Hans Journal of Biomedicine 生物医学, 2023, 13(2), 219-227
Published Online April 2023 in Hans. https://www.hanspub.org/journal/hjbm
https://doi.org/10.12677/hjbm.2023.132025

Hans汉斯

白细胞介素-8在炎症反应中的作用及其表达调控机制

朱秀云，吴　敏*

浙江师范大学生命科学学院，浙江　金华

收稿日期：2023年2月23日；录用日期：2023年4月4日；发布日期：2023年4月19日

摘　要

白细胞介素-8是诱导炎症反应发生的主要趋化因子。其前体含99个氨基酸残基，经裂解活化后则由细胞分泌释放。白细胞介素-8可与免疫细胞和肿瘤细胞的细胞膜上受体结合，主要经由偶联G蛋白来激活下游相关的信号通路，如丝裂原活化蛋白激酶、磷脂酰肌醇-3-激酶、蛋白激酶C等。本综述将重点阐述这些信号通路的活化机制及其生理和免疫功能。此外，也将概括说明诱导白细胞介素-8表达的转录因子和促进其分泌的机制，并详述主要转录因子，核因子-κB的作用机理。了解白细胞介素-8的功能和调控机制，有助于阐明炎症反应发生的过程和开发新的抗炎药物。

关键词

白细胞介素-8，炎症，信号通路，激酶，NF-κB

Role and Expression Regulation of Interleukin-8 in Inflammatory Reaction

Xiuyun Zhu, Min Wu*

College of Life Sciences, Zhejiang Normal University, Jinhua Zhejiang

Received: Feb. 23rd, 2022; accepted: Apr. 4th, 2023; published: Apr. 19th, 2023

Abstract

Interleukin-8 (IL-8) is a major chemotaxin that elicits the inflammation response. The proprotein of IL-8 including 99 amino acid residues is activated by proteolysis and then secreted by the cell. IL-8 binds to the receptor on the cell membrane of immune or tumor cells and via G protein-coupled

*通讯作者。

文章引用: 朱秀云, 吴敏. 白细胞介素-8 在炎症反应中的作用及其表达调控机制[J]. 生物医学, 2023, 13(2): 219-227.
DOI: 10.12677/hjbm.2023.132025

mechanisms stimulates downstream signaling pathways, such as mitogen-activated protein kinase, inositol phosphate-3 kinase and protein kinase C, etc. This review mainly focuses on the activation mechanism of these signaling pathways and related physiological function and immune system. In addition, the review covers the transcription factors that stimulate IL-8 expression and secretion with a great attention on the major factor, nuclear factor-κB. Understanding the function and regulation of IL-8 may elucidate the development of inflammation and discover new anti-inflammatory drugs.

Keywords

Interleukin-8, Inflammation, Signal Pathway, Kinase, NF-κB

1. 引言

人体因感染或损伤而激活免疫系统，引发炎症反应[1]。炎症发生的过程与许多大小为 8~10 kD 的多肽分子－趋化因子有关[2] [3] [4]。其中白细胞介素-8 (Interleukin-8, IL-8)，又称 CXCL8，是典型的趋化因子[5] [6]。当细菌被上皮细胞表面 Toll-like 受体识别后，会诱导白细胞介素-8 的表达和分泌[7] [8]。另外，巨噬细胞也会大量释放白细胞介素-8，以招募其他白细胞到感染部位，进而引发炎症反应[1]。炎症环境的存在，也会进一步诱导呼吸道上皮细胞、平滑肌细胞和血管内皮细胞大量释放白细胞介素-8，产生免疫反应[1] [9] [10]。研究发现在人脐静脉内皮细胞中，白细胞介素-8 经过重组人类白细胞介素-1B 处理 24 小时后可被诱导产生，另外的组胺处理使人脐静脉内皮细胞以及粘膜内皮细胞的白细胞介素-8 分泌量增加一倍[9]。还有研究指出，血清 2 型或 4 型肺炎球菌即使在没有多糖胶囊的情况下，也只能从上皮细胞系中诱导的白细胞介素-8 表达[11]。A549 细胞与用维生素 D 分化的巨噬细胞样 THP-1 细胞系或单核细胞来源的巨噬细胞共培养增强了白细胞介素-8 的释放[11]。

白细胞介素-8 前体蛋白含有 99 个氨基酸残基[12] [13]，经过加工后，在非免疫细胞中形成 77 个氨基酸的活性蛋白[14] [15]。在单核细胞和巨噬细胞中形成的活性蛋白则含 72 个氨基酸[2] [4] [14]。活化成熟的白细胞介素-8 含有四个半胱氨酸残基且没有糖基化[16]。由于包含许多碱性氨基酸，如赖氨酸和精氨酸，成熟的白细胞介素-8 的等电点大于 8.5 [17]。

综上所述，白细胞介素-8 是促使炎症反应发生的主要趋化因子，所以了解其诱导分泌机制将有助于研发新的抗炎药物。因此，以下将探讨白细胞介素-8 的功能及调控机制。

2. 白细胞介素-8 的功能及其调控的信号通路

白细胞介素-8 在炎症反应中主要有两个作用，一是参与中性粒细胞的激活，诱导中性粒细胞和其他免疫细胞向感染部位迁移[18] [19]，以促进炎症反应的发生。二是在免疫细胞(主要是中性粒细胞)到达炎症部位后，白细胞介素-8 可诱导其产生吞噬作用[20] [21] 。

已知白细胞介素-8 与其受体结合会增加细胞内 Ca^{2+}浓度[22] [23]。白细胞介素-8 通过与细胞膜表面受体结合来发挥功能，而其受体有两种：白细胞介素-8 受体 α (IL-8RA)，或称 CXCR1 [24] [25]；白细胞介素-8 受体 β (IL-8RB)，或称 CXCR2 [24] [25]。白细胞介素-8 与 CXCR1 的结合具有高特异性[26] [27]，而与表达在基质细胞、内皮细胞和肿瘤细胞上的 CXCR2 结合的特异性较低[26][27][28]。CXCR1/2 为细

胞表面 G 蛋白偶联受体，它们可活化 G 蛋白相关的许多信号通路[24] [25]，包括丝裂原活化蛋白激酶(MAPK)、磷脂酰肌醇-3-激酶(PI3K)、蛋白激酶 C(PKC)、粘着斑激酶(FAK)和非受体酪氨酸激酶(Src) [29]。白细胞介素-8 与受体结合可激活多种转录因子，如核因子-κB (NF-κB)、激活蛋白-1 (AP-1)、低氧诱导因子-1 (HIF-1)、信号转导和转录激活因子 3 (STAT3) [29]。

上述磷脂酰肌醇-3-激酶是 G 蛋白异三聚体(Gαi，β 和 γ)的主要靶点之一，其活性增强可以促进中性粒细胞的趋化作用[29]。磷脂酰肌醇-3-激酶通过增加其底物丝氨酸/苏氨酸激酶 PKB/Akt 磷酸化[30]，增加其活性。在癌细胞系(如前列腺癌细胞系)中，白细胞介素-8 也藉由相似机理来发挥功能[31]。

白细胞介素-8 还可以经由调控丝裂原活化蛋白激酶信号通路，活化丝氨酸/苏氨酸激酶分子，使其与细胞表面受体附近的支架蛋白相互作用[29]。例如，支架蛋白 Ras 激酶抑制子(KSR，Kinase Suppressor Ras)通过与 Raf-1 相互作用的方式去激活其相关信号通路[32]。同理，在中性粒细胞[33]和癌细胞[31] [34] [35]中，丝氨酸/苏氨酸激酶可经由 Raf-1/MAP/ERK 激酶 1/Erk 级联信号通路，增加下游 Erk1/2 的磷酸化[33]。

白细胞介素-8 受体 CXCR1 与 Gαi 蛋白偶联，可以激活磷脂酶 C [36]，促进膜相关脂质转化为甘油二酯和肌醇三磷酸，导致细胞质内钙的含量增加和蛋白激酶 C 异构体的激活[36]。白细胞介素-8 可诱导中性粒细胞中多种类型的蛋白激酶 C 如 PKCα，PKCβI 和 PKCβII 的磷酸化，促进细胞的分泌功能，呼吸氧化活性和 Mac-1 介导的粘附作用[37] [38]。有研究指出，在 RBL-2H3 细胞中，活化受体 CXCR1 介导的信号通路可以激活新发现的蛋白激酶 C 亚型-PKCε [37]。同时，活化蛋白激酶 C 经由改变细胞内 Ca^{2+}信号，可以调节由白细胞介素-8 诱导的人膀胱癌细胞的趋化性，这一反应被认为是蛋白激酶 C 介导的对肌动蛋白细胞骨架调节的结果[29]。另外，在癌细胞中也证实，白细胞介素-8 也可以活化磷脂酶 C 信号通路[39]。

白细胞介素-8 信号通路中的蛋白质酪氨酸激酶是肿瘤和内皮细胞中研究细胞增殖和细胞存活的靶点。研究表明，在卵巢癌和血管内皮细胞中，白细胞介素-8 可以激活表皮生长因子受体，从而激活下游丝裂原活化蛋白激酶信号通路[30] [40]。在血管内皮细胞中，白细胞介素-8 信号通路可以促进生长因子受体-2 的磷酸化[41]，以及调节内皮屏障的通透性[42] [43]。非受体酪氨酸激酶(Src)也是白细胞介素-8 诱导信号级联的重要中间物[44]。在 CXCR1/2 重组细胞系 HEK293 以及大鼠嗜碱性粒细胞性白血病细胞中，白细胞介素-8 刺激 Src 家族成员和 p125 [44] [45]从而促进了它们的磷酸化[46] 。在前列腺癌活检组织的恶性细胞中发现白细胞介素-8 的表达和信号转导与粘着斑激酶(FAK)自磷酸化的增加有关，又有免疫印迹实验表明，在前列腺癌细胞系中白细胞介素-8 诱导 FAK-Src-皮质激素信号通路[47]。FAK 和 Src 的激活可能与细胞增殖、细胞存活和化疗耐药性有关系，也可能参与细胞扩散、运动性和侵袭性的调节[48] [49]。有研究指出，活化联合的 FAK 和 c-Src (Src 家族成员)可能通过 ERK2 激活和诱导细胞周期蛋白 D 和 E 表达来促进间变性星形细胞瘤细胞的增殖[50]。其中，Src 的异常活性会促进许多过程的失调，包括侵袭、迁移、增殖、血管生成和凋亡[48]。例如，Pories 等人[51]表明在大鼠上皮细胞系，c-Src 过表达后结肠肿瘤细胞的软琼脂生长和侵袭潜力增加。Irby 等人[52]发现在裸鼠野生型细胞中，过表达 c-Src 会使结肠肿瘤细胞的原发性肿瘤的生长显着增强。Roche 等人表明，c-Src 或其近亲也是细胞分裂发生所必需的[53]。

白细胞介素-8 参与的信号通路也可调控细胞增殖、组织重塑和血管生成[54]。白细胞介素-8 与受体 CXCR1 的 mRNA 在收缩的骨骼肌中增加[55]。肌肉细胞产生的白细胞介素-8 可能以旁分泌的方式局部作用于毛细血管内皮细胞，与毛细血管内皮细胞表面的 CXCR2 结合促进肌肉组织的新血管形成[55] [56]。

这些研究表明，白细胞介素-8 相关的许多信号通路和下游各种信号分子，在免疫学、病理学以及生理学上扮演着重要角色。

3. 促进白细胞介素-8 表达的可能途径

在正常生理条件下，白细胞介素-8 在细胞内的表达是极少的，不容易检测到[56]。但在一些情况下

它可以被刺激产生：1) 存在促炎细胞因子，如肿瘤坏死因子 α 和 IL-1β [57] [58]；2) 类固醇激素，如雄激素、雌激素和地塞米松[59]；3) 活性氧物质[60]；4) 细菌[61] [62]和病毒产物[63]；5) 化学药剂和环境因素，如暴露于化疗药物、缺氧状态[29]、酸中毒、高血糖和辐射条件下[64]。另外，基因突变的肿瘤细胞也会促使白细胞介素-8 或其受体 CXCR1/2 表达增加[65]。

4. 转录因子 NF-κB 调控白细胞介素-8 表达的分子机制

与 NF-κB、AP-1 等转录因子相关的信号通路中，有多种可诱导白细胞介素-8 的表达[66]。例如，RAS-RAF 信号通路可激活 NF-κB 转录因子，从而导致大量白细胞介素-8 的产生[67]。在恶性肿瘤中，持续活化的 NF-κB，会促进肿瘤的增大、转移及血管的生成[68] [69] [70]。除 NF-κB 外，AP-1 和 NF-IL-6 也参与调控白细胞介素-8 的表达[71] [72]。NF-κB 通过协同 AP-1 和 NF-IL-6 促进白细胞介素-8 的转录[59] [60]。其中 NF-IL-6 是 C/EBP 家族的成员[73]。与 NF-κB 不同，在有些细胞中，AP-1 和 NF-IL-6 这两个转录因子结合位点不是白细胞介素-8 基因转录所必需的[74] [75] [76]。

调控白细胞介素-8 表达的转录因子 NF-κB 与炎症反应息息相关。NF-κB 不仅参与诱导先天免疫细胞中各种促炎细胞因子的表达，还调控 T 细胞的激活、分化及其效应功能[77] [78]。NF-κB 是二聚体蛋白复合物，由下列五个成员组成，即 NF-κB1 (p50 及其前体 p105)、NF-κB2 (p52 及其前体 p100)、c-REL、REL A (p65)和 REL B [79]，它们通过组成同源或异源二聚体来调控基因转录。在细胞质中，抑制蛋白 IκB 与 NF-κB 结合[80]，IkB 激酶(IKKα/β 和 IKKγ/Nemo)会磷酸化 IκB 蛋白中的两个 N-端丝氨酸位点[81]，磷酸化的 IκB 被泛素化后，由蛋白酶体快速降解，从而释放 NF-κB 二聚体，包括 p50/RelA 和 p50/c-Rel [82]。活化的 NF-κB 二聚体进一步转移到细胞核中与白细胞介素-8 和其他白介素的基因组上游启动子区域结合，促进这些基因的转录和表达[80]。其中，IKKs 不仅磷酸化 IκB，也磷酸化 NF-κB 成员分子[83]。因此，这些 NF-κB 成员分子 p105，p100，c-Rel 和 p65 以组成型磷酸化的状态存在[84] [85] [86]。同时，它们的磷酸化也会在一些刺激物作用下进一步增强[78]。例如，用十四烷酰佛波醇乙酸酯、植物血凝素、过氧化氢或 TNF-α 处理细胞可诱导 p105 磷酸化[85] [86] [87]。NF-κB 诱导的转录活性也因辅激活因子的结合而增强[88] 。

综上所述，白细胞介素-8 的表达不止受一种信号分子调控[29]，参与其中的还有 AP-1 和 NF-IL-6，其中的机制较为复杂，但主要的调控因子还是 NF-κB [29]。

5. 讨论与结论

巨噬细胞、上皮细胞和其他相关细胞会少量分泌白细胞介素-8，因此，在健康组织中，几乎检测不到其存在，但在促炎细胞因子、细菌或病毒产物以及细胞应激的作用下，其分泌量会增加 10~100 倍[57] [58] [63] [89]。此外，白细胞介素-8 受体也在癌细胞、内皮细胞以及肿瘤相关的巨噬细胞等细胞上表达[29]。而且在肿瘤中，白细胞介素-8 可招募中性粒细胞到肿瘤微环境中[90]。因此白细胞介素-8 信号因子及其相关的促血管生成 CXC 趋化因子可作为许多实体瘤，例如，胃、胰腺、黑色素瘤、卵巢、膀胱和前列腺的研究靶点[29]。可见，白细胞介素-8 除了在免疫生理调控上有重要的功能，在肿瘤疾病治疗方面也具有着重要的应用性与前瞻性。

致　谢

诚挚感谢陈正豪老师对论文撰写的指导，及科研经费的支持。

基金项目

本研究得到了浙江省自然科学基金资助项目(LY20C050001)、浙江省自然科学基金资助项目(LQ23C110001)和金华市科技计划项目(KYZ04Y22372)的支持。

参考文献

[1] Bhusal, R.P., Foster, S.R. and Stone, M.J. (2020) Structural Basis of Chemokine and Receptor Interactions: Key Regulators of Leukocyte Recruitment in Inflammatory Responses. *Protein Science*, **29**, 420-432. https://doi.org/10.1002/pro.3744

[2] Walz, A., Peveri, P., Aschauer, H. and Baggiolini, M. (1987) Purification and Amino Acid Sequencing of NAF, a Novel Neutrophil-Activating Factor Produced by Monocytes. *Biochemical and Biophysical Research Communications*, **149**, 755-761. https://doi.org/10.1016/0006-291X(87)90432-3

[3] Kownatzki, E., Kapp, A. and Uhrich, S. (1986) Novel Neutrophil Chemotactic Factor Derived from Human Peripheral Blood Mononuclear Leucocytes. *Clinical and Experimental Immunology*, **64**, 214-222.

[4] Yoshimura, T., Matsushima, K., Oppenheim, J.J. and Leonard, E.J. (1987) Neutrophil Chemotactic Factor Produced by Lipopolysaccharide (LPS)-Stimulated Human Blood Mononuclear Leukocytes: Partial Characterization and Separation from Interleukin 1 (IL 1). *The Journal of Immunology*, **139**, 788-793. https://doi.org/10.4049/jimmunol.139.3.788

[5] Proosti, P., Wuytsi, A. and Van Damme, J. (1996) The Role of Chemokines in Inflammation. *International Journal of Clinical and Laboratory Research*, **26**, 211-223. https://doi.org/10.1007/BF02602952

[6] Matsushima, K., Baldwin, E.T. and Mukaida, N. (1992) Interleukin-8 and MCAF Novel Leukocyte Recruitment and Activating Cytokines Inducible by IL 1 and TNF. *Cytokine*, **1**, 2-13. https://doi.org/10.1016/1043-4666(89)91043-0

[7] Kim, Y., Jo, A.R., Jang, D.H., *et al*. (2012) Toll-Like Receptor 9 Mediates Oral Bacteria-Induced IL-8 Expression in Gingival Epithelial Cells. *Immunology & Cell Biology*, **90**, 655-663. https://doi.org/10.1038/icb.2011.85

[8] Zhou, C., Ma, F.Z., Deng, X.J., Yuan, H. and Ma, H.S. (2008) Lactobacilli Inhibit Interleukin-8 Production Induced by *Helicobacter pylori* Lipopolysaccharide-Activated Toll-Like Receptor 4. *World Journal of Gastroenterology*, **14**, 5090-5095. https://doi.org/10.3748/wjg.14.5090

[9] Utgaard, J.O., Jahnsen, F.L., Bakka, A., Brandtzaeg, P. and Haraldsen, G. (1998) Rapid Secretion of Prestored Interleukin 8 from Weibel-Palade Bodies of Microvascular Endothelial Cells. *Brief Definitive Report*, **188**, 1751-1756. https://doi.org/10.1084/jem.188.9.1751

[10] Wolff, B., Burns, A.R., Middleton, J. and Rot, A. (1998) Endothelial Cell "Memory" of Inflammatory Stimulation: Human Venular Endothelial Cells Store Interleukin 8 in Weibel-Palade Bodies. *Brief Definitive Report*, **188**, November 2, 1757-1762. https://doi.org/10.1084/jem.188.9.1757

[11] Marriott, H.M., Gascoyne, K.A., Gowda, R., *et al*. (2011) Interleukin-1β Regulates CXCL8 Release and Influences Disease Outcome in Response to *Streptococcus pneumoniae*, Defining Intercellular Cooperation between Pulmonary Epithelial Cells and Macrophages. *Infection and Immunity*, **80**, 1140-1149. https://doi.org/10.1128/IAI.05697-11

[12] Schmid, J. and Weissmann, C. (1987) Induction of mRNA for a Serine Protease and a Beta-Thromboglobulin-Like Protein in Mitogen-Stimulated Human Leukocytes. *The Journal of Immunology*, **139**, 250-256. https://doi.org/10.4049/jimmunol.139.1.250

[13] Matsushima, K., Morishita, K., Yoshimura, T., *et al*. (1988) Molecular Cloning of a Human Monocyte-Derived Neutrophil Chemotactic Factor (MDNCF) and the Induction of MDNCF mRNA by Interleukin 1 and Tumor Necrosis Factor. *Journal of Experimental Medicine*, **167**, 1883-1893. https://doi.org/10.1084/jem.167.6.1883

[14] Hébert, C.A., Luscinskas, F.W., Kiely, J.M., *et al*. (1990) Endothelial and Leukocyte Forms of IL-8. Conversion by Thrombin and Interactions with Neutrophils. *The Journal of Immunology*, **145**, 3033-3040. https://doi.org/10.4049/jimmunol.145.9.3033

[15] Gimbrone and Baker, J.B. (1990) Endothelial and Leukocyte Forms of IL-8. Conversion by Thrombin and Interactions with Neutrophils. *The Journal of Immunology*, **145**, 3033-3040. https://doi.org/10.4049/jimmunol.145.9.3033

[16] Baggiolini, M., Dewald, B. and Moser, B. (1993) Interleukin-8 and Related Chemotactic Cytokines—CXC and CC Chemokines. *Advances in Immunology*, **55**, 97-179. https://doi.org/10.1016/S0065-2776(08)60509-X

[17] Mukaida, N. and Matsushima, K. (1998) Interleukin 8 and Its Receptor. In: Delves, P.J., Ed., *Encyclopedia of Immunology*, 2nd Edition, Elsevier, Amsterdam, 1466-1471. https://doi.org/10.1006/rwei.1999.0374

[18] Benakanakere, M.R., Finoti, L.S., Tanaka, U., *et al*. (2016) Investigation of the Functional Role of Human Interleukin-8 Gene Haplotypes by CRISPR/Cas9 Mediated Genome Editing. *Scientific Reports*, **6**, Article No. 31180. https://doi.org/10.1038/srep31180

[19] Remick, D.G. (2005) Interleukin-8. *Critical Care Medicine*, **33**, S466-S467. https://doi.org/10.1097/01.CCM.0000186783.34908.18

[20] Flannagan, R.S., Jaumouille, V. and Grinstein, S. (2012) The Cell Biology of Phagocytosis. *Annual Review of Pathology*, **7**, 61-98. https://doi.org/10.1146/annurev-pathol-011811-132445

[21] Lee, W.L., Harrison, R.E. and Grinstein, S. (2003) Phagocytosis by Neutrophils. *Microbes and Infection*, **5**, 1299-1306.

https://doi.org/10.1016/j.micinf.2003.09.014

[22] Kruskal, B.A. and Maxfield, F.R. (1987) Cytosolic Free Calcium Increases before and Oscillates during Frustrated Phagocytosis in Macrophages. *The Journal of Cell Biology*, **105**, 2685-2693. https://doi.org/10.1083/jcb.105.6.2685

[23] Sawyer, D.W., Sullivan, J.A. and Mandell, G.L. (1985) Intracellular Free Calcium Localization in Neutrophils during Phagocytosis. *Science*, **230**, 663-666. https://doi.org/10.1126/science.4048951

[24] Murphy, P.M. and Tiffany, H.L. (1991) Share Cloning of Complementary DNA Encoding a Functional Human Interleukin-8 Receptor. *Science*, **253**, 1280-1283. https://doi.org/10.1126/science.1891716

[25] Holmes, W.E., Lee, J., Kuang, W.J., Rice, G.C. and Wood, W.I. (1991) Structure and Functional Expression of a Human Interleukin-8 Receptor. *Science*, **253**, 1278-1280. https://doi.org/10.1126/science.1840701

[26] Cerretti, D.P., Kozlosky, C.J., VandenBos, T., Nelson, N., Gearing, D.P. and Beckmann, M.P. (1993) Molecular Characterization of Receptors for Human Interleukin-8, GRO/Melanoma Growth-Stimulatory Activity and Neutrophil Activating Peptide-2. *Molecular Immunology*, **30**, 359-367. https://doi.org/10.1016/0161-5890(93)90065-J

[27] Hammond, M.E., Shyamala, V., Siani, M.A., *et al*. (1996) Receptor Recognition and Specificity of Interleukin-8 Is Determined by Residues That Cluster near a Surface-Accessible Hydrophobic Pocket. *Journal of Biological Chemistry*, **271**, 8228-8235. https://doi.org/10.1074/jbc.271.14.8228

[28] Lee, J., Horuk, R., Rice, G.C., *et al*. (1992) Characterization of Two High Affinity Human Interleukin-8 Receptors. *Journal of Biological Chemistry*, **267**, 16283-16287. https://doi.org/10.1016/S0021-9258(18)41997-7

[29] Waugh, D.J.J. and Wilson, C. (2008) The Interleukin-8 Pathway in Cancer. *Clinical Cancer Research*, **14**, 6735-6741. https://doi.org/10.1158/1078-0432.CCR-07-4843

[30] Knall, C., Worthen, G.S. and Johnson, G.L. (1997) Interleukin 8 Stimulated Phosphatidylinositol-3-Kinase Activity Regulates the Migration of Human Neutrophils Independent of Extracellular Signal-Regulated Kinase and p38 Mitogen-Activated Protein Kinases. *Proceedings of the National Academy of Sciences of the United States of America*, **94**, 3052-3057. https://doi.org/10.1073/pnas.94.7.3052

[31] MacManus, C.F., Pettigrew, J., Seaton, A., *et al*. (2007) Interleukin-8 Signaling Promotes Translational Regulation of Cyclin D in Androgen-Independent Prostate Cancer Cells. *Molecular Cancer Research*, **5**, 737-748. https://doi.org/10.1158/1541-7786.MCR-07-0032

[32] Xing, H.M., Kornfeld, K. and Muslin, A.J. (1997) The Protein Kinase KSR Interacts with 14-3-3 Protein and Raf. *Current Biology*, **7**, 294-300. https://doi.org/10.1016/S0960-9822(06)00152-7

[33] Knall, C., Young, S., Nick, J.A., *et al*. (1996) Interleukin-8 Regulation of the Ras/Raf/Mitogen-Activated Protein Kinase Pathway in Human Neutrophils. *Journal of Biological Chemistry*, **271**, 2832-2838. https://doi.org/10.1074/jbc.271.5.2832

[34] Luppi, F., Longo, A.M., de Boer, W.I., Rabe, K.F. and Hiemstra, P.S. (2007) Interleukin-8 Stimulates Cell Proliferation in Nonsmall Cell Lung Cancer through Epidermal Growth Factor Receptor Transactivation. *Lung Cancer*, **56**, 25-33. https://doi.org/10.1016/j.lungcan.2006.11.014

[35] Venkatakrishnan, G., Salgia, R. and Groopman, J.E. (2000) Chemokine Receptors CXCR-1/2 Activate Mitogen-Activated Protein Kinase via the Epidermal Growth Factor Receptor in Ovarian Cancer Cells. *Journal of Biological Chemistry*, **275**, 6868-6875. https://doi.org/10.1074/jbc.275.10.6868

[36] Richardson, R.M., Ali, H., Pridgen, B.C., Haribabu, B. and Snyderman, R. (1998) Multiple Signaling Pathways of Human Interleukin-8 Receptor A. Independent Regulation by Phosphorylation. *Journal of Biological Chemistry*, **273**, 10690-10695. https://doi.org/10.1074/jbc.273.17.10690

[37] Nasser, M.W., Marjoram, R.J., Brown, S.L. and Richardson, R.M. (2005) Cross-Desensitization among CXCR1, CXCR2, and CCR5: Role of Protein Kinase C-ε. *The Journal of Immunology*, **174**, 6927-6933. https://doi.org/10.4049/jimmunol.174.11.6927

[38] Takami, M., Terry, V. and Petruzzelli, L. (2002). Signaling Pathways Involved in IL-8-Dependent Activation of Adhesion through Mac-1. *The Journal of Immunology*, **168**, 4559-4566. https://doi.org/10.4049/jimmunol.168.9.4559

[39] Lang, K., Niggemann, B., Zanker, K.S. and Entschladen, F. (2002) Signal Processing in Migrating T24 Human Bladder Carcinoma Cells: Role of the Autocrine Interleukin-8 Loop. *International Journal of Cancer*, **99**, 673-680. https://doi.org/10.1002/ijc.10424

[40] Schraufstatter, I.U., Trieu, K., Zhao, M., Rose, D.M., Terkeltaub, R.A. and Burger, M. (2003) IL-8 Mediated Cell Migration in Endothelial Cells Depends on Cathepsin B Activity and Transactivation of the Epidermal Growth Factor Receptor. *The Journal of Immunology*, **171**, 6714-6722. https://doi.org/10.4049/jimmunol.171.12.6714

[41] Hennequin, L.F., Thomas, A.P., Johnstone, C., *et al*. (1999) Design and Structure-Activity Relationship of a New Class of Potent VEGF Receptor Tyrosine Kinase Inhibitors. *Journal of Medicinal Chemistry*, **42**, 5369-5389. https://doi.org/10.1021/jm990345w

[42] Fukumoto, T., Matsukawa, A., Yoshimura, T., *et al*. (1998) IL-8 Is an Essential Mediator of the Increased Delayed-Phase Vascular Permeability in LPS-Induced Rabbit Pleurisy. *Journal of Leukocyte Biology*, **63**, 584-590. https://doi.org/10.1002/jlb.63.5.584

[43] Yamamoto, T., Kajikawa, O., Martin, T.R., *et al*. (1998) The Role of Leukocyte Emigration and IL-8 on the Development of Lipopolysaccharide-Induced Lung Injury in Rabbits. *The Journal of Immunology*, **161**, 5704-5709. https://doi.org/10.4049/jimmunol.161.10.5704

[44] Petreaca, M.L., Yao, M., Lui, Y., Defea, K. and Martins-Green, M. (2007) Transactivation of Vascular Endothelial Growth Factor Receptor-2 by Interleukin-8 (IL-8/CXCL8) Is Required for IL-8/CXCL8-Induced Endothelial Permeability. *Molecular Biology of the Cell*, **18**, 5014-5023. https://doi.org/10.1091/mbc.e07-01-0004

[45] Cohen-Hillel, E., Yron, I., Meshel, T., Soria, G., Attal, H. and Ben-Baruch, A. (2006) CXCL8-Induced FAK Phosphorylation via CXCR1 and CXCR2: Cytoskeleton- and Integrin-Related Mechanisms Converge with FAK Regulatory Pathways in a Receptor-Specific Manner. *Cytokine*, **33**, 1-16. https://doi.org/10.1016/j.cyto.2005.11.006

[46] Lee, L.F., Louie, M.C., Desai, S.J., *et al*. (2004) Interleukin-8 Confers Androgen-Independent Growth and Migration of LNCaP: Differential Effects of Tyrosine Kinases Src and FAK. *Oncogene*, **23**, 2197-2205. https://doi.org/10.1038/sj.onc.1207344

[47] McFarlane, S., Seaton, A., Chacko, A., *et al*. (2006) Focal Adhesion Kinase Is a Key Signaling Intermediate in Interleukin-8 Promoted Chemotaxis and Adhesion of Prostate Cancer Cells to Bone Marrow Endothelium. *EJC Supplements*, **4**, 18.

[48] Kopetz, S., Shah, A.N. and Gallick, G.E. (2007) Src Continues Aging: Current and Future Clinical Directions. *Clinical Cancer Research*, **13**, 7232-7236. https://doi.org/10.1158/1078-0432.CCR-07-1902

[49] Siesser, P.M. and Hanks, S.K. (2006) The Signaling and Biological Implications of FAK Overexpression in Cancer. *Clinical Cancer Research*, **12**, 3233-3237. https://doi.org/10.1158/1078-0432.CCR-06-0456

[50] Hecker, T.P., Grammer, J.R., Gillespie, G.Y., Stewart, J. and Gladson, C.L. (2002) Focal Adhesion Kinase Enhances Signaling through the Shc/Extracellular Signal-Regulated Kinase Pathway in Anaplastic Astrocytoma Tumor Biopsy Samples. *Cancer Research*, **62**, 2699-2707.

[51] Pories, S.E., Hess, D.T., Swenson, K., *et al*. (1998) Overexpression of pp60c-src Elicits Invasive Behavior in Rat Colon Epithelial Cells. *Gastroenterology*, **114**, 1287-1295. https://doi.org/10.1016/S0016-5085(98)70435-4

[52] Irby, R., Mao, W., Coppola, D., *et al*. (1997) Overexpression of Normal c-Src in Poorly Metastatic Human Colon Cancer Cells Enhances Primary Tumor Growth but Not Metastatic Potential. *Cell Growth and Differentiation*, **8**, 1287-1295.

[53] Ning, Y., Manegold, P.C., Hong, Y.K., *et al*. (2011) Interleukin-8 Is Associated with Proliferation, Migration, Angiogenesis and Chemosensitivity *in Vitro* and *in Vivo* in Colon Cancer Cell Line Models. *International Journal of Cancer*, **128**, 2038-2049. https://doi.org/10.1002/ijc.25562

[54] Roche, S., Fumagalli, S. and Courtneidge, S.A. (1995) Requirement for Src Family Protein Tyrosine Kinases in GZ for Fibroblast Cell Division. *Science*, **269**, 1567-1569. https://doi.org/10.1126/science.7545311

[55] Legård, G.E. and Pedersen, B.K. (2019) Muscle as an Endocrine Organ. In: Zoladz, J.A., Ed., *Muscle and Exercise Physiology*, Elsevier, Amsterdam, 285-307. https://doi.org/10.1016/B978-0-12-814593-7.00013-X

[56] Hoffmann, E., Dittrich-Breiholz, O., Holtmann, H. and Kracht, M. (2002) Multiple Control of Interleukin-8 Gene Expression. *Journal of Leukocyte Biology*, **72**, 847-855. https://doi.org/10.1189/jlb.72.5.847

[57] Kasahara, T., Mukaida, N., Yamashita, K., *et al*. (1991) IL-1 and TNF-Alpha Induction of IL-8 and Monocyte Chemotactic and Activating Factor (MCAF) mRNA Expression in a Human Astrocytoma Cell Line. *Immunology*, **74**, 60-67.

[58] Brasier, A.R., Jamaluddin, M., Casola, A., *et al*. (1998) A Promoter Recruitment Mechanism for Tumor Necrosis Factor-Alpha-Induced Interleukin-8 Transcription in Type II Pulmonary Epithelial Cells. Dependence on Nuclear Abundance of Rel A, NF-kappaB1, and c-Rel Transcription Factors. *The Journal of Biological Chemistry*, **273**, 3551-3561. https://doi.org/10.1074/jbc.273.6.3551

[59] Brat, D.J., Bellail, A.C. and van Meir, E.G. (2005) The Role of Interleukin-8 and Its Receptors in Gliomagenesis and Tumoral Angiogenesis. *Neuro-Oncology*, **7**, 122-133. https://doi.org/10.1215/S1152851704001061

[60] Yuzhalin, A.E. and Kutikhin, A.G. (2015) The Rest of Interleukins. In: Yuzhalin, A.E. and Kutikhin, A.G., Eds., *Interleukins in Cancer Biology*, Elsevier, Amsterdam, 291-318. https://doi.org/10.1016/B978-0-12-801121-8.00009-9

[61] Aihara, M., Tsuchimoto, D., Takizawa, H., *et al*. (1997) Mechanisms Involved in *Helicobacter pylori*-Induced Interleukin-8 Production by a Gastric Cancer Cell Line, MKN45. *Infection and Immunity*, **65**, 3218-3224. https://doi.org/10.1128/iai.65.8.3218-3224.1997

[62] Hobbie, S., Chen, L.M., Davis, R.J. and Galán, J.E. (1997) Involvement of Mitogen-Activated Protein Kinase Pathways in the Nuclear Responses and Cytokine Production Induced by *Salmonella typhimurium* in Cultured Intestinal

Epithelial Cells. *The Journal of Immunology*, **159**, 5550-5559. https://doi.org/10.4049/jimmunol.159.11.5550

[63] Murayama, T., Ohara, Y., Obuchi, M., *et al*. (1997) Human Cytomegalovirus Induces Interleukin-8 Production by a Human Monocytic Cell Line, THP-1, through Acting Concurrently on AP-1- and NF-kappaB-Binding Sites of the Interleukin-8 Gene. *Journal of Virology*, **71**, 5692-5695. https://doi.org/10.1128/jvi.71.7.5692-5695.1997

[64] Shi, Q., Xiong, Q., Le, X. and Xie, K. (2001) Regulation of Interleukin-8 Expression by Tumor-Associated Stress Factors. *Journal of Interferon & Cytokine Research*, **21**, 553-566. https://doi.org/10.1089/10799900152547812

[65] Sparmann, A. and Bar-Sagi, D. (2004) Ras-Induced Interleukin-8 Expression Plays a Critical Role in Tumor Growth and Angiogenesis. *Cancer Cell*, **6**, 447-458. https://doi.org/10.1016/j.ccr.2004.09.028

[66] Lin, Y., Huang, R., Chen, L., Li, S., Shi, Q., Jordan, C. and Huang, R.P. (2004) Identification of Interleukin-8 as Estrogen Receptor-Regulated Factor Involved in Breast Cancer Invasion and Angiogenesis by Protein Arrays. *International Journal of Cancer*, **109**, 507-515. https://doi.org/10.1002/ijc.11724

[67] Mantovani, A., Bonecchi, R. and Locati, M. (2006) Tuning Inflammation and Immunity by Chemokine Sequestration: Decoys and More. *Nature Reviews Immunology*, **6**, 907-918. https://doi.org/10.1038/nri1964

[68] Greten, F.R., Eckmann, L., Greten, T.F., Park, J.M., Li, Z.W., Egan, L.J., Kagnoff, M.F. and Karin, M. (2004) IKKβ Links Inflammation and Tumorigenesis in a Mouse Model of Colitis-Associated Cancer. *Cell*, **118**, 285-296. https://doi.org/10.1016/j.cell.2004.07.013

[69] Terzic, J., Grivennikov, S., Karin, E. and Karin, M. (2010) Inflammation and Colon Cancer. *Gastroenterology*, **138**, 2101-2114e2105. https://doi.org/10.1053/j.gastro.2010.01.058

[70] Pikarsky, E., Porat, R.M., Stein, I., Abramovitch, R., Amit, S., Kasem, S., Gutkovich-Pyest, E., Urieli-Shoval, S., Galun, E. and Ben-Neriah, Y. (2004) NF-kappaB Functions as a Tumour Promoter in Inflammation-Associated Cancer. *Nature*, **431**, 461-466. https://doi.org/10.1038/nature02924

[71] Karin, M., Cao, Y., Greten, F.R. and Li, Z.W. (2002) NF-kappaB in Cancer: From Innocent Bystander to Major Culprit. *Nature Reviews Cancer*, **2**, 301-310. https://doi.org/10.1038/nrc780

[72] Zhang, Y., Wang, L., Zhang, M., Jin, M., Bai, C. and Wang, X. (2012) Potential Mechanism of Interleukin-8 Production from Lung Cancer Cells: An Involvement of EGF-EGFR-PI3KAkt-Erk Pathway. *Journal of Cellular Physiology*, **227**, 35-43. https://doi.org/10.1002/jcp.22722

[73] Akira, S., Isshiki, H., Sugita, T., *et al*. (1990) A Nuclear Factor for IL-6 Expression (NF-IL6) Is a Member of a C/EBP Family. *The EMBO Journal*, **9**, 1897-1906. https://doi.org/10.1002/j.1460-2075.1990.tb08316.x

[74] Mukaida, N., Okamoto, S., Ishikawa, Y. and Matsushima, K. (1994) Molecular Mechanism of Interleukin-8 Gene Expression. *Journal of Leukocyte Biology*, **56**, 554-558. https://doi.org/10.1002/jlb.56.5.554

[75] Mukaida, N., Morita, M., Ishikawa, Y., Rice, N., Okamoto, S., Kasahara, T. and Matsushima, K. (1994) Novel Mechanism of Glucocorticoid-Mediated Gene Repression. Nuclear Factor-Kappa B Is Target for Glucocorticoid-Mediated Interleukin 8 Gene Repression. *Journal of Biological Chemistry*, **269**, 13289-13295. https://doi.org/10.1016/S0021-9258(17)36831-X

[76] Matsukaka, T., Fujikawa, K., Nishio, Y., Mukaida, N., Matsushima, K., Kishimoto, T. and Akira, S. (1993) Transcription Factors NF-IL6 and NF-kappa B Synergistically Activate Transcription of the Inflammatory Cytokines, Interleukin 6 and Interleukin 8. *Proceedings of the National Academy of Sciences of the United States of America*, **90**, 10193-10197. https://doi.org/10.1073/pnas.90.21.10193

[77] Lawrence, T. (2009) The Nuclear Factor NF-kappaB Pathway in Inflammation. *Cold Spring Harbor Perspectives in Biology*, **1**, a001651. https://doi.org/10.1101/cshperspect.a001651

[78] Tak, P.P. and Firestein, G.S. (2001) NF-kappaB: A Key Role in Inflammatory Diseases. *Journal of Clinical Investigation*, **107**, 7-11. https://doi.org/10.1172/JCI11830

[79] De Zoete, M.R., Palm, N.W., Zhu, S. and Flavell, R.A. (2014) Inflammasomes. *Cold Spring Harbor Perspectives in Biology*, **6**, a016287. https://doi.org/10.1101/cshperspect.a016287

[80] Ghosh, S., May, M.J. and Kopp, E.B. (1998) NF-κB and Rel Proteins: Evolutionarily Conserved Mediators of Immune Responses. *Annual Review of Immunology*, **16**, 225-260. https://doi.org/10.1146/annurev.immunol.16.1.225

[81] Shi, C.S., Shenderov, K., Huang, N.N., *et al*. (2012) Activation of Autophagy by Inflammatory Signals Limits IL-1beta Production by Targeting Ubiquitinated Inflammasomes for Destruction. *Nature Immunology*, **13**, 255-263. https://doi.org/10.1038/ni.2215

[82] Beinke, S. and Ley, S.C. (2004) Functions of NF-kappaB1 and NF-kappaB2 in Immune Cell Biology. *Biochemical Journal*, **382**, 393-409. https://doi.org/10.1042/BJ20040544

[83] Lienhard Schmitz, M., Bacher, S. and Kracht, M. (2001) IκB-Independent Control of NF-κB Activity by Modulatory Phosphorylations. *Trends in Biochemical Sciences*, **26**, 186-190. https://doi.org/10.1016/S0968-0004(00)01753-9

[84] Neumann, M., *et al*. (1992) Identification of Complex Formation between Two Intracellular Tyrosine Kinase Sub-

strates: Human c-Rel and the p105 Precursor of p50 NF-κB. *Oncogene*, **7**, 2095-2104.

[85] Li, C.C., *et al*. (1994) NF-κB/Rel Family Members Are Physically Associated Phosphoproteins. *Biochemical Journal*, **303**, 499-506. https://doi.org/10.1042/bj3030499

[86] Naumann, M. and Scheidereit, C. (1994) Activation of NF-κB *in Vivo* Is Regulated by Multiple Phosphorylations. *EMBO Journal*, **13**, 4597-4607. https://doi.org/10.1002/j.1460-2075.1994.tb06781.x

[87] Heissmeyer, V., Krappmann, D., Wulczyn, F.G. and Scheidereit, C. (1999) NF-kappaB p105 Is a Target of IkappaB Kinases and Controls Signal Induction of Bcl-3-p50 Complexes. *EMBO Journal*, **18**, 4766-4778. https://doi.org/10.1093/emboj/18.17.4766

[88] Baeuerle, P.A. and Baltimore, D. (1996) NF-κB: Ten Years after. *Cell*, **87**, 13-20. https://doi.org/10.1016/S0092-8674(00)81318-5

[89] Sonoda, Y., Kasahara, T., Yamaguchi, Y., Kuno, K., Matsushima, K. and Mukaida, N. (1997) Stimulation of Interleukin-8 Production by Okadaic Acid and Vanadate in a Human Promyelocyte Cell Line, an HL-60 Subline. Possible Role of Mitogen-Activated Protein Kinase on the Okadaic Acid-Induced NF-kappaB Activation. *Journal of Biological Chemistry*, **272**, 15366-15372. https://doi.org/10.1074/jbc.272.24.15366

[90] DeLarco, J.E., Wuertz, B.R. and Furcht, L.T. (2004) The Potential Role of Neutrophils in Promoting the Metastatic Phenotype of Tumors Releasing Interleukin-8. *Clinical Cancer Research*, **10**, 4895-4900. https://doi.org/10.1158/1078-0432.CCR-03-0760