·专题讲座·

动脉粥样硬化斑块易损性炎性标志物及其临床意义

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【摘要】 炎症反应机制在动脉粥样硬化的发生与发展中发挥重要作用。多项基础与临床研究均提示炎性标志物表达变化与动脉粥样硬化程度密切相关，针对炎性因子的治疗可能给动脉粥样硬化患者带来益处。本文总结近年取得一些研究进展的传统和新型炎性标志物，如C-反应蛋白、白细胞介素-17、分泌型磷脂酶A2、脂蛋白相关磷脂酶A2、内皮糖蛋白、趋化因子受体和5脂氧合酶等，从基础与临床角度综述其作用机制和治疗前景。

【关键词】 动脉粥样硬化； 炎症； 生物学标记； 综述

Biomarkers of atherosclerotic plaque vulnerability and their clinical significance

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【Abstract】 Inflammatory reaction plays a crucial role in the occurence and development of atherosclerosis. Both basic and clinical trials have provided evidence that the expression of inflammatory biomarkers are closely related with the degree of atherosclerosis. Treatment towards inflammatory factors would bring benefit to atherosclerotic patients. This review highlighted the mechanistic rationale and specific therapies targeting traditional and novel inflammatory biomarkers, including C-reactive protein (CRP), interleukin-17 (IL-17), secretory phospholipase A2 (sPLA2), lipoprotein-associated phospholipase A2 (Lp-PLA2), endoglin, chemokine receptor and 5-lipoxygenase (5-LO), so as to review its mechanism of action and treatment prospect.

【Key words】 Atherosclerosis; Inflammation; Biological markers; Review

针对动脉粥样硬化发病机制的研究已经持续100余年。上世纪50年代即有文献报道胆固醇与动脉粥样硬化之间的关系。1986年，Jonasson等[1]发现，氧化修饰低密度脂蛋白胆固醇(ox-LDL-C)经清道夫受体被巨噬细胞吞噬，首次将炎性细胞与动脉壁脂质沉积相联系。1999年，Ross[2]将“动脉粥样硬化”进一步定义为血管壁炎症性退行性变，认为动脉粥样硬化始于血管内皮损伤致单核细胞和T淋巴细胞浸润，炎症反应参与动脉粥样硬化的发生发展及向易损性转化的过程。这一理论沿用至今，围绕炎症反应机制的研究一直是动脉粥样硬化研究的热点。1992年，Kannel等[3]研究显示，外周血炎性细胞计数与心血管事件风险存在相关性，这一结论将炎症反应与动脉粥样硬化的关系提升至临床层面。此后的研究显示，多种炎性因子均与心脑血管事件风险增加相关[4-5]。某些全身性炎性标志物可以筛查无症状性动脉粥样硬化、评价血栓事件风险并对高危患者进行干预。目前已有多项临床试验研究抗炎症反应对延缓动脉粥样硬化进展、预防冠心病或脑卒中的作用[6-7]，证实仅少数炎性因子可应用于临床。本文对传统和新型炎性标志物的临床意义和治疗前景进行概述。

一、动脉粥样硬化斑块炎性标志物

1. C-反应蛋白 C-反应蛋白(CRP)是炎症反应急性期的非特异性标志物，是目前研究最广泛的炎性标志物。其具有五聚体环形蛋白结构[8]，主要由肝脏在白细胞介素-6(IL-6)的刺激下合成，少部分由斑块内平滑肌细胞和巨噬细胞生成[9]。主要作用是激活补体系统并介导吞噬作用[10]，参与血管炎症反应和动脉粥样硬化进展。有研究显示，高水平的

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C-反应蛋白与缺血性心脑血管病相关[11]。一项长达12年的临床试验显示，血清C-反应蛋白水平升高的无症状性动脉粥样硬化患者心血管事件发生率增加58%[12]。因此，C-反应蛋白与其他已知的传统危险因素共同成为无症状性动脉粥样硬化患者启动调脂治疗的指标[13]。外周血C-反应蛋白检测方法具有稳定性高、可重复性高和敏感性高的特点，与普通检测方法相比，超敏C-反应蛋白（hs-CRP）能够更敏感地检出血液样本中的微量C-反应蛋白水平，常用检测方法有免疫比浊法或酶联免疫吸附试验（ELISA）。目前对C-反应蛋白表达上调尚无针对性治疗药物，有文献报道，他汀类调脂药能够在减少脑卒中和心血管事件的同时降低血清C-反应蛋白水平[14]。

2. 白细胞介素-1β　白细胞介素-1（IL-1）是拥有11名成员的蛋白家族，是主要作用于血管内皮细胞和平滑肌细胞的炎性因子。其中，IL-1β主要由单核细胞和巨噬细胞分泌进入血液循环，通过与IL-1受体（IL-1R）结合发挥上调血管细胞黏附分子（VCAM）、促进血管平滑肌增生的作用，从而加速动脉粥样硬化进展，相反，抑制IL-1β表达可以延缓斑块进展[15]。相关研究显示，动脉粥样硬化患者血浆IL-1β水平升高[16]，*IL-1β*基因多态性与血管再狭窄相关[17]。目前正在进行的临床试验研究抗IL-1单克隆抗体对动脉粥样硬化或心血管病的作用，尽管证实抗IL-1单克隆抗体可以增加冠状动脉血流储备、改善内皮功能、降低炎性标志物水平[18]，但尚无大样本的临床试验证实其可以有效预防缺血性事件的发生。

3. 白细胞介素-17　白细胞介素-17（IL-17）是近年发现的与动脉粥样硬化相关的细胞因子家族，其蛋白结构特征为含高度保守的4个胱氨酸残基，由辅助性T细胞（Th）、中性粒细胞、单核细胞、自然杀伤T细胞（NKT），或血管平滑肌细胞和内皮细胞产生[19]。IL-17通过激活多种信号转导通路调节动脉粥样硬化过程，如核因子-κB（NF-κB）、P38、细胞外信号调节激酶（ERK）1/2和活化蛋白1（AP-1）[20]。研究显示，IL-17在动脉粥样硬化中具有双面性，同时具有促动脉粥样硬化和抗动脉粥样硬化的作用：既可以诱导趋化因子释放，募集中性粒细胞和单核细胞向动脉粥样硬化病变迁移，刺激巨噬细胞释放IL-6、肿瘤坏死因子-α（TNF-α）和IL-1β以增加斑块易损性[21]，又可以促进斑块内血管平滑肌细胞和胶原增生以维持斑块稳定性[22]。Hot等[23]发现，辛伐他汀可以降低血管内皮细胞IL-17表达水平，但其他研究并未发现类似结果[24]。此外，抗IL-17单克隆抗体对动脉粥样硬化的作用也正在研究中[25]。目前尚缺乏针对IL-17表达上调的治疗药物。

4. 干扰素　干扰素（IFN）是内源性和获得性免疫调节机制中的重要成分，主要由3个亚型组成，其中Ⅰ和Ⅱ型在免疫调节中发挥重要作用[26]。干扰素可以激活斑块中的巨噬细胞，后者是动脉粥样硬化病变的重要成分[27]；激活的巨噬细胞亦可以增加干扰素的合成，促使白细胞向病变聚集，相反，抑制干扰素表达可以减少巨噬细胞的聚集[21]。此外，干扰素在血管内皮细胞激活和泡沫细胞形成中均发挥重要作用。动脉粥样硬化后期，干扰素还可以促进巨噬细胞凋亡和疾病进展[28]。尽管干扰素具有肯定的促动脉粥样硬化作用，但试图通过抑制干扰素表达而减轻动脉粥样硬化的临床试验并未获得成功，主要原因可能与严重的感染并发症有关[26]。现有的临床经验仍提示我们，采用抑制干扰素表达的短疗程、高针对性治疗动脉粥样硬化值得进一步尝试。

5. 肿瘤坏死因子-α　肿瘤坏死因子-α作为炎性因子参与多种慢性炎症反应过程，可以通过CD40/CD40L受体与T或B淋巴细胞相结合，还可以作用于肿瘤坏死因子受体相关因子（TRAF）[29]。肿瘤坏死因子-α致动脉粥样硬化的作用包括上调血管细胞黏附分子、募集巨噬细胞、增加微血管通透性[30]，以及调节一氧化氮合成致血管内皮功能障碍[31]。动物实验显示，*TNF-αR*基因敲除大鼠的斑块体积减少40%，且细胞间黏附分子-1（ICAM-1）、血管细胞黏附分子-1和单核细胞趋化蛋白-1（MCP-1）等炎性因子表达水平降低[32]。临床研究显示，动脉粥样硬化患者斑块内肿瘤坏死因子-α表达水平升高，且与动脉粥样硬化程度相关[33]。抗肿瘤坏死因子-α单克隆抗体治疗类风湿性关节炎（RA）过程中，动脉粥样硬化炎性标志物、颈动脉内-中膜厚度（IMT）和血管事件发生率均显著下降，这也为肿瘤坏死因子-α参与动脉粥样硬化提供直接证据[34]。目前，针对肿瘤坏死因子-α表达上调的治疗仅应用于某些慢性炎症如类风湿性关节炎或炎症性肠病，尚未应用于其他疾病。

6. P-选择素　选择素（selectin）是血小板和血管内皮细胞表达的细胞表面糖蛋白，主要介导细胞间

相互作用。其中，P-选择素（P-selectin）主要表达于血小板α颗粒和血管内皮细胞Weibel-Palade小体，主要通过与白细胞P选择素糖蛋白配体-1（PSGL-1）相结合而发挥作用[35]。予P-选择素抑制剂可以有效减少血小板聚集和血小板与白细胞的粘附[36]。动脉粥样硬化早期，P-选择素介导白细胞在血管内皮的迁移和血小板的激活；病变形成后，参与纤维蛋白的形成[37]。动物实验显示，载脂蛋白E（ApoE）和低密度脂蛋白胆固醇（LDL-C）受体缺陷小鼠敲除*P-selectin*基因，可以显著减少斑块体积[38]。临床研究亦可在动脉粥样硬化患者的病变中检出P-选择素[39]。研究显示，不稳定型心绞痛患者斑块内P-选择素水平高于稳定型心绞痛患者[40]，且血清可溶性P-选择素表达变化与病死率呈正相关[41]。目前，临床试验已经证实抗P-选择素单克隆抗体治疗冠心病有效，可以减轻心肌损害[42]，其他作用尚待进一步研究。

7. 高密度脂蛋白胆固醇　高密度脂蛋白胆固醇（HDL-C）的主要生理功能是参与胆固醇逆向转运、减少血管细胞黏附分子和炎性因子释放、抑制泡沫细胞生成，从而发挥抗炎症反应作用、减轻动脉粥样硬化程度[43]。高密度脂蛋白胆固醇和极高密度脂蛋白胆固醇（VHDL-C）可以减少动脉壁脂质沉积，进而减小斑块体积。静脉滴注高密度脂蛋白胆固醇可以减少斑块内巨噬细胞数目和炎性因子水平[44]。研究显示，血浆高密度脂蛋白胆固醇表达变化与心血管事件发生率呈负相关，提示升高高密度脂蛋白胆固醇水平或增强其功能可以为动脉粥样硬化患者带来益处。目前尚无证据显示低水平的高密度脂蛋白胆固醇与预后不良相关。此外，慢性疾病患者存在高密度脂蛋白胆固醇功能障碍并具有促炎症反应作用[45]。目前有4项临床试验研究静脉滴注高密度脂蛋白胆固醇对冠状动脉粥样硬化的作用，但遗憾的是，无一项研究结果差异达到统计学意义[46-49]。

8. 分泌型磷脂酶A2　分泌型磷脂酶A2（sPLA2）和脂蛋白相关性磷脂酶A2（Lp-PLA2）可以催化甘油水解为溶血磷脂酸和游离脂肪酸，与动脉粥样硬化密切相关[50]。其中，sPLA2能够通过血管蛋白聚糖促进脂蛋白沉积而具有促炎症反应和动脉粥样硬化进展的作用，加速血小板激活和低密度脂蛋白胆固醇氧化[51]，且sPLA2表达变化与无症状性动脉粥样硬化患者预后呈负相关[52]。Lp-PLA2由*PLA2G7*基因编码，含441个氨基酸，主要由巨噬细胞和泡沫细胞合成，血液循环中约2/3的Lp-PLA2由低密度脂蛋白胆固醇携带。Lp-PLA2在动脉粥样硬化斑块中呈高表达，直接参与动脉粥样硬化进展和斑块破裂[53]，通过分泌溶血磷脂酰胆碱（LPC）和将非酯化脂肪酸氧化为氧化型低密度脂蛋白胆固醇，激活巨噬细胞和血管平滑肌细胞，导致血管内皮功能障碍而加速动脉粥样硬化进展[54-55]。多项研究显示，血浆Lp-PLA2水平与缺血性心脑血管病存在相关性，高水平的Lp-PLA2可以使无症状性动脉粥样硬化患者心血管病风险增加1.15～2.00倍且独立于其他传统心血管病危险因素[56-57]。然而，抑制sPLA2或Lp-PLA2表达的大样本临床试验均未获得临床获益的阳性结果[58-59]。因此，sPLA2和Lp-PLA2作为炎性标志物对动脉粥样硬化患者预后的临床价值尚不明确[60]。

9. 内皮糖蛋白　内皮糖蛋白（endoglin）是一种表达于血管内皮细胞和平滑肌细胞的跨膜糖蛋白二聚体[61]，作为肿瘤生长因子-β（TGF-β）受体，调节肿瘤生长因子-β的信号转导，与内皮型一氧化氮合酶（eNOS）表达、血管壁损伤、斑块内新生血管形成和斑块内胶原增生有关[62]。内皮糖蛋白在正常血管内皮表达水平极低，在冠状动脉和颈动脉斑块中，尤其是新生血管部位表达水平明显升高[63]。伴高脂血症、重度冠状动脉粥样硬化和急性心肌梗死的患者，或具有不稳定性斑块和斑块破裂的患者外周血内皮糖蛋白水平明显升高[64]。动脉粥样硬化进程中，内皮糖蛋白参与血管内皮损伤修复和新生血管形成，此外，还可以通过调节内皮型一氧化氮合酶释放以改善血管内皮功能。有文献报道，阿托伐他汀可以升高斑块内内皮糖蛋白表达水平、减小斑块体积[65]。然而，目前尚无抗内皮糖蛋白单克隆抗体应用于临床的报道。

10. 趋化因子受体　趋化因子（chemokine）是结构相似且具有趋化功能的细胞因子家族，根据氨基末端（N末端）胱氨酸残基位置可以分为两大亚组，CC趋化因子（C-C motif）和CXC趋化因子（C-X-C motif）。除具有趋化功能、募集白细胞向炎症部位迁移外，趋化因子还具有自身活性功能。动脉粥样硬化早期，血管内皮细胞释放CXC趋化因子配体，后者与CXC趋化因子受体（CXCR）相结合，从而促进单核细胞和中性粒细胞向动脉粥样硬化病变迁移[66]。Poupel等[67]采用CXC趋化因子受体1

(CXCR1)抑制剂缩小动脉粥样硬化动物模型病变范围并选择性抑制单核细胞粘附和募集。因此,趋化因子受体是治疗动脉粥样硬化的具有希望的靶点之一。关于抗CC趋化因子受体2(CCR2)单克隆抗体的Ⅱ期临床试验,采用单一剂量的抗CCR2单克隆抗体可以使血清超敏C-反应蛋白水平降低26.7%[68]。尽管上述动物实验和临床研究均证实抑制白细胞迁移可以阻止动脉粥样硬化进展,然而抗趋化因子受体抗体对动脉粥样硬化的作用并未在临床试验中得到证实[7]。

11.5脂氧合酶 5脂氧合酶(5-LO)主要由单核细胞和巨噬细胞释放,是生物合成白三烯的重要成分[69],主要作用是调节白三烯亚型白三烯B4(LTB4)和半胱氨酸白三烯的生成,增强白细胞与血管内皮的粘附,并且促进血管平滑肌细胞增生和迁移[70]。此外,白三烯作为炎症反应中的脂质介质还可以在中性粒细胞和T淋巴细胞诱导下增加单核细胞趋化蛋白-1和IL-6的释放。有研究显示,动脉粥样硬化斑块高表达5脂氧合酶,且与临床症状呈负相关[71]。5脂氧合酶曾认为是动脉粥样硬化中抑制炎症反应的治疗靶点,然而关于其抑制剂的临床试验并未获得阳性结果[72]。

二、动脉粥样硬化的抗炎症反应治疗前景

早在1970年即已开展抗动脉粥样硬化药物的临床试验[73],动物实验显示肾上腺皮质激素[74]和阿司匹林[75]对动脉粥样硬化的进展有抑制作用。此后,针对多条炎症反应通路以逆转动脉粥样硬化进展的尝试始终未曾停止,并有一些基础研究成果在临床试验中得到检验。本文综述近年来动脉粥样硬化炎症反应机制的研究进展,主要为临床前研究,然而,大多数动物实验取得成功的药物并未在临床试验中获得验证。目前,动脉粥样硬化的临床治疗仍以他汀类调脂药和抗血小板药物为主。随着对炎症反应机制研究的深入以及越来越多关于各种炎性因子的临床研究的开展,抗炎症反应治疗有望成为新的治疗靶点之一[7]。此外,通过特异性抗体进行免疫调节治疗也是动脉粥样硬化治疗的具有希望的途径[76]。对于动脉粥样硬化这一慢性疾病而言,新的治疗方法除考虑有效性外,还应考虑其药物不良反应和长期治疗带来的社会经济负担。除长期药物治疗外,亦应考虑采用短疗程药物治疗现有治疗方法难以控制的易损性斑块以达到稳定斑块、减少易损性的目的[77]。

参 考 文 献

[1] Jonasson L, Holm J, Skalli O, Bondjers G, Hansson GK. Regional accumulations of T cells, macrophages, and smooth muscle cells in the human atherosclerotic plaque. Arteriosclerosis, 1986, 6:131-138.

[2] Ross R. Atherosclerosis: an inflammatory disease. N Engl J Med, 1999, 340:115-126.

[3] Kannel WB, Anderson K, Wilson PW. White blood cell count and cardiovascular disease: insights from the Framingham Study. JAMA, 1992, 267:1253-1256.

[4] Shah PK. Biomarkers of plaque instability. Curr Cardiol Rep, 2014, 16:547.

[5] Gilstrap LG, Wang TJ. Biomarkers and cardiovascular risk assessment for primary prevention: an update. Clin Chem, 2012, 58:72-82.

[6] Kozarov E, Huber K, Wojta J. Infection-associated biomarkers of inflammation in atherosclerosis. Curr Pharm Des, 2015, 21: 1776-1782.

[7] Mendel I, Yacov N, Harats D, Breitbart E. Therapies targeting innate immunity for fighting inflammation in atherosclerosis. Curr Pharm Des, 2015, 21:1185-1195.

[8] Koenig W, Khuseyinova N. Biomarkers of atherosclerotic plaque instability and rupture. Arterioscler Thromb Vasc Biol, 2007, 27: 15-26.

[9] Calabró P, Willerson JT, Yeh ET. Inflammatory cytokines stimulated C-reactive protein production by human coronary artery smooth muscle cells. Circulation, 2003, 108:1930-1932.

[10] Stone PA, Kazil J. The relationships between serum C-reactive protein level and risk and progression of coronary and carotid atherosclerosis. Semin Vasc Surg, 2014, 27(3/4):138-142.

[11] Kaptoge S, Di Angelantonio E, Lowe G, Pepys MB, Thompson SG, Collins R, Danesh J; Emerging Risk Factors Collaboration. C-reactive protein concentration and risk of coronary heart disease, stroke, and mortality: an individual participant meta-analysis. Lancet, 2010, 375:132-140.

[12] Danesh J, Wheeler JG, Hirschfield GM, Eda S, Eiriksdottir G, Rumley A, Lowe GD, Pepys MB, Gudnason V. C-reactive protein and other circulating markers of inflammation in the prediction of coronary heart disease. N Engl J Med, 2004, 350: 1387-1397.

[13] Kaptoge S, Di Angelantonio E, Pennells L, Wood AM, White IR, Gao P, Walker M, Thompson A, Sarwar N, Caslake M, Butterworth AS, Amouyel P, Assmann G, Bakker SJ, Barr EL, Barrett-Connor E, Benjamin EJ, Björkelund C, Brenner H, Brunner E, Clarke R, Cooper JA, Cremer P, Cushman M, Dagenais GR, D'Agostino RB Sr, Dankner R, Davey-Smith G, Deeg D, Dekker JM, Engström G, Folsom AR, Fowkes FG, Gallacher J, Gaziano JM, Giampaoli S, Gillum RF, Hofman A, Howard BV, Ingelsson E, Iso H, Jørgensen T, Kiechl S, Kitamura A, Kiyohara Y, Koenig W, Kromhout D, Kuller LH, Lawlor DA, Meade TW, Nissinen A, Nordestgaard BG, Onat A, Panagiotakos DB, Psaty BM, Rodriguez B, Rosengren A, Salomaa V, Kauhanen J, Salonen JT, Shaffer JA, Shea S, Ford I, Stehouwer CD, Strandberg TE, Tipping RW, Tosetto A, Wassertheil-Smoller S, Wennberg P, Westendorp RG, Whincup PH, Wilhelmsen L, Woodward M, Lowe GD, Wareham NJ, Khaw KT, Sattar N, Packard CJ, Gudnason V, Ridker PM, Pepys MB, Thompson SG, Danesh J; Emerging Risk Factors Collaboration. C-reactive protein, fibrinogen, and cardiovascular disease prediction. N Engl J Med, 2012, 367:1310-1320.

[14] Ridker PM, Danielson E, Fonseca FA, Genest J, Gotto AM Jr, Kastelein JJ, Koenig W, Libby P, Lorenzatti AJ, MacFadyen JG,

Nordestgaard BG, Shepherd J, Willerson JT, Glynn RJ; JUPITER Study Group. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. N Engl J Med, 2008, 359:2195-2207.

[15] Ishida Y, Migita K, Izumi Y, Nakao K, Ida H, Kawakami A, Abiru S, Ishibashi H, Eguchi K, Ishii N. The role of IL-18 in the modulation of matrix metalloproteinases and migration of human natural killer (NK) cells. FEBS Lett, 2004, 569(1-3):156-160.

[16] Patti G, Di Sciascio G, D´Ambrosio A, Dicuonzo G, Abbate A, Dobrina A. Prognostic value of interleukin-1 receptor antagonist in patients undergoing percutaneous coronary intervention. Am J Cardiol, 2002, 89:372-376.

[17] Francis SE, Camp NJ, Dewberry RM, Gunn J, Syrris P, Carter ND, Jeffery S, Kaski JC, Cumberland DC, Duff GW, Crossman DC. Interleukin-1 receptor antagonist gene polymorphism and coronary artery disease. Circulation, 1999, 99:861-866.

[18] Ridker PM. Closing the loop on inflammation and atherothrombosis: why perform the CIRT and CANTOS trials? Trans Am Clin Climatol Assoc, 2013, 124:174-190.

[19] Galkina E, Ley K. Immune and inflammatory mechanisms of atherosclerosis. Annu Rev Immunol, 2009, 27:165-197.

[20] Gaffen SL. Structure and signalling in the IL-17 receptor family. Nat Rev Immunol, 2009, 9:556-567.

[21] Smith E, Prasad KM, Butcher M, Dobrian A, Kolls JK, Ley K, Galkina E. Blockade of interleukin-17A results in reduced atherosclerosis in apolipoprotein E-deficient mice. Circulation, 2010, 121:1746-1755.

[22] Gisterå A, Robertson AK, Andersson J, Ketelhuth DF, Ovchinnikova O, Nilsson SK, Lundberg AM, Li MO, Flavell RA, Hansson GK. Transforming growth factor-beta signaling in T cells promotes stabilization of atherosclerotic plaques through an interleukin-17-dependent pathway. Sci Transl Med, 2013, 5:196.

[23] Hot A, Lavocat F, Lenief V, Miossec P. Simvastatin inhibits the pro-inflammatory and pro-thrombotic effects of IL-17 and TNF-alpha on endothelial cells. Ann Rheum Dis, 2013, 72:754-760.

[24] Erbel C, Dengler TJ, Wangler S, Lasitschka F, Bea F, Wambsganss N, Hakimi M, Böckler D, Katus HA, Gleissner CA. Expression of IL-17A in human atherosclerotic lesions is associated with increased inflammation and plaque vulnerability. Basic Res Cardiol, 2011, 106:125-134.

[25] Busse WW, Holgate S, Kerwin E, Chon Y, Feng J, Lin J, Lin SL. Randomized, double-blind, placebo-controlled study of brodalumab, a human anti-IL-17 receptor monoclonal antibody, in moderate to severe asthma. Am J Respir Crit Care Med, 2013, 188:1294-1302.

[26] Boshuizen MC, de Winther MP. Interferons as essential modulators of atherosclerosis. Arterioscler Thromb Vasc Biol, 2015, 35:1579-1588.

[27] Goossens P, Gijbels MJ, Zernecke A, Eijgelaar W, Vergouwe MN, van der Made I, Vanderlocht J, Beckers L, Buurman WA, Daemen MJ, Kalinke U, Weber C, Lutgens E, de Winther MP. Myeloid type I interferon signaling promotes atherosclerosis by stimulating macrophage recruitment to lesions. Cell Metab, 2010, 12:142-153.

[28] Inagaki Y, Yamagishi S, Amano S, Okamoto T, Koga K, Makita Z. Interferon-gamma-induced apoptosis and activation of THP-1 macrophages. Life Sci, 2002, 71:2499-2508.

[29] Ha H, Han D, Choi Y. TRAF-mediated TNFR-family signaling. Curr Protoc Immunol, 2009, Chapter 11:Unit11.9D.

[30] Mackesy DZ, Goalstone ML. Insulin augments tumor necrosis factor-alpha stimulated expression of vascular cell adhesion molecule-1 in vascular endothelial cells. J Inflamm (Lond), 2011, 8:34.

[31] Gao X, Xu X, Belmadani S, Park Y, Tang Z, Feldman AM, Chilian WM, Zhang C. TNF-alpha contributes to endothelial dysfunction by upregulating arginase in ischemia/reperfusion injury. Arterioscler Thromb Vasc Biol, 2007, 27:1269-1275.

[32] Brånén L, Hovgaard L, Nitulescu M, Bengtsson E, Nilsson J, Jovinge S. Inhibition of tumor necrosis factor-alpha reduces atherosclerosis in apolipoprotein E knockout mice. Arterioscler Thromb Vasc Biol, 2004, 24:2137-2142.

[33] Tipping PG, Hancock WW. Production of tumor necrosis factor and interleukin-1 by macrophages from human atheromatous plaques. Am J Pathol, 1993, 142:1721-1728.

[34] Barnabe C, Martin BJ, Ghali WA. Systematic review and meta-analysis: anti-tumor necrosis factor alpha therapy and cardiovascular events in rheumatoid arthritis. Arthritis Care Res (Hoboken), 2011, 63:522-529.

[35] Frenette PS, Denis CV, Weiss L, Jurk K, Subbarao S, Kehrel B, Hartwig JH, Vestweber D, Wagner DD. P-selectin glycoprotein ligand 1 (PSGL-1) is expressed on platelets and can mediate platelet-endothelial interactions in vivo. J Exp Med, 2000, 191:1413-1422.

[36] Merten M, Thiagarajan P. P-selectin expression on platelets determines size and stability of platelet aggregates. Circulation, 2000, 102:1931-1936.

[37] Vestweber D, Blanks JE. Mechanisms that regulate the function of the selectins and their ligands. Physiol Rev, 1999, 79:181-213.

[38] Kumar A, Hoover JL, Simmons CA, Lindner V, Shebuski RJ. Remodeling and neointimal formation in the carotid artery of normal and P-selectin-deficient mice. Circulation, 1997, 96:4333-4342.

[39] Johnson-Tidey RR, McGregor JL, Taylor PR, Poston RN. Increase in the adhesion molecule P-selectin in endothelium overlying atherosclerotic plaques: coexpression with intercellular adhesion molecule-1. Am J Pathol, 1994, 144:952-961.

[40] Tenaglia AN, Buda AJ, Wilkins RG, Barron MK, Jeffords PR, Vo K, Jordan MO, Kusnick BA, Lefer DJ. Levels of expression of P-selectin, E-selectin, and intercellular adhesion molecule-1 in coronary atherectomy specimens from patients with stable and unstable angina pectoris. Am J Cardiol, 1997, 79:742-747.

[41] Scialla JJ, Plantinga LC, Kao WH, Jaar B, Powe NR, Parekh RS. Soluble P-selectin levels are associated with cardiovascular mortality and sudden cardiac death in male dialysis patients. Am J Nephrol, 2011, 33:224-230.

[42] Tardif JC, Tanguay JF, Wright SR, Duchatelle V, Petroni T, Grégoire JC, Ibrahim R, Heinonen TM, Robb S, Bertrand OF, Cournoyer D, Johnson D, Mann J, Guertin MC, L´Allier PL. Effects of the P-selectin antagonist inclacumab on myocardial damage after percutaneous coronary intervention for non-ST-segment elevation myocardial infarction: results of the SELECT-ACS trial. J Am Coll Cardiol, 2013, 61:2048-2055.

[43] Barter PJ, Baker PW, Rye KA. Effect of high-density lipoproteins on the expression of adhesion molecules in endothelial cells. Curr Opin Lipidol, 2002, 13:285-288.

[44] Ibanez B, Giannarelli C, Cimmino G, Santos-Gallego CG, Alique M, Pinero A, Vilahur G, Fuster V, Badimon L, Badimon JJ. Recombinant HDL (Milano) exerts greater anti-inflammatory and plaque stabilizing properties than HDL (wild-type). Atherosclerosis, 2012, 220:72-77.

[45] Namiri-Kalantari R, Gao F, Chattopadhyay A, Wheeler AA, Navab KD, Farias-Eisner R, Reddy ST. The dual nature of

HDL: anti-inflammatory and pro-inflammatory. Biofactors, 2015, 41:153-159.

[46] Waksman R, Torguson R, Kent KM, Pichard AD, Suddath WO, Satler LF, Martin BD, Perlman TJ, Maltais JA, Weissman NJ, Fitzgerald PJ, Brewer HB Jr. A first - in - man, randomized, placebo-controlled study to evaluate the safety and feasibility of autologous delipidated high-density lipoprotein plasma infusions in patients with acute coronary syndrome. J Am Coll Cardiol, 2010, 55:2727-2735.

[47] Tardif JC, Ballantyne CM, Barter P, Dasseux JL, Fayad ZA, Guertin MC, Kastelein JJ, Keyserling C, Klepp H, Koenig W, L´Allier PL, Lespérance J, Lüscher TF, Paolini JF, Tawakol A, Waters DD; Can HDL Infusions Significantly QUicken Atherosclerosis REgression (CHI - SQUARE) Investigators. Effects of the high-density lipoprotein mimetic agent CER-001 on coronary atherosclerosis in patients with acute coronary syndromes: a randomized trial. Eur Heart J, 2014, 35:3277-3286.

[48] Nissen SE, Tsunoda T, Tuzcu EM, Schoenhagen P, Cooper CJ, Yasin M, Eaton GM, Lauer MA, Sheldon WS, Grines CL, Halpern S, Crowe T, Blankenship JC, Kerensky R. Effect of recombinant ApoA - Ⅰ Milano on coronary atherosclerosis in patients with acute coronary syndromes: a randomized controlled trial. JAMA, 2003, 290:2292-2300.

[49] Tardif JC, Grégoire J, L´Allier PL, Ibrahim R, Lespérance J, Heinonen TM, Kouz S, Berry C, Basser R, Lavoie MA, Guertin MC, Rodés-Cabau J; Effect of rHDL on Atherosclerosis-Safety and Efficacy (ERASE) Investigators. Effects of reconstituted high-density lipoprotein infusions on coronary atherosclerosis: a randomized controlled trial. JAMA, 2007, 297:1675-1682.

[50] Oörni K, Kovanen PT. Lipoprotein modification by secretory phospholipase A(2) enzymes contributes to the initiation and progression of atherosclerosis. Curr Opin Lipidol, 2009, 20:421-427.

[51] Sartipy P, Camejo G, Svensson L, Hurt - Camejo E. Phospholipase A (2) modification of low density lipoproteins forms small high density particles with increased affinity for proteoglycans and glycosaminoglycans. J Biol Chem, 1999, 274: 25913-25920.

[52] Boekholdt SM, Keller TT, Wareham NJ, Luben R, Bingham SA, Day NE, Sandhu MS, Jukema JW, Kastelein JJ, Hack CE, Khaw KT. Serum levels of type Ⅱ secretory phospholipase A2 and the risk of future coronary artery disease in apparently healthy men and women: the EPIC - Norfolk Prospective Population Study. Arterioscler Thromb Vasc Biol, 2005, 25: 839-846.

[53] Anderson JL. Lipoprotein - associated phospholipase A2: an independent predictor of coronary artery disease events in primary and secondary prevention. Am J Cardiol, 2008, 101:23-33.

[54] Zalewski A, Macphee C. Role of lipoprotein - associated phospholipase A2 in atherosclerosis: biology, epidemiology, and possible therapeutic target. Arterioscler Thromb Vasc Biol, 2005, 25:923-931.

[55] Shi Y, Zhang P, Zhang L, Osman H, Mohler ER 3rd, Macphee C, Zalewski A, Postle A, Wilensky RL. Role of lipoprotein - associated phospholipase A2 in leukocyte activation and inflammatory responses. Atherosclerosis, 2007, 191:54-62.

[56] Packard CJ, O´Reilly DS, Caslake MJ, McMahon AD, Ford I, Cooney J, Macphee CH, Suckling KE, Krishna M, Wilkinson FE, Rumley A, Lowe GD; West of Scotland Coronary Prevention Study Group. Lipoprotein - associated phospholipase A2 as an independent predictor of coronary heart disease. N Engl J Med, 2000, 343:1148-1155.

[57] Ballantyne CM, Hoogeveen RC, Bang H, Coresh J, Folsom AR, Heiss G, Sharrett AR. Lipoprotein-associated phospholipase A2, high - sensitivity C - reactive protein, and risk for incident coronary heart disease in middle-aged men and women in the Atherosclerosis Risk in Communities (ARIC) study. Circulation, 2004, 109:837-842.

[58] STABILITY Investigators; White HD, Held C, Stewart R, Tarka E, Brown R, Davies RY, Budaj A, Harrington RA, Steg PG, Ardissino D, Armstrong PW, Avezum A, Aylward PE, Bryce A, Chen H, Chen MF, Corbalan R, Dalby AJ, Danchin N, De Winter RJ, Denchev S, Diaz R, Elisaf M, Flather MD, Goudev AR, Granger CB, Grinfeld L, Hochman JS, Husted S, Kim HS, Koenig W, Linhart A, Lonn E, López-Sendón J, Manolis AJ, Mohler ER 3rd, Nicolau JC, Pais P, Parkhomenko A, Pedersen TR, Pella D, Ramos-Corrales MA, Ruda M, Sereg M, Siddique S, Sinnaeve P, Smith P, Sritara P, Swart HP, Sy RG, Teramoto T, Tse HF, Watson D, Weaver WD, Weiss R, Viigimaa M, Vinereanu D, Zhu J, Cannon CP, Wallentin L. Darapladib for preventing ischemic events in stable coronary heart disease. N Engl J Med, 2014, 370:1702-1711.

[59] Mullard A. GSK´s darapladib failures dim hopes for anti-inflammatory heart drugs. Nat Rev Drug Discov, 2014, 13:481-482.

[60] Nicholls SJ, Kastelein JJ, Schwartz GG, Bash D, Rosenson RS, Cavender MA, Brennan DM, Koenig W, Jukema JW, Nambi V, Wright RS, Menon V, Lincoff AM, Nissen SE; VISTA - 16 Investigators. Varespladib and cardiovascular events in patients with an acute coronary syndrome: the VISTA - 16 randomized clinical trial. JAMA, 2014, 311:252-262.

[61] Cheifetz S, Bellón T, Calés C, Vera S, Bernabeu C, Massagué J, Letarte M. Endoglin is a component of the transforming growth factor-beta receptor system in human endothelial cells. J Biol Chem, 1992, 267:19027-19030.

[62] Nachtigal P, Zemankova Vecerova L, Rathouska J, Strasky Z. The role of endoglin in atherosclerosis. Atherosclerosis, 2012, 224:4-11.

[63] Luque A, Slevin M, Turu MM, Juan - Babot O, Badimon L, Krupinski J. CD105 positive neovessels are prevalent in early stage carotid lesions, and correlate with the grade in more advanced carotid and coronary plaques. J Angiogenes Res, 2009, 1:6.

[64] Cui S, Lü SZ, Chen YD, He GX, Meng LJ, Liu JP, Song ZY, Liu XL, Song XT, Ge CJ, Liu H. Relationship among soluble CD105, hypersensitive C-reactive protein and coronary plaque morphology: an intravascular ultrasound study. Chin Med J (Engl), 2008, 121:128-132.

[65] Vecerova L, Strasky Z, Rathouska J, Slanarova M, Brcakova E, Micuda S, Nachtigal P. Activation of TGF-beta receptors and Smad proteins by atorvastatin is related to reduced atherogenesis in ApoE/LDLR double knockout mice. J Atheroscler Thromb, 2012, 19:115-126.

[66] Zhou Z, Subramanian P, Sevilmis G, Globke B, Soehnlein O, Karshovska E, Megens R, Heyll K, Chun J, Saulnier-Blache JS, Reinholz M, van Zandvoort M, Weber C, Schober A. Lipoprotein-derived lysophosphatidic acid promotes atherosclerosis by releasing CXCL1 from the endothelium. Cell Metab, 2011, 13:592-600.

[67] Poupel L, Boissonnas A, Hermand P, Dorgham K, Guyon E, Auvynet C, Charles FS, Lesnik P, Deterre P, Combadiere C. Pharmacological inhibition of the chemokine receptor, CX3CR1, reduces atherosclerosis in mice. Arterioscler Thromb Vasc Biol, 2013, 33:2297-2305.

[68] van Breukelen-van der Stoep DF, Klop B, van Zeben D, Hazes

JM, Castro Cabezas M. Cardiovascular risk in rheumatoid arthritis: how to lower the risk? Atherosclerosis, 2013, 231:163-172.
[69] Mehrabian M, Allayee H, Wong J, Shi W, Wang XP, Shaposhnik Z, Funk CD, Lusis AJ. Identification of 5-lipoxygenase as a major gene contributing to atherosclerosis susceptibility in mice. Circ Res, 2002, 91:120-126.
[70] Cipollone F, Mezzetti A, Fazia ML, Cuccurullo C, Iezzi A, Ucchino S, Spigonardo F, Bucci M, Cuccurullo F, Prescott SM, Stafforini DM. Association between 5-lipoxygenase expression and plaque instability in humans. Arterioscler Thromb Vasc Biol, 2005, 25:1665-1670.
[71] Qiu H, Gabrielsen A, Agardh HE, Wan M, Wetterholm A, Wong CH, Hedin U, Swedenborg J, Hansson GK, Samuelsson B, Paulsson-Berne G, Haeggström JZ. Expression of 5-lipoxygenase and leukotriene A4 hydrolase in human atherosclerotic lesions correlates with symptoms of plaque instability. Proc Natl Acad Sci USA, 2006, 103:8161-8166.
[72] Tardif JC, L'allier PL, Ibrahim R, Grégoire JC, Nozza A, Cossette M, Kouz S, Lavoie MA, Paquin J, Brotz TM, Taub R, Pressacco J. Treatment with 5-lipoxygenase inhibitor VIA-2291 (Atreleuton) in patients with recent acute coronary syndrome. Circ Cardiovasc Imaging, 2010, 3:298-307.
[73] Shimamoto T, Atsumi T, Yamashita S, Motomiya T, Isokane N, Ishioka T, Sakuma A. Clinical pharmacologic evaluation of the antiatherosclerotic agent, pyridinolcarbamate: a double-blind crossover trial in the treatment of atherosclerosis obliterans. Am Heart J, 1970, 79:5-19.
[74] Bailey JM, Butler J. Anti-inflammatory drugs in experimental atherosclerosis. Ⅰ: relative potencies for inhibiting plaque formation. Atherosclerosis, 1973, 17:515-522.
[75] Wood L. Treatment of atherosclerosis and thrombosis with aspirin. Lancet, 1972, 2:532-534.
[76] van Leeuwen M, Kemna MJ, de Winther MP, Boon L, Duijvestijn AM, Henatsch D, Bos NA, Gijbels MJ, Tervaert JW. Passive immunization with hypochlorite-oxLDL specific antibodies reduces plaque volume in LDL receptor-deficient mice. PLoS One, 2013, 8:E68039.
[77] Maranhao RC, Leite Jr AC. Development of anti-atherosclerosis therapy based on the inflammatory and proliferative aspects of the disease. Curr Pharm Des, 2015, 21:1196-1204.

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·小词典·

中英文对照名词词汇（二）

反转角 flip angle（FA）
反转时间 inversion time（TI）
放射免疫沉淀法 radioimmunoprecipitation assay（RIPA）
非运动症状 non-motor symptoms（NMS）
分泌型磷脂酶A2 secretory phospholipase A2（sPLA2）
风疹病毒 rubella virus（RV）
辅助性T细胞 T helper cell（Th）
复发-缓解型多发性硬化 relapsing-remitting multiple sclerosis（RRMS）
复发性视神经脊髓炎 relapsing neuromyelitis optica（RNMO）
复发性视神经炎 recurrent optic neuritis（RON）
复合动作电位 compound action potential（CAP）
复合肌肉动作电位 compound muscle action potential（CMAP）
副肿瘤性边缘性脑炎 paraneoplastic limbic encephalitis（PLE）
副肿瘤综合征 neurological paraneoplastic syndrome（PNS）
富亮氨酸胶质瘤失活基因1 leucine-rich glioma-inactivated 1（LGI1）
改良Rankin量表 modified Rankin Scale（mRS）
干燥综合征 Sjögren's syndrome（SS）
高密度脂蛋白胆固醇 high-density lipoprotein cholesterol（HDL-C）
弓形虫 toxoplasma（TOX）
谷氨酸受体 glutamate receptor（GluR）
寡克隆区带 oligoclonal bands（OB）
光学相干断层扫描术 optical coherence tomography（OCT）
广泛成就测验修订版 Wide Range Achievement Test-Revised（WRAT-R）
国际视神经脊髓炎诊断小组 International Panel for Neuromyelitis Optica Diagnosis（IPND）
国家成人阅读测验 National Adult Reading Test（NART）
过氧化氢 hydrogen peroxide（H_2O_2）
汉语词语阅读测验 Chinese Words Reading Test（CWRT）
核因子-κB nuclear factor-κB（NF-κB）
黑色素性神经鞘瘤 melanotic schwannoma（MS）
横贯性脊髓炎 transverse myelitis（TM）
花生四烯酸 arachidonic acid（AA）
化学发光免疫分析 chemiluminescence immunoassay（CIA）
黄嘌呤脱氢酶 xanthine dehydrogenase（XD）
黄嘌呤氧化酶 xanthine oxidase（XO）
回波时间 echo time（TE）
活化蛋白1 activator protein 1（AP-1）
霍普金斯词语学习测验修订版 Hopkins Verbal Learning Test-Revised（HVLT-R）
霍奇金淋巴瘤 Hodgkin's lymphoma（HL）
肌酸激酶 creatine kinase（CK）
积极降低胆固醇预防脑卒中再发研究 Stroke Prevention by Aggressive Reduction in Cholesterol Levels（SPARCL）study
激光寻址免疫磁珠分析法 addressable laser bead immunoassay（ALBIA）
激励次数 number of excitation（NEX）
吉兰-巴雷综合征 Guillain-Barré syndrome（GBS）