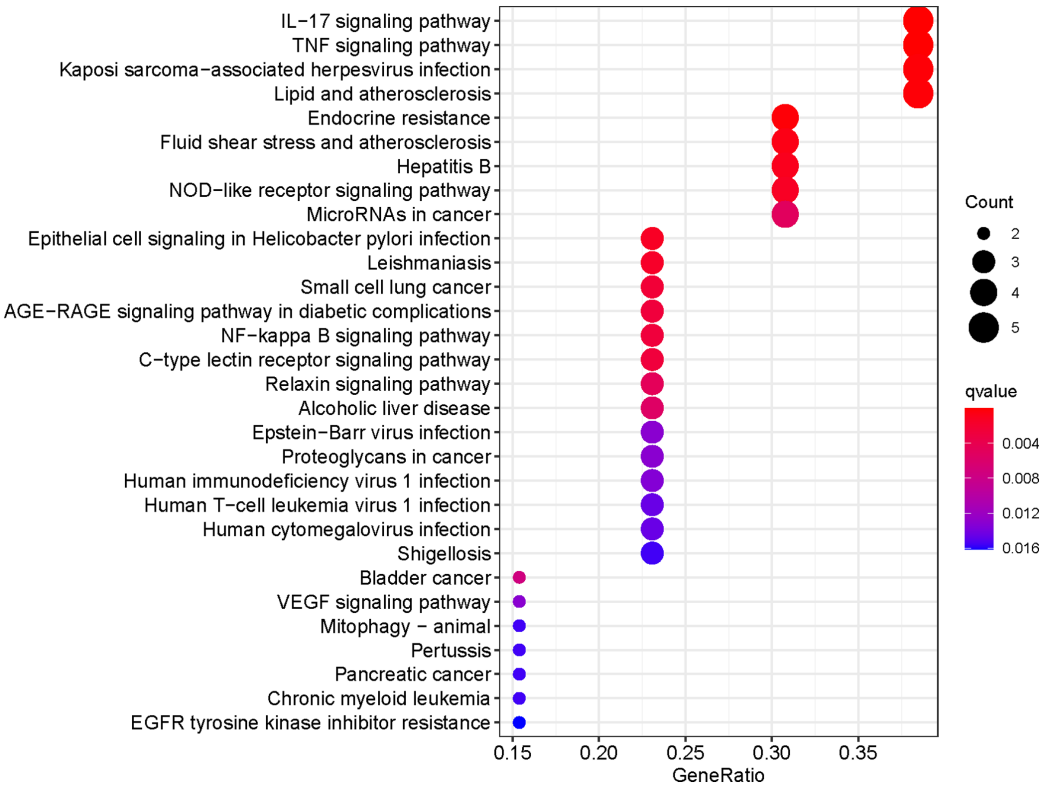

Figure 6. KEGG analysis bubble chart
图 6. KEGG 分析气泡图

细胞(DC)、EC、血管平滑肌细胞(VSMC)、ILs、粘附分子和肿瘤坏死因子(TNF-α)等许多细胞和细胞因子参与炎症过程[9]，并表达单核细胞趋化蛋白、白细胞介素(IL)-8、细胞间粘附分子 1(ICAM-1)、血管粘附分子 1 (VCAM-1)、E-选择素、P-选择素和其他炎症因子，浸润动脉壁的淋巴细胞和单核细胞，加重人体的炎症反应[10]。在此过程中，例如大量低密度脂蛋白(LDL)被氧化为 oxLDL 并在血管内壁积聚，导致动脉粥样硬化斑块的发展[6]。单核细胞吞噬 oxLDL 沉积物后转化为泡沫细胞的巨噬细胞[11]。促炎单核细胞优先积聚在动脉粥样硬化斑块中，并在体外粘附于细胞因子刺激的内皮细胞[12]。而 DC、T 细胞、B 细胞和中性粒细胞等其他类型的免疫细胞参与斑块内炎症。因此，AS 的发展机制是一种复杂且相互联系涉及炎症及代谢的疾病。

本研究表明，Quercetin、wogonin、baicalein、beta-sitosterol、Stigmasterol 等物质是黄芩、黄连中含有 AS 疾病靶点较多的成分。其中，槲皮素(Quercetin)是一种黄酮类化合物，已被证明具有心血管保护作用和抗动脉粥样硬化作用[13]。槲皮素可通过抑制活性氧(ROS)产生和激活 PI3K/AKT 信号通路来抑制高果糖喂养的 C57BL/6 小鼠的动脉粥样硬化斑块发展[14]。槲皮素可明显改善高脂肪饮食的 APOE-/-小鼠的动脉粥样硬化斑块的面积、脂质积累水平，并增加了动脉粥样硬化斑块中的胶原纤维[15]。黄芩素(baicalein)是从唇形科植物黄芩的干根中提取的复合黄酮，具有抗菌、抗病毒、抗炎、抗癌等多种药理作用[16] [17] [18]。目前黄芩素用于治疗脑血管病后瘫痪[19]。黄芩素可以通过抑制炎症反应来改善大鼠的心脏收缩功能[20]。黄芩素还可以通过线粒体氧化信号传导减轻阿霉素诱导的心肌缺血再灌注损伤[21]和心肌细胞损伤[22]。汉黄芩素(wogonin)是从黄芩中提取的一种重要的黄酮类化合物，已被证明具有抗炎、抗氧化、抗过敏和抗凋亡的特性[23] [24]。多项研究表明，它可以保护心脏免受糖尿病、肥胖和缺血－再灌注损伤[25] [26] [27]。β-谷甾醇(beta-sitosterol)是具有抗炎特性的化合成分，能通过抑制 TNF-α 及 ICAM-1 减轻人内皮细胞上的炎症反应并阻断中性粒细胞与内皮单层的粘附[28]。豆甾醇(Stigmasterol)可以抑制 ROS、cyclin A、CDK2、PCNA、bax 和 bcl-2 的表达水平，升高 p53、SOD 和 CAT 蛋白水平进而降低主动脉平滑肌细胞系增殖[29]。

PPI 结果显示，KCNH2、SCN5A、PTGS2、SLC6A2、ACHE、BCL2L1、MMP9、JUN、THBD、CXCL2、E2F2、ERBB3、FASN、MAPK1 参与了 AS 的发展，且能被黄芩、黄连所干预。研究表明，钾电压门控通道亚家族 H 成员(KCNH)，包含 6 个跨膜和一个成孔结构域蛋白，通常负责组织的兴奋性[30]。KCNH2 是快速复极期的关键基因，在心脏中多呈现高表达的状态，其突变常与心律失常有关[31]。最近，KCNH2 通道参与调节细胞增殖和凋亡[32]。Kcnh2 的纯合缺失可导致心脏发育缺陷，最终导致胚胎致死[33] [34]。SCN5A 基因是编码主要心脏钠通道 Nav1.5 的 α 亚基，负责维持内向钠电流的正常功能，Na 电流是快速去极化阶段的主要成分，调控心脏中激发－收缩耦合级联和电脉冲的传导[35]。PTGS2，也称为环氧合酶 2 (COX2)，是生物学中铁死亡的中心基因[36]。PTGS2 在动脉粥样硬化的晚期阶段上调，且它的表达与动脉粥样硬化的严重程度呈正相关[37]。PTGS2 的多态性也与冠状动脉疾病的发生发展密切相关[38]。PTGS2 表达的上升会加重心血管的炎症反应[39]。在先天性白细胞中，中性粒细胞是 MMP9 的主要来源，MMP9 与不稳定的动脉粥样硬化斑块密切相关[40]，也可调节 AS 模型中血管平滑肌细胞的增殖和迁移[41]。c-Jun 是激活蛋白-1 复合物中研究最广泛的蛋白质，参与增殖、凋亡、存活、肿瘤发生和组织形态等多种细胞活动的发生[42]。c-Jun/AP-1 信号通路促进 VSMCs 的增殖和迁移[43]。THBD (血栓调节蛋白)是一种在内皮细胞中表达的抗凝跨膜因子[44]。除凝血外，THBD 还可影响不同病理疾病和器官的炎症和屏障功能[45]。血管内皮损伤后，整个血管内皮中的 THBD 会导致大量血栓形成和高凝状态[46]。CXCL2 是一类引起白细胞定向迁移的趋化因子。CXCL2 在心肌中的过表达常引起心肌细胞损伤，甚至导致心肌梗死。CXCL2 可以通过血流将中性粒细胞快速募集到炎症部位或受伤组织，以响应感染或损伤[47] [48]。此外，CXCL2 还参与维持嗜中性粒细胞的稳态，并调节嗜中性粒细胞从骨髓的迁移，使嗜中性粒细胞粘附到内皮细胞或释放到血液种[49]。ANG II 和 AVP 是人体重要的血管收缩激素，它们可以促进 VSMC

中的 G1/S 转换和 DNA 复制，导致动脉粥样硬化患者的血管异常[50]。E2F2 是 VSMC 中细胞对各种刺激物的反应的关键靶点之一[51]。E2F2 在调节细胞周期相关基因表达方面发挥核心作用，并为血管生长的治疗性调节提供了理想的靶标[52]。

KEGG 结果表明，黄芩、黄连对 AS 患者 IL-17、TNF、AGE-RAGE、NF-kappa B、血管内皮生长因子等信号传导途径有较好的调控作用。IL-17 被确定为由称为 Th17 的 CD4 + T 辅助(Th)细胞亚群产生的促炎细胞因子[53]。Th17 细胞释放 IL-17 (IL-17 A)，这是标志性细胞因子，其结构中含有二硫键连接的同型二聚体糖蛋白[54]，在保护宿主免受细胞外病原体侵害方面具有关键作用[55]。IL-17 促进许多下游信号通路，包括 NF-κB，导致产生编码促炎细胞因子的基因[56]。IL-17 信号传导诱导靶细胞中生长介质、组织重塑酶和其他次级因子的表达[57]。单独的 IL-17 通常会刺激较弱的反应，但它可能与不同的细胞因子(如 TNFα、IFN-γ、GM-CSF、IL-1β 和 IL-22)协同作用，以增加炎症介质(如 IL-6 和 IL-8)的产生，导致增加和延长促炎反应[58]。TNF-α 是一种多功能促炎细胞因子，已知参与 AS 的发病机制[59]。

总之，本研究发现，黄芩、黄连改善 AS 的作用机制可能是通过影响 KCNH2、SCN5A、PTGS2、SLC6A2、ACHE、BCL2L1、MMP9、JUN、THBD、CXCL2、E2F2、ERBB3、FASN、MAPK1 等基因的表达进而调控了 IL-17、TNF、AGE-RAGE、NF-κB、血管内皮生长因子等信号传导途径实现的。

参考文献

[1] Otreba, M., Kosmider, L. and Rzepecka-Stojko, A. (2021) Polyphenols' Cardioprotective Potential: Review of Rat Fibroblasts as Well as Rat and Human Cardiomyocyte Cell Lines Research. *Molecules*, **26**, Article No. 774. https://doi.org/10.3390/molecules26040774

[2] Palasubramaniam, J., Wang, X.W. and Peter, K. (2019) Myocardial Infarction—From Atherosclerosis to Thrombosis Uncovering New Diagnostic and Therapeutic Approaches. *Arteriosclerosis, Thrombosis, and Vascular Biology*, **39**, E176-E185. https://doi.org/10.1161/ATVBAHA.119.312578

[3] Chen, J., Zhang, X., Millican, R., *et al*. (2021) Recent Advances in Nanomaterials for Therapy and Diagnosis for Atherosclerosis. *Advanced Drug Delivery Reviews*, **170**, 142-199. https://doi.org/10.1016/j.addr.2021.01.005

[4] Bruikman, C.S., Stoekenbroek, R.M., *et al*. (2017) New Drugs for Atherosclerosis. *Canadian Journal of Cardiology*, **33**, 350-357. https://doi.org/10.1016/j.cjca.2016.09.010

[5] 赵立凤, 于红红, 田维毅. 中药单体调控血管内皮细胞自噬干预动脉粥样硬化的研究进展[J]. 中华中医药学刊, 2021, 39(11): 117-120.

[6] Boezio, B., Audouze, K., Ducrot, P., *et al*. (2017) Network-Based Approaches in Pharmacology. *Molecular Informatics*, **36**, Article ID: 1700048. https://doi.org/10.1002/minf.201700048

[7] Ning, K., Zhao, X., Poetsch, A., *et al*. (2017) Computational Molecular Networks and Network Pharmacology. *BioMed Research International*, **2017**, Article ID: 7573904. https://doi.org/10.1155/2017/7573904

[8] Conti, P. and Shaik-Dasthagirisaeb, Y. (2015) AS: A Chronic Inflammatory Disease Mediated by Mast Cells. *Central European Journal of Immunology*, **40**, 380-386. https://doi.org/10.5114/ceji.2015.54603

[9] Ranjit, N., Diez-Roux, A.V., Shea, S., *et al*. (2007) Psychosocial Factors and Inflammation in the Multi-Ethnic Study of Atherosclerosis. *Archives of Internal Medicine*, **167**, 174-181. https://doi.org/10.1001/archinte.167.2.174

[10] Chistiakov, D.A., Melnichenko, A.A., Grechko, A.V., *et al*. (2018) Potential of Anti-Inflammatory Agents for Treatment of Atherosclerosis. *Experimental and Molecular Pathology*, **104**, 114-124. https://doi.org/10.1016/j.yexmp.2018.01.008

[11] Pirillo, A., Norata, G.D. and Catapano, A.L. (2013) LOX-1, OxLDL, and Atherosclerosis. *Mediators of Inflammation*, **2013**, Article ID: 152786. https://doi.org/10.1155/2013/152786

[12] Swirski, F.K., Nahrendorf, M. and Libby, P. (2016) Mechanisms of Myeloid Cell Modulation of Atherosclerosis. *Microbiology Spectrum*, **4**, 1-15. https://doi.org/10.1128/microbiolspec.MCHD-0026-2015

[13] Lara-Guzman, O.J., Tabares-Guevara, J.H., Leon-Varela, Y.M., *et al*. (2012) Proatherogenic Macrophage Activities Are Targeted by the Flavonoid Quercetin. *Journal of Pharmacology and Experimental Therapeutics*, **343**, 296-306. https://doi.org/10.1124/jpet.112.196147

[14] Lu, X.L., Zhao, C.H. and Yao, X.L. (2017) Quercetin Attenuates High Fructose Feeding-Induced Atherosclerosis by Suppressing Inflammation and Apoptosis Via ROS-Regulated PI3K/AKT Signaling Pathway. *Biomed Pharmacother*,

85, 658-671. https://doi.org/10.1016/j.biopha.2016.11.077

[15] Jia, Q., Cao, H., Shen, D., *et al*. (2019) Quercetin Protects against Atherosclerosis by Regulating the Expression of PCSK9, CD36, PPARγ, LXR*α* and ABCA1. *International Journal of Molecular Medicine*, **44**, 893-902. https://doi.org/10.3892/ijmm.2019.4263

[16] Jang, E.J., Cha, S.M., Choi, S.M., *et al*. (2014) Combination Effects of Baicalein with Antibiotics against Oral Pathogens. *Archives of Oral Biology*, **59**, 1233-1241. https://doi.org/10.1016/j.archoralbio.2014.07.008

[17] Li-Weber, M. (2009) New Therapeutic Aspects of Flavones: The Anticancer Properties of *Scutellaria* and Its Main Active Constituents Wogonin, Baicalein and Baicalin. *Cancer Treatment Reviews*, **35**, 57-68. https://doi.org/10.1016/j.ctrv.2008.09.005

[18] Lin, C.C. and Shieh, D.E. (1996) The Anti-Inflammatory Activity of *Scutellaria Rivularis* Extracts and Its Active Components, Baicalin, Baicalein and Wogonin. *The American Journal of Chinese Medicine*, **24**, 31-36. https://doi.org/10.1142/S0192415X96000050

[19] Srinivas, N.R. (2010) Baicalin, an Emerging Multi-Therapeutic Agent: Pharmacodynamics, Pharmacokinetics, and Considerations from Drug Development Perspectives. *Xenobiotica*, **40**, 357-367. https://doi.org/10.3109/00498251003663724

[20] Lee, Y.M., Cheng, P.Y., Chim, L.S., *et al*. (2011) Baicalein, an Active Component of *Scutellaria Baicalensis* Georgi, Improves Cardiac Contractile Function in Endotoxaemic Rats via Induction of Heme Oxygenase-1 and Suppression of Inflammatory Responses. *Journal of Ethnopharmacology*, **135**, 179-185. https://doi.org/10.1016/j.jep.2011.03.009

[21] Chang, W.T., Li, J., Hoek, M.V., Zhu, X.D., *et al*. (2013) Baicalein Preconditioning Protects Cardiomyocytes from Ischemia-Reperfusion Injury via Mitochondrial Oxidant Signaling. *American Journal of Chinese Medicine*, **41**, 315-331. https://doi.org/10.1142/S0192415X13500237

[22] Chang, W.T., Li, J., Haung, H.H., Liu, H., Han, M., *et al*. (2011) Baicalein Protects against Doxorubicin-Induced Cardiotoxicity by Attenuation of Mitochondrial Oxidant Injury and JNK Activation. *Journal of Cellular Biochemistry*, **112**, 2873-2881. https://doi.org/10.1002/jcb.23201

[23] Khan, N.M., Haseeb, A., Ansari, M.Y., *et al*. (2017) Wogonin, a Plant Derived Small Molecule, Exerts Potent Anti-Inflammatory and Chondroprotective Effects through the Activation of ROS/ERK/Nrf2 Signaling Pathways in Human Osteoarthritis Chondrocytes. *Free Radical Biology and Medicine*, **106**, 288-301. https://doi.org/10.1016/j.freeradbiomed.2017.02.041

[24] Lucas, C.D., Dorward, D.A., Sharma, S., *et al*. (2015) Wogonin Induces Eosinophil Apoptosis and Attenuates Allergic Airway Inflammation. *American Journal of Respiratory and Critical Care Medicine*, **191**, 626-636. https://doi.org/10.1164/rccm.201408-1565OC

[25] Shi, X., Zhang, B., Chu, Z., *et al*. (2021) Wogonin Inhibits Cardiac Hypertrophy by Activating Nrf-2-Mediated Antioxidant Responses. *Cardiovascular Therapeutics*, **2021**, Article ID: 9995342. https://doi.org/10.1155/2021/9995342

[26] Hang, W.T., Shao, Z.H., Vanden Hoek, T.L., *et al*. (2006) Cardioprotective Effects of GrapE Seed Proanthocyanidins, Baicalin and Wogonin: Comparison Between Acute and Chronic Treatments. *The American Journal of Chinese Medicine*, **34**, 363-365. https://doi.org/10.1142/S0192415X06003898

[27] Bei, W., Jing, L. and Chen, N. (2020) Cardio Protective Role of Wogonin Loaded Nanoparticle against Isoproterenol Induced Myocardial Infarction by Moderating Oxidative Stress and Inflammation. *Colloids and Surfaces B*: *Biointerfaces*, **185**, Article ID: 110635. https://doi.org/10.1016/j.colsurfb.2019.110635

[28] Gupta, P., Balwani, S., Kumar, S., *et al*. (2010) Beta-Sitosterol among Other Secondary Metabolites of *Piper Galeatum* Shows Inhibition of TNFalpha-Induced Cell Adhesion Molecule Expression on Human Endothelial Cells. *Biochimie*, **92**, 1213-1221. https://doi.org/10.1016/j.biochi.2010.06.005

[29] Li, C., Liu, Y., Xie, Z., *et al*. (2015) Stigmasterol Protects against Ang II-Induced Proliferation of the A7r5 Aortic Smooth Muscle Cell-Line. *Food & Function*, **6**, 2266-2272. https://doi.org/10.1039/C5FO00031A

[30] Lorinczi, E., Gomez Posada, J.C., De La Pena, P., *et al*. (2015) Voltage-Dependent Gating of KCNH Potassium Channels Lacking a Covalent Link between Voltage-Sensing and Pore Domains. *Nature Communications*, **6**, Article No. 6672. https://doi.org/10.1038/ncomms7672

[31] Anderson, C.L., Delisle, B.P., Anson, B.D., *et al*. (2006) Most LQT2 Mutations Reduce Kv11.1 (hERG) Current by a Class 2 (Trafficking-Deficient) Mechanism. *Circulation*, **113**, 365-373. https://doi.org/10.1161/CIRCULATIONAHA.105.570200

[32] Jehle, J., Schweizer, P.A. and Katus, H.A. (2011) Novel Roles for HERG K(+) Channels in Cell Proliferation and Apoptosis. *Cell Death & Disease*, **2**, e193. https://doi.org/10.1038/cddis.2011.77

[33] Teng, G.Q., Zhao, X., Lees-Miller, J.P., *et al*. (2008) Homozygous Missense N629D HERG (KCNH2) Potassium Channel Mutation Causes Developmental Defects in the Right Ventricle and Its Outflow Tract and Embryonic Lethality. *Circulation Research*, **103**, 1483-1491. https://doi.org/10.1161/CIRCRESAHA.108.177055

[34] Teng, G., Zhao, X., Lees-Miller, J.P., *et al*. (2015) Role of Mutation and Pharmacologic Block of Human KCNH2 in Vasculogenesis and Fetal Mortality Partial Rescue by Transforming Growth Factor-*β*. *Circulation*: *Arrhythmia and Electrophysiolog*, **8**, 420-428. https://doi.org/10.1161/CIRCEP.114.001837

[35] Aronsen JM, Swift F, Sejersted OM. (2013) Cardiac Sodium Transport and Excitation-Contraction Coupling. *Journal of Molecular and Cellular Cardiology*, **61**, 11-19. https://doi.org/10.1016/j.yjmcc.2013.06.003

[36] Zhu, L., Yang, F., Wang, L., *et al*. (2021) Identification the Ferroptosis-Related Gene Signature in Patients with Esophageal Adenocarcinoma. *Cancer Cell International*, **21**, Article No. 124. https://doi.org/10.1186/s12935-021-01821-2

[37] Zhou, Y., Zhou, H., Hua, L., *et al*. (2021) Verification of Ferroptosis and Pyroptosis and Identification of PTGS2 as the Hub Gene in Human Coronary Artery Atherosclerosis. *Free Radical Biology and Medicine*, **171**, 55-68. https://doi.org/10.1016/j.freeradbiomed.2021.05.009

[38] Xuan, C.L., Yan, W. and Xuan, L. (2014) *PTGS2* Gene Polymorphism-765G>C Is Associated with Coronary Artery Disease: A Meta-Analysis. *Genetics and Molecular Research*, **13**, 1491-1496. https://doi.org/10.4238/2014.January.14.10

[39] Ruan, Z., Wang, S. and Yu, W. (2019) LncRNA MALAT1 Aggravates Inflammation Response through Regulating PTGS2 by Targeting MiR-26b in Myocardial Ischemia-Reperfusion Injury. *International Journal of Cardiology*, **288**, 122. https://doi.org/10.1016/j.ijcard.2019.04.015

[40] Yabluchanskiy, A., Ma, Y., Iyer, R.P., *et al*. (2013) Matrix Metalloproteinase-9: Many Shades of Function in Cardiovascular Disease. *Physiology*, **28**, 391-403. https://doi.org/10.1152/physiol.00029.2013

[41] Wang, N., Yuan, Y. and Sun, S. (2020) MicroRNA-204-5p Participates in Atherosclerosis via Targeting MMP-9. *Open Medicine*, **15**, 231-239. https://doi.org/10.1515/med-2020-0034

[42] Meng, Q. and Xia, Y. (2011) C-Jun, at the Crossroad of the Signaling Network. *Protein & Cell*, **2**, 889-898. https://doi.org/10.1007/s13238-011-1113-3

[43] Ji, R., Gu, Y., Zhang, J., *et al*. (2020) TRIM7 Promotes Proliferation and Migration of Vascular Smooth Muscle Cells in Atherosclerosis through Activating C-Jun/AP-1. *IUBMB Life*, **72**, 247-258. https://doi.org/10.1002/iub.2181

[44] Esmon, C.T. and Owen, W.G. (1981) Identification of an Endothelial Cell Cofactor for Thrombin-Catalyzed Activation of Protein C. *Proceedings of the National Academy of Sciences of the United States of America*, **78**, 2249-2252. https://doi.org/10.1073/pnas.78.4.2249

[45] Wenzel, J., Assmann, J.C. and Schwaninger, M. (2014) Thrombomodulin—A New Target for Treating Stroke at the Crossroad of Coagulation and Inflammation. *Current Medicinal Chemistry*, **21**, 2025-2034. https://doi.org/10.2174/09298673216661312282048 39

[46] Isermann, B., Hendrickson, S.B., Zogg, M., *et al*. (2001) Endothelium-Specific Loss of Murine Thrombomodulin Disrupts the Protein C Anticoagulant Pathway and Causes Juvenile-Onset Thrombosis. *Journal of Clinical Investigation*, **108**, 537-546. https://doi.org/10.1172/JCI200113077

[47] White, G.E., Iqbal, A.J. and Greaves, D.R. (2013) CC Chemokinereceptors and Chronic Inflammation-Therapeutic Opportunities and Pharmacological Challenges. *Pharmacological Reviews* **65**, 47-89. https://doi.org/10.1124/pr.111.005074

[48] Kobayashi, Y. (2008) The Role of Chemokines in Neutrophil Biology. *Frontiers in Bioscience*, **13**, 2400-2407. https://doi.org/10.2741/2853

[49] Day RB, Link DC. (2012) Regulation of Neutrophil Trafficking from Thebone Marrow. *Cellular and Molecular Life Sciences*, **69**, 1415-1423. https://doi.org/10.1007/s00018-011-0870-8

[50] Fujita, N., Furukawa, Y., Itabashi, N., Okada, K., Saito, T. and Ishibashi, S. (2002) Differences in E2F Subunit Expression in Quiescent and Proliferating Vascular Smooth Muscle Cells. *American Journal of Physiology-Heart and Circulatory Physiology*, **283**, H204-H212. https://doi.org/10.1152/ajpheart.00545.2001

[51] Fujita, N., Furukawa, Y., Itabashi, N., *et al*. (1999) Failure of Cdc2 Promoter Activation and G2/M Transition by ANG II and AVP in Vascular Smooth Musclecells. *American Journal of Physiology-Heart and Circulatory Physiology*, **277**, H515-H523. https://doi.org/10.1152/ajpheart.1999.277.2.H515

[52] Wenzel, P.L., Chong, J.-L., Sáenz-Robles, M.T., *et al*. (2011) Cell Proliferation in the Absence of E2F1-3. *Developmental Biology*, **351**, 35-45. https://doi.org/10.1016/j.ydbio.2010.12.025

[53] Yao, Z., Painter, S.L., Fanslow, W.C., Ulrich, D., *et al*. (1995) Human IL-17: A Novel Cytokine Derived from T Cells. *The Journal of Immunology*, **155**, 5483-5486.

[54] Weaver, C.T., Hatton, R.D., Mangan, P.R., *et al*. (2007) IL-17 Family Cytokines and the Expanding Diversity of Effector T Cell Lineages. *Annual Review of Immunology*, **25**, 821-852. https://doi.org/10.1146/annurev.immunol.25.022106.141557

[55] Gaffen, S.L. (2009) Structure and Signalling in the IL-17 Receptor Family. *Nature Reviews Immunology*, **9**, 556-567. https://doi.org/10.1038/nri2586

[56] Iwakura, Y., Ishigame, H., Saijo, S., *et al*. (2011) Functional Specialization of Inter-Leukin-17 Family Members. *Immunity*, **34**, 149-162. https://doi.org/10.1016/j.immuni.2011.02.012

[57] Monin, L. and Gaffen, S.L. (2018) Interleukin 17 Family Cytokines: Signaling Mechanisms, Biological Activities, and Therapeutic Implications. *Cold Spring Harbor Perspectives in Biology*, **10**, Article ID: A028522. https://doi.org/10.1101/cshperspect.a028522

[58] Beringer, A., Noack, M. and Miossec, P. (2016) IL-17 in Chronic Inflammation: From Discovery to Targeting. *Trends in Molecular Medicine*, **22**, 230-241. https://doi.org/10.1016/j.molmed.2016.01.001

[59] McKellar, G.E., McCarey, D.W., *et al*. (2009) Role for TNF in Atherosclerosis? Lessons from Autoimmune Disease. *Nature Reviews Cardiology*, **6**, 410-417. https://doi.org/10.1038/nrcardio.2009.57