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药理学

本书文章选自 *Trends in Pharmacological Sciences*

NEW FOCUS in
Life Sciences
生命科学新视野 9

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New Focus in Life Sciences

9

药理学

生命科学新视野

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图字：01-2007-3731 号

图书在版编目（CIP）数据

药理学＝Pharmacology：英文/（英）巴尔（Barr，A. J.）等编著. —北京：科学出版社，2007
（生命科学新视野；9）
ISBN 978-7-03-019499-2

Ⅰ. 药… Ⅱ. 巴… Ⅲ. 药理学－英文
Ⅳ. R96

中国版本图书馆 CIP 数据核字（2007）第 116631 号

责任编辑：田慎鹏 贾明月
责任印制：钱玉芬
地　　址：北京市东城区东黄城根北街 16 号 1-515
邮政编码：100717
电子邮箱：keai@mail.sciencep.com
网　　址：http://www.kbooks.cn

科学出版社 出版
双青印刷厂印刷
北新华文设计制作

定　价：50.00 元

Source journals:

Trends in Pharmacological Sciences ISSN 0165-6147

8 MAPK-specific tyrosine phosphatases: new targets for drug discovery?

Trends in Pharmacological Sciences, Volume 27, Issue 10, October 2006, Pages 525-530

Alastair J. Barr and Stefan Knapp

MAPK 特异性酪氨酸磷酸酶：药物发现的新靶点？

蛋白酪氨酸磷酸酶（PTPs）在很多细胞生理过程中发挥了重要作用。它们的失调与一些人类疾病相关。很多 PTPs 是公认的潜在药物靶标。然而，抑制剂的开发仅仅局限于少数几个酶，最著名的是与 II 型糖尿病及肥胖相关的PTP1B，以及与癌症相关的MKP1和CDC25。目前快速发展的蛋白酪氨酸磷酸酶（PTPome）结构生物学将极大地促进 PTPs 选择性抑制剂的研发，并有助于其发展。本文中，我们着重关注丝裂原活化蛋白激酶家族（MAPK 家族）特异的酪氨酸磷酸酶——PTPN5 [也称纹状体浓缩磷酸酶（STEP）]，PTPN7（也称造血PTP）以及PTPRR（也称PCI2 PTP 或类 STEP 样 PTP），同时讨论了应用最近发明的高分辨 X- 射线测定晶体结构的方法，在分子水平上获得 MAPK-PTPs 选择性的途径。我们相信，特异性抑制剂的研究进展将提供一套有价值的实验药理学工具，来研究这些磷酸酶的生理学作用以及探讨它们在人类疾病中可能的作用。

（马捷译，祝晓玲校）

14 Ca^{2+} signalling and pancreatitis: effects of alcohol, bile and coffee

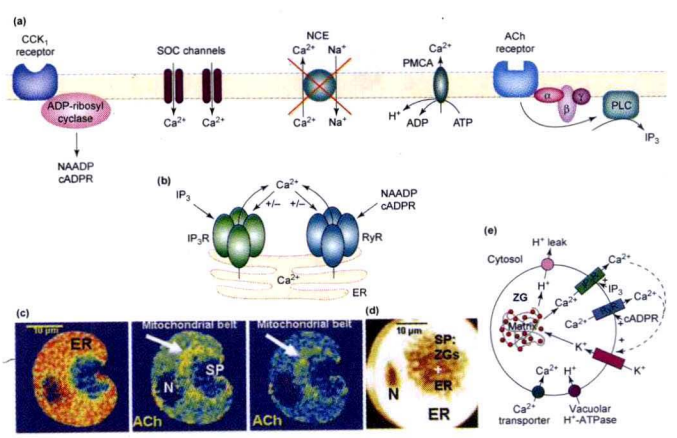
Trends in Pharmacological Sciences, Volume 27, Issue 2, February 2006, Pages 113-120

Ole H. Petersen and Robert Sutton

Ca^{2+} 信号和胰腺炎：酒精、胆汁和咖啡的作用

Ca^{2+}是一广泛存在的细胞内信使，参与控制很多细胞的生理过程。在胰腺的腺泡细胞中，乙酰胆碱和胆囊收缩素通过在细胞游离面反复的局部胞质Ca^{2+}信号的产生来调节胰腺腺泡细胞分泌。胆汁酸和非氧化型的乙醇代谢物能够引起异常的胞质内 Ca^{2+} 信号，这些异常信号广泛而持续地存在，引起细胞坏死。特异性通道释放Ca^{2+}和抑制细胞内储库的钙泵，引起内质网中Ca^{2+}的过量损失，导致细胞坏死，随后细胞外的 Ca^{2+} 内流。在此过程中细胞 ATP 水平的降低起着关键作用。这些可被咖啡因抑制的异常的 Ca^{2+} 信号，解释了过量摄入酒精以及胆汁疾病是如何引起急性胰腺炎的。急性胰腺炎是人类一种常见的致命性疾病，以消化胰腺自身和周围组织为特征。

（陈丽华译，祝晓玲校）



22 The function of breast cancer resistance protein in epithelial barriers, stem cells and milk secretion of drugs and xenotoxins

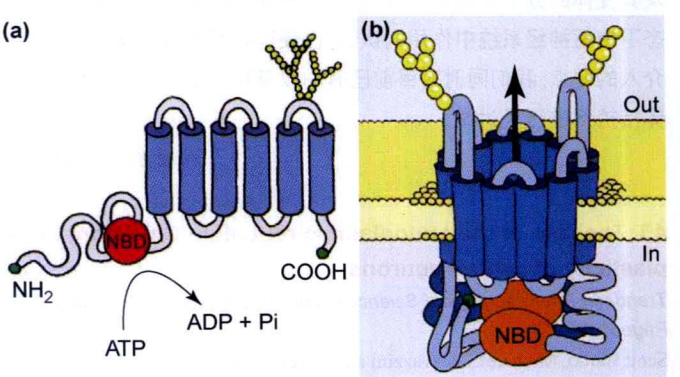
Trends in Pharmacological Sciences, Volume 27, Issue 1, January 2006, Pages 10-16

Antonius E. van Herwaarden and Alfred H. Schinkel

乳腺癌耐药蛋白在上皮屏障、干细胞以及乳汁分泌药物和外毒素中的作用

乳腺癌耐药蛋白[BCRP（又名ABCG2）]属于ATP依赖性跨膜药物转运蛋白类，即ABC超家族的成员。BCRP具有广泛的底物特异性，可以有效地将多种药物、致癌物和食源性毒素从细胞中排出。位于小肠、大肠和肾脏近曲小管上皮细胞质膜顶端以及肝细胞胆管膜上的BCRP，可以降低其底物的口服利用度和在机体的分布。在几种血 - 组织屏障中，BCRP 能够降低其底物的组织通透性，保护造血干细胞免受毒性物质的损害。此外，BCRP 表达于妊娠期和哺乳期乳腺腺泡上皮细胞，主动排泌多种药物、毒素及致癌物至乳汁中。与BCRP对于母体的解毒作用明显相反，这种乳汁污染会使得哺乳婴儿和奶制品消费者接触到外毒素。因此，BCRP对于药理学和毒理学的许多重要方面均有影响。

（何朝勇译，祝晓玲校）



29 Use of P-glycoprotein and BCRP inhibitors to improve oral bioavailability and CNS penetration of anticancer drugs

Trends in Pharmacological Sciences, Volume 27, Issue 1, January 2006, Pages 17-24

Pauline Breedveld, Jos H. Beijnen and Jan H.M. Schellens

利用 P- 糖蛋白和 BCRP 抑制剂改善抗癌药物的口服生物利用度和中枢神经系统渗透性

P- 糖蛋白（ABCB1）和乳腺癌耐药蛋白[BCRP（又名ABCG2）]是两种药物外排转运子，属于ATP结合盒转运子（ABC）

超家族蛋白。P-糖蛋白和BCRP均分布于上皮细胞（例如肠壁和血-脑屏障）膜游离面，在此位置它们可以主动外排多种结构多样的药物及其代谢物。外排的后果是，底物药物的口服吸收率和中枢神经系统渗透性较低且变化较大。因此，理论上认为抑制P-糖蛋白和BCRP是提高抗癌药物的口服吸收率、中枢神经系统渗透性、向脑瘤病灶或中枢神经系统转移灶转运的一种策略。如本文所述，改良的口服药代动力学这一概念在抗癌药物紫杉醇、托泊替康的临床前模型和患者中均已得到充分地验证，在紫杉醇、紫杉萜和伊马替尼临床前模型中也被证明可以提高药物对于中枢神经系统的渗透性。

（何朝勇译，祝晓玲校）

37 The expression and function of chemokines involved in CNS inflammation

Trends in Pharmacological Sciences, Volume 27, Issue 1, January 2006, Pages 48-55

Eroboghene E. Ubogu, Michael B. Cossoy and Richard M. Ransohoff

中枢神经系统炎症中趋化因子的表达和功能

趋化因子及其受体对于正常生理条件下和病理条件下白细胞定向移动具有重要的作用。趋化因子系统在中枢神经系统不同部分表达的差异对于理解正常免疫监视过程和病理条件下免疫介导的效应因子过程具有启示意义。对一种人类中枢神经系统炎症性疾病（多发性硬化症）和该疾病的一种动物模型（实验性自身脊髓炎）的研究有助于进一步理解趋化因子介导的炎症的复杂性。对于趋化因子及其受体的分子生物学、特定趋化因子配体和受体在健康和疾病状态下中枢神经系统中作用的认识，已使这些蛋白成为神经炎症治疗介入的靶点。我们同时对目前已有的以及有应用潜力的趋化因子受体拮抗剂进行了讨论。

（何朝勇译，祝晓玲校）

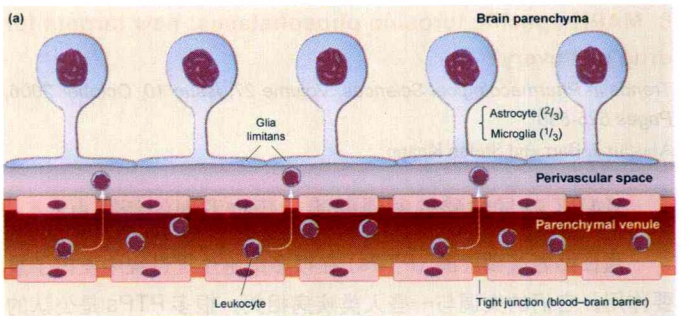
45 The role of the endoplasmic reticulum Ca^{2+} store in the plasticity of central neurons

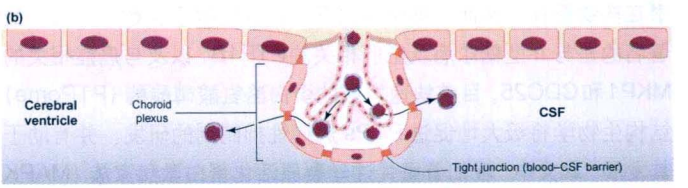
Trends in Pharmacological Sciences, Volume 27, Issue 2, February 2006, Pages 78-84

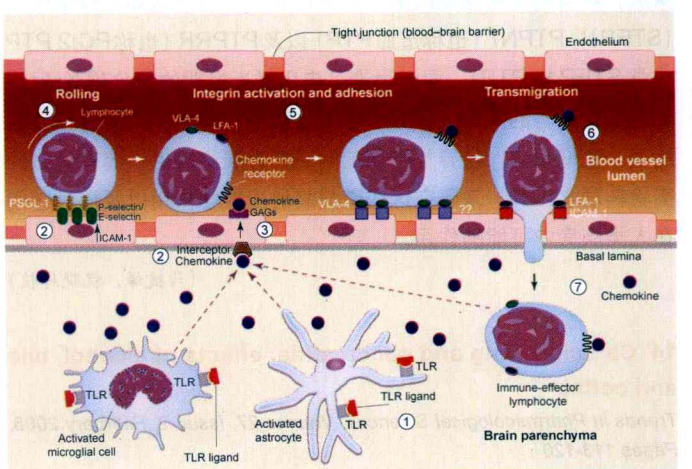
Scott Bardo, Michele G. Cavazzini and Nigel Emptage

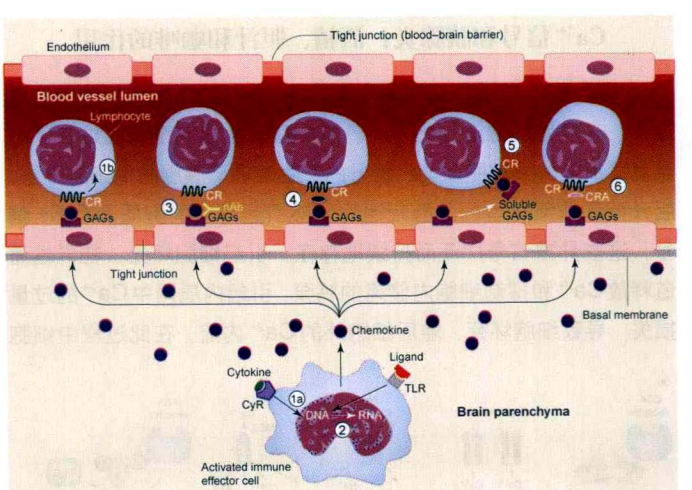
内质网钙池在中枢神经元可塑性中的作用

滑面内质网(SER)作为神经元轴突和树突区Ca^{2+}的缓冲区和来源，已得到良好阐释。刺激钙释放通道（亦称ryanodine受体）或肌醇(1, 4, 5)-三羟甲基氨基甲烷磷酸盐[Ins (1, 4, 5) P3]受体可以诱发滑面内质网中Ca^{2+}的释放。这两种受体均与内质网浆膜上的神经递质门控受体和电压门控Ca^{2+}通道的激活相偶联，从而使得滑面内质网可以辨别不同类型的神经元活动。在轴突末端，Ca^{2+}诱导的Ca^{2+}释放（CICR）介导自发的、可诱导的和易化的神经传导活动。钙池的释放还可以调节突触小泡的活动和再循环。在树突室区，Ins (1, 4, 5) P_3和ryanodine受体的分布可以影响神经元活动的细胞内编码。因此，钙池的功能能够影响突触效能









中Ca^{2+}依赖性刺激变化的极性和扩展程度。例如在海马神经元中，棘突中的CICR是同源性突触可塑性的基础，而异源性突触的可塑性则通过Ins (1, 4, 5) P_3依赖的Ca^{2+}信号来调节。浦肯野神经元主要在棘突表达Ins (1, 4, 5) P_3受体，而突触效能的长时程抑制则主要依赖于Ins (1, 4, 5) P_3。

（陈丽华译，祝晓玲校）

52 Novel class of pain drugs based on antagonism of NGF

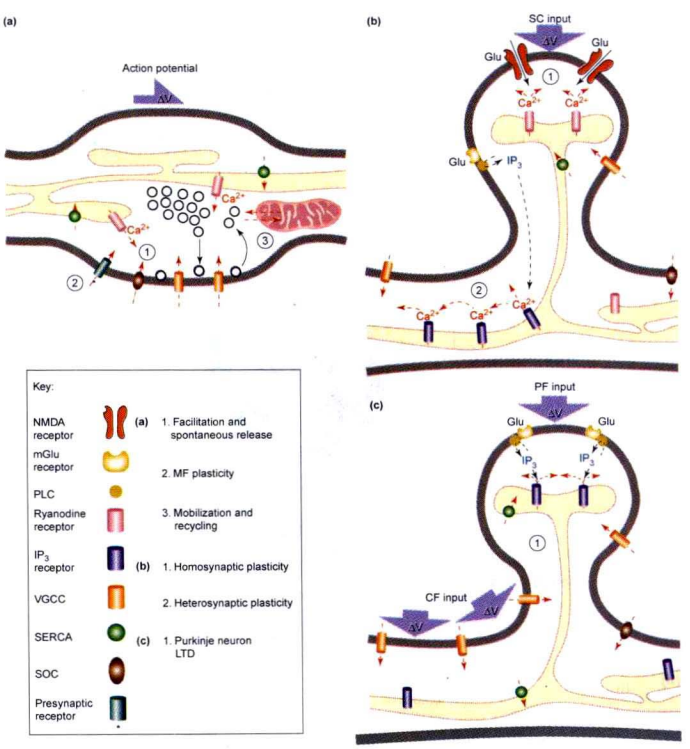
Trends in Pharmacological Sciences, Volume 27, Issue 2, February 2006, Pages 85-91

Franz F. Hefti, Arnon Rosenthal, Patricia A. Walicke, Sean Wyatt, German Vergara, David L. Shelton and Alun M. Davies

拮抗神经生长因子的新一类镇痛药

神经生长因子（NGF）最初被认为是发育中的神经系统的感觉神经元和交感神经元的促存活因子。对成人而言，神经生长因子并不是生存所必需的，但它在几种急性和慢性疼痛状态中疼痛的发生以及痛觉过敏上起到了关键作用。神经生长因子在受损和炎症组织中高表达，感受伤害的神经元中的神经生长因子受体酪氨酸激酶trkA的活化可以通过多种机制促发和增强疼痛的信号传导。在啮齿类动物的疼痛模型中，抑制神经生长因子的功能和信号可以起到与环氧合酶抑制剂和阿片制剂同样的阻断痛感的作用。一些制药公司根据拮抗神经生长因子的多种方法，积极开展了药物研发计划，这些方法包括神经生长因子的“捕获”，阻断其与酪氨酸激酶A的结合以及抑制酪氨酸激酶A的信号等。神经生长因子拮抗药有望成为高效治疗多种疼痛的方法，同时又没有传统镇痛药的不良反应。

（陈丽华译，祝晓玲校）



59 Behavioural pharmacology: 40+ years of progress, with a focus on glutamate receptors and cognition

Trends in Pharmacological Sciences, Volume 27, Issue 3, March 2006, Pages 141-148

Trevor W. Robbins and Emily R. Murphy

行为药理学：有关谷氨酸受体与认知40余年研究进展

行为药理学是多学科间的交汇，这些学科的研究领域最终均可应用于临床药物研发以及阐明脑的认知和行为功能。本文简要综述了有关英国行为药理学研究的发展和现状，重点阐述了我们对于学习和记忆理解的进展，这些进展来自于谷氨酸受体药理学以及行为神经科学的理论和方法学进展的发现。描述了关于NMDA受体在海马介导的空间学习和长时程增强的最初的突破性研究，以及近来证明谷氨酸受体参与工作记忆、认知记忆、刺激-反应学习与记忆，以及高级认知功能的研究进展。同时讨论了NMD受体的独特功能以及AMPA受体在包括收录、合并和提取等这些记忆形式中发挥基本作用的研究进展。

（祝晓玲译，林志彬校）

67 The quantitative analysis of drug-receptor interactions: a short history

Trends in Pharmacological Sciences, Volume 27, Issue 3, March 2006, Pages 149-157

David Colquhoun

药物－受体相互作用的定量分析：一段简短的历史

药理学真正开始发展成为定量科学是在1909年。那时，A.V. Hill在研究尼古丁和箭毒药理作用时推论出了朗格缪尔方程。此后的发展过程既有卓越的洞察也有错失了的机会，也表明还有许多工作要做，比如仍然没有数学模型去定量描述G蛋白偶联受体激动剂的作用，尽管在描述激动剂活化的离子通道方面取得了很大的进展，但这是因为离子通道比较简单之故。

（马捷译，祝晓玲校）

76 Smooth muscle research: from Edith Bülbring onwards

Trends in Pharmacological Sciences, Volume 27, Issue 3, March 2006, Pages 158-165

Alison F. Brading

始于 Edith Bülbring 的平滑肌研究

平滑肌的特性目前已有广泛的研究。实际上，这种纤小的肌细胞及其表现的广泛行为使之成为当前研究令人瞩目的焦点。但过去的情况却并非如此。平滑肌的这些特性使其最初的研究较横纹肌困难。而比其体积大的已分化的横纹肌则是当时的前沿研究者注意的焦点。在英国 EdithBülbring 的领导下，牛津大学药理学系开始了平滑肌的生理学研究。Edith Bülbring 的早期研究结果吸引了人们很多的注意，由此形成了一个活跃的国际平滑肌研究小组。尽管目前令人感兴趣的几个平滑肌研究领域并非追随于该牛津大学研究小组，但这些领域的很多进展与 Büilbring 及其小组明显相关。

（祝晓玲译，林志彬校）

84 Historical review: ATP as a neurotransmitter

Trends in Pharmacological Sciences, Volume 27, Issue 3, March 2006, Pages 166-176

Geoffrey Burnstock

关于神经递质 ATP 的历史性回顾

现代研究认为，嘌呤能信号传导在神经系统中有广泛的活性，包括神经蛋白、自主神经功能的中枢调控、神经细胞与神经胶质

细胞的相互作用、血管紧张度与血管新生的调控、疼痛和机械力感受转导以及特殊感觉的生理学。作者回顾了在20世纪70年代最初发现的嘌呤能神经传导、由此引发的争议及其被人们接受的过程（大约20年）、嘌呤能神经元共同传递的扩展、以及当ATP受体亚型被克隆和最终被证实以及在90年代初大脑与外周神经节神经元之间嘌呤能突触传递被发现后，最终使得嘌呤能神经传导被接受的经历。本文还讨论了该领域的最新进展，包括目前病理生理学对嘌呤能信号的关注及其潜在的治疗应用。

（马捷译，祝晓玲校）

95 Endogenous inverse agonists and constitutive receptor activity in the melanocortin system

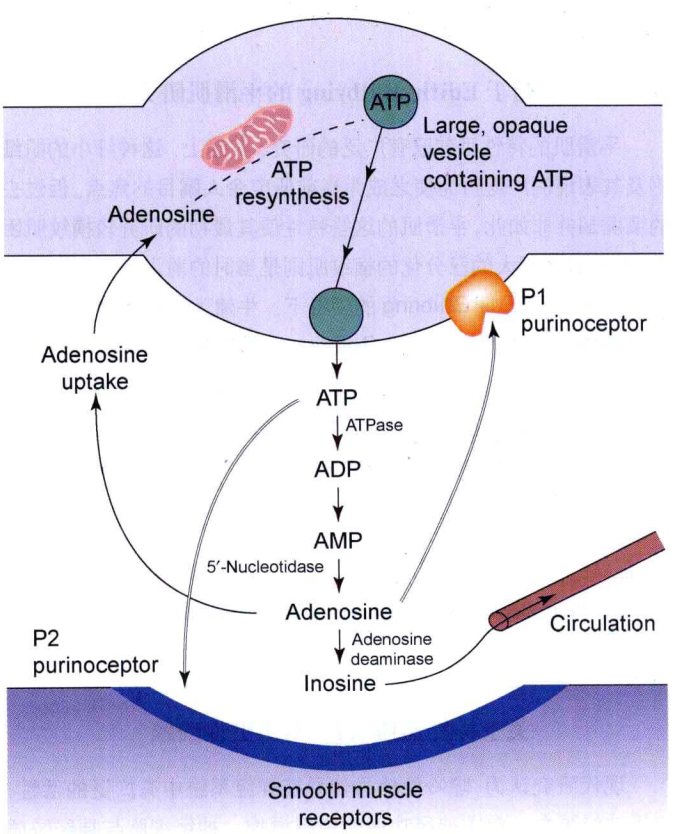
Trends in Pharmacological Sciences, Volume 27, Issue 4, April 2006, Pages 183-186

Roger A.H. Adan

内源性反向激动剂调节黑素细胞皮质激素固有受体活性

最近人们发现黑素细胞皮质激素受体突变选择性地降低肥胖者体内的这种固有受体的活性，此发现支持固有黑素细胞皮质激素受体活性与其受内源性反向激动剂的调控之间有着生理相关性。使用缺乏内源性黑素细胞皮质激素受体激动剂的小鼠的研究进一步表明，皮毛颜色的改变由黑素细胞皮质激素受体信号转导的不同程度引起，该信号受内源性反向激动剂调控。因此，固有黑素细胞皮质激素受体活性的调节对正常色素形成以及体重的稳定起了重要作用。

（祝晓玲译，林志彬校）



99 New light on multidrug binding by an ATP-binding-cassette transporter

Trends in Pharmacological Sciences, Volume 27, Issue 4, April 2006, Pages 195-203

Richard A. Shilling, Henrietta Venter, Saroj Velamakanni, Akanksha Bapna, Barbara Woebking, Sanjay Shahi and Hendrik W. van Veen

关于ATP结合盒转运蛋白介导的多药结合新见解

ATP结合盒（ABC）多药转运蛋白将结构无关的化疗药物排出细胞，使得病源微生物及人的肿瘤细胞耐药。而ABC多药转运蛋白结合和转运药物的分子基础尚不清楚。过去14年的基因分析研究揭示，哺乳类多药耐药的P糖蛋白发生了很多个体氨基酸的置换，从而影响到细胞耐药，但是这些研究未能确认作为一个改良药物结合位点一部分的一级氨基酸序列的特殊区域。最近，细菌P糖蛋白的同源物MsbA以及人P糖蛋白的MsbA同源模型的X射线晶体学结构分析提供了机会，可以用转运蛋白的三维结构，比较最初的突变形成数据。这种比较揭示了改变专一性的突变发生在P糖蛋白膜结构域中的三维“热点”区域。

（祝晓玲译，林志彬校）

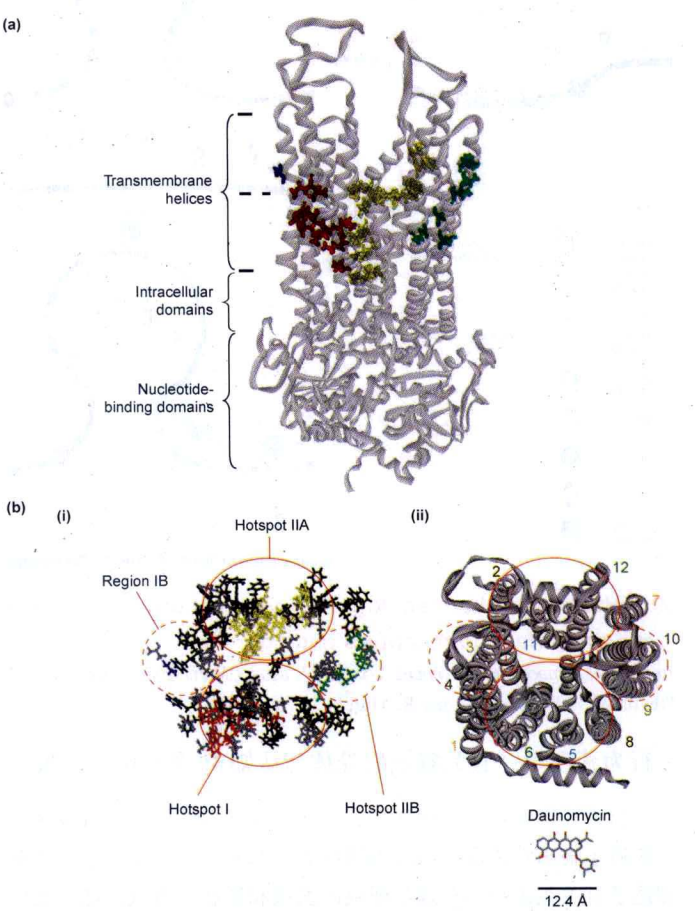
108 P2 receptors and cancer

Trends in Pharmacological Sciences, Volume 27, Issue 4, April 2006, Pages 211-217

Nicholas White and Geoffrey Burnstock

P2受体与肿瘤

嘌呤类信号传导系统涉及很多生理过程，ATP和其他胞外核



苷可能经由嘌呤能P2受体信号转导产生治疗肿瘤的效果。不同的P2受体亚型在大量不同类型肿瘤，包括原代人肿瘤组织样本和细胞系中均得到确定。近来的研究表明，不同受体亚型介导了不同的病理生理功能，如增殖、分化和凋亡等。体内实验显示，运用ATP能够降低肿瘤生长率，第一个临床试验也已完成。因此，作用于P2受体的药物可能成为新的肿瘤治疗工具。本文提供了有关嘌呤信号传导系统以及嘌呤受体亚型的背景知识并详细讨论了ATP在不同肿瘤中可能发挥的作用，包括体内实验和动物模型的讨论、临床实验以及所涉及的P2受体亚型的讨论。

（祝晓玲译，林志彬校）

115 Techniques: New pharmacological perspectives for the leptin receptor

Trends in Pharmacological Sciences, Volume 27, Issue 4, April 2006, Pages 218-225

Frank Peelman, Cyril Couturier, Julie Dam, Lennart Zabeau, Jan Tavernier and Ralf Jockers

技术：瘦素受体新的药理学前景

瘦素的功能由最初确定的维持体内能量动态稳定和控制肥胖，扩展到其对生殖、葡萄糖稳态、骨形成、伤口愈合以及免疫系统的调节。对瘦素的分子靶标，瘦素受体（LR），的刺激或抑制可能用于疾病治疗。最近的研究进展阐明了LR活化机制，因而可以设计出LR的拮抗剂。人们已研发出几种筛选和评价LR配体的分析方法。LR的细胞内和细胞外结构域均可成为药物靶标。生物发光共振能量转移技术可用来筛选作用靶标为LR胞外区的化合物，而新的逆相哺乳动物蛋白 - 蛋白交互作用陷阱技术可用来筛选影响LR胞内信号转导的化合物。无疑地，这些新的技术同样适用于其他药理学相关受体的研究。

（祝晓玲译，林志彬校）

123 Targets in ALS: designing multidrug therapies

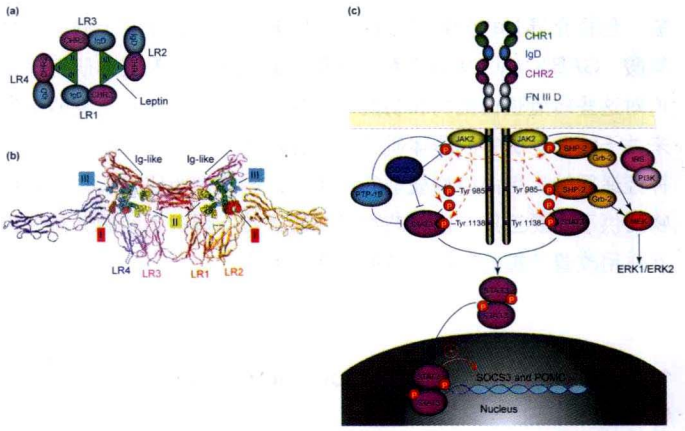
Trends in Pharmacological Sciences, Volume 27, Issue 5, May 2006, Pages 267-273

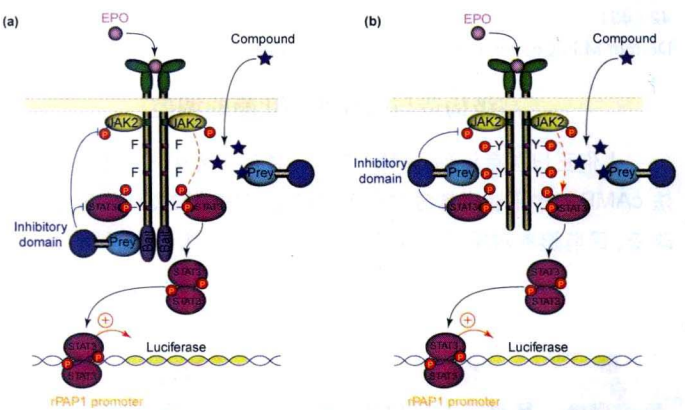
Maria Teresa Carrì, Giuliano Grignaschi and Caterina Bendotti

设计多药治疗肌萎缩性脊髓侧索硬化症的靶标

肌萎缩性脊髓侧索硬化症（ALS）是一种不可治愈的的疾病，其原因是运动神经元的渐进性丧失。即使像在Cu-Zn超氧化物歧化酶（SOD1）的基因突变中那样由单基因缺失所引起，ALS也是一种复杂的级联放大反应的结果，该反应涉及运动神经元，神经胶质和肌肉细胞的交叉干扰，并通过聚集毒素的机制使病情进一步发展。表达人类突变基因SOD1的啮齿类转基因动物可以演变发展一种渐进性的麻痹症，因此这种转基因动物被广泛用于潜在治疗方法的筛选。有报道表明，干扰神经毒素级联过程中特殊靶标的治疗能够有效延长啮齿类动物的寿命。多种干扰疗法，包括阻断损伤和向易感细胞传递分子，目前被证明是很有效的。因此，从多种药物治疗和/或通过病毒载体传递生长因子，与运动和食物疗法联合应用，可得到富有前景的新的治疗方案。

（马捷泽，祝晓玲校）





130 Angiogenesis: from plants to blood vessels

Trends in Pharmacological Sciences, Volume 27, Issue 6, June 2006, Pages 297-309

Tai-Ping Fan, Ju-Ching Yeh, Kar Wah Leung, Patrick Y.K. Yue and Ricky N.S. Wong

血管生成：从药用植物到血管

血管生成是诸如癌症和冠心病等疾病的主要病理改变。虽然人们在此方面的研究取得很大进展并获得一些令人鼓舞的临床结果，但仍需要更为安全而有效的方法。源于植物的新药鉴别有着悠久而成功的历史，某些促血管生成和抗血管生成的植物有效成分已在中医药中应用了几千年。与西医综合治疗相似，中医运用植物提取物的混合物，即所谓“复方”来增效减毒。更多的循证研究和对这些植物中提取的化合物化学结构的优化，将会进一步提高这些源于植物的约物在血管生成疗法中的疗效。

（祝晓玲泽，林志彬校）

143 Neurotransmitter transporters: molecular function of important drug targets

Trends in Pharmacological Sciences, Volume 27, Issue 7, July 2006, Pages 375-383

Ulrik Gether, Peter H. Andersen, Orla M. Larsson and Arne Schousboe

神经递质转运蛋白：重要的药物作用靶标的分子功能

细胞外间隙中神经递质的浓度由不同种类的膜转运蛋白控制。本篇综述着重探讨存在于神经细胞和神经胶质细胞上的两类神经递质转运蛋白的分子功能：（1）溶质转运蛋白（SLC）I家族，包括介导Na^+依赖性谷氨酸摄取的转运蛋白；（2）SLC6转运蛋白家

族，包括介导 Na^+ 依赖性多巴胺、5-羟色胺、去甲肾上腺素、甘氨酸、GABA（γ-氨基丁酸）摄取的转运蛋白。最近的研究让我们对这些转运蛋白结构和功能有了深入的认识。特别重要的是近来关于细菌同源物的晶体研究，它促成了第一个可靠的哺乳动物神经递质转运蛋白结构模型的产生。这些模型为研究某些特殊药物提供了重要工具，这些药物可以通过转运蛋白之间的选择性相互作用改善严重的神经和精神疾病的治疗。

（马捷译，祝晓玲校）

152 Higher-order organization and regulation of adenylyl cyclases

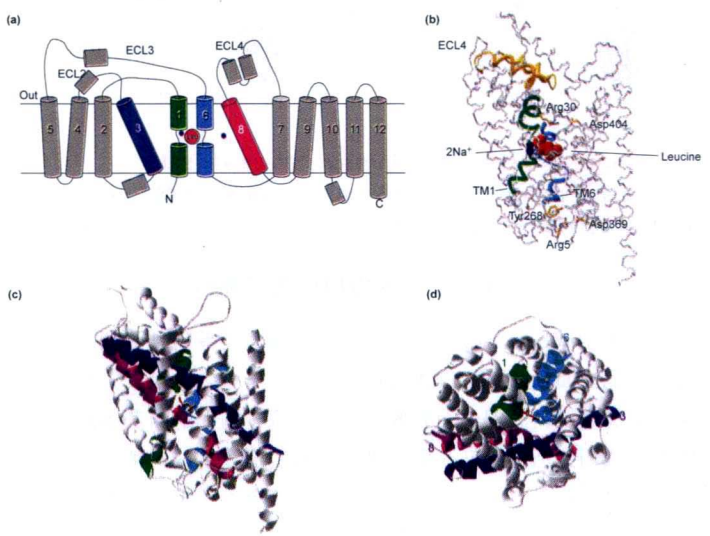
Trends in Pharmacological Sciences, Volume 27, Issue 8, August 2006, Pages 426-431

Dermot M.F. Cooper and Andrew J. Crossthwaite

高级构造与腺苷酸环化酶的调控

人们正日益意识到 cAMP 信号转导存在区室化，通过这种方法，cAMP 的水平在有着独立局部效应细胞内的独立结构域中发生改变。目前随着对质膜上腺苷酸环化酶构造的认识，最早的 cAMP 区室化部分是如何发生的正在被阐明。此篇综述论述了最近有关腺苷酸环化酶三个层次构造的研究发现：即寡聚化、定位膜脂筏、参与多蛋白信号转导复合体。这种构造与支架蛋白共同发挥了安置 cAMP 下游效应器的作用，可帮助识别有利于将酶的激活转变为局部效应的复合体。

（祝晓玲译，林志彬校）



158 Transport of glutathione and glutathione conjugates by MRP1

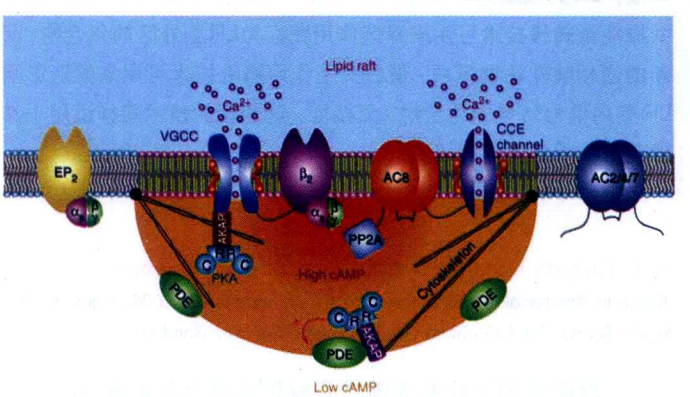
Trends in Pharmacological Sciences, Volume 27, Issue 8, August 2006, Pages 438-446 438-446

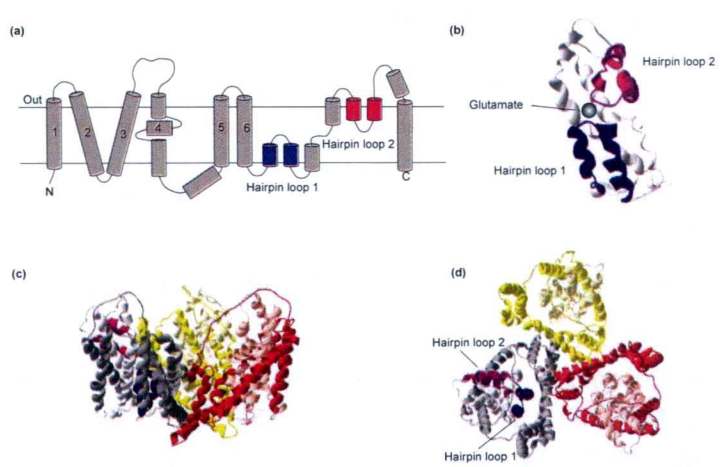
Susan P.C. Cole and Roger G. Deeley

MRPI 介导谷胱苷肽及谷胱苷肽偶联物的转运

偶联谷胱苷肽（GSH）的外源性化学物质以及偶联 GSH 的代谢物（如半胱氨酰白二烯 C4）若要从机体内去除或作用于其细胞靶点，必须首先由其产生的细胞中转运出去。这种排出常常经由多药耐药蛋白 1（MRP1）转运蛋白介导，这种转运蛋白可保护正常细胞免受毒物的损害，但也使得肿瘤细胞耐药。除了药物与 GSH 偶联物，MRP1 也将 GSH 和 GSH 二硫化物排出，因此可能在细胞对氧化压力的反应中发挥了作用。MPR1转运出某些药物以及偶联的有机阴离子需要GSH，但尚不清楚GSH（及其类似物）如何加强转运。定点突变形成以及生物物理研究让我们对MRP1结构决定簇有了深入的了解，该决定簇影响到 GSH 和 GSH 偶联物的结合及转运。

（祝晓玲译，林志彬校）





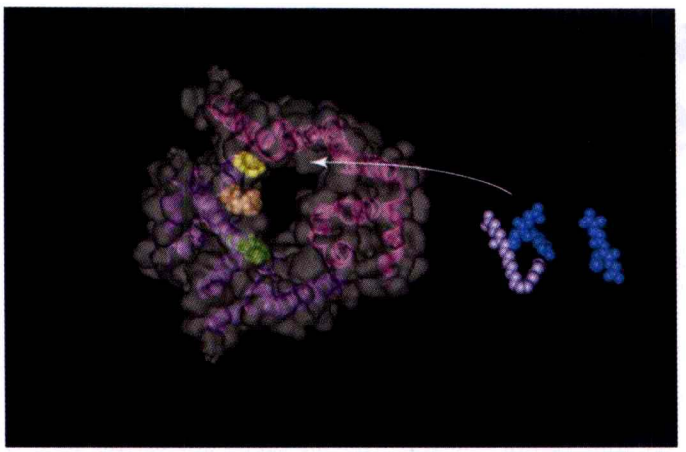
167 Analgesic strategies beyond the inhibition of cyclooxygenases

Trends in Pharmacological Sciences, Volume 27, Issue 9, September 2006, Pages 467-474

Hanns Ulrich Zeilhofer and Kay Brune

环氧合酶抑制途径以外的止痛策略

一个多世纪以来，人们用环氧合酶（COX）抑制剂阻断前列腺素的生成来治疗炎症疼痛，虽然能够提供良好的疼痛缓解作用，但其严重的副反应（主要是上消化道溃疡）阻碍了它们的长期使用。COX-2 选择性抑制剂（coxibs）的研制极大地降低了胃肠道毒性，但临床对照试验和实验研究表明，应用 coxibs 有引起显著的心血管不良反应的危险。最近，COX-2 阻断途径的下游信号元



件已经被鉴别出来，由此提供了更多可能的靶点。本综述主要阐述了前列腺素E合酶、前列腺素受体以及前列腺素在周围神经系统和中枢神经系统的下游效应器，包括瞬时受体的潜在通道、河豚毒素耐受的Na^+通道和抑制性甘氨酸受体等。这些新靶点应该能使炎症性疼痛的治疗特异性更高，副作用更少。

（李敏译，祝晓玲校）

175 Allosteric agonists of 7TM receptors: expanding the pharmacological toolbox

Trends in Pharmacological Sciences, Volume 27, Issue 9, September 2006, Pages 475-481

Christopher J. Langmead and Arthur Christopoulos

七次跨膜受体的异构激动剂：更广泛的药理学应用

高等生物中近1%的基因组编码七次跨膜的G蛋白偶联受体，此受体控制着一个广泛的生理过程，并且代表了目前使用的近一半药物的靶点。迄今为止，多数以七次跨膜受体为靶点的药物通过与内源性激动剂相同的区域（称为临位空间位点）与受体作用。然而新的功能筛选测定法极大地提高了已鉴别异构配体的数量。这些配体结合于七次跨膜受体上的不同位点。除了调控临位空间配体的亲和性，异构配体也能够改变其效能并通过自己的方式活化七次跨膜受体。本文对七次跨膜受体异构激动剂的研究现状做了简要综述，讨论了该配体给药理学家和药物研发业带来的前景和挑战。

（李敏译，祝晓玲校）

182 Chemokine receptors as therapeutic targets in chronic obstructive pulmonary disease

Trends in Pharmacological Sciences, Volume 27, Issue 10, October 2006, Pages 546-553

Louise E. Donnelly and Peter J. Barnes

趋化因子受体作为慢性阻塞性肺部疾病的治疗靶标

慢性阻塞性肺部疾病（COPD）是一种日益严重的全球性健康问题，尚无有效的改善疾病的治疗方法，COPD通过募集炎症细胞，引发小气道和肺实质的慢性炎症。炎症细胞的运输由多种趋化因子协调完成，因此，在治疗此疾病时，使用选择性拮抗剂阻断趋化因子受体可能会是一种有效的抗炎策略。一些研究也支持一些趋化因子及其受体在肺慢性阻塞性疾病中的作用，包括趋化因子受体CXCR2和CXCR3。研发中的小分子受体拮抗剂可能成为抗炎治疗策略。相关药理学提供了抑制白细胞募集，进而降低COPD炎症反应的作用机制，而目前还没有能够影响该炎症反应的药物治疗。

（马捷译，祝晓玲校）

190 How important is protein kinase C in μ-opioid receptor desensitization and morphine tolerance?

Trends in Pharmacological Sciences, Volume 27, Issue 11, November 2006, Pages 558-565

Chris P. Bailey, Forrest L. Smith, Eamonn Kelly, William L. Dewey and Graeme Henderson

蛋白激酶C在μ-阿片受体脱敏和吗啡耐受中如何发挥重要作用？

阿片类药物如吗啡的反复使用会引起对镇痛剂的耐受、奖赏反应（欣快感）和呼吸道抑制效应的发生。因此，为了在以后的治疗中获得同样的药物疗效必须加大药物的剂量。耐受性的出现限制了阿片类药物的临床疗效，并且增加了为获取欣快感而滥用阿片类药物所引发的社会问题。关于吗啡耐受产生的机制仍然颇多争论。本文中，我们提出了蛋白激酶C在吗啡引起的μ-阿片受体脱敏过程中发挥了重要作用，并且这种细胞过程有助于体内吗啡耐受的发展和维持。

（陈丽华译，祝晓玲校）

198 Emerging cancer therapeutic opportunities target DNA-repair systems

Trends in Pharmacological Sciences, Volume 27, Issue 6, June 2006, Pages 338-344

Jian Ding, Ze-Hong Miao, Ling-Hua Meng and Mei-Yu Geng

靶向DNA修复系统展露出抗肿瘤治疗新机会

DNA损伤剂在当前的肿瘤临床非手术治疗中起着中心作用。DNA损伤与修复之间的平衡决定其最终的治疗效果。肿瘤细胞DNA修复能力的增强将导致耐药或放射耐受，从而严重限制DNA损伤剂的治疗能力。DNA修复系统中潜藏着多种抗肿瘤靶标；有数种针对这些靶标的小分子化合物正在进行临床试验。干扰DNA修复系统有望成为抗肿瘤联合治疗中一条重要的新途径。

（本中文摘要由原文作者——中科院上海药物研究所所长丁健研究员提供）

To cite this article, use the original reference: Barr, A.J. & Knapp, S. (2006) Trends Pharmacol. Sci. 27, 525–530

MAPK-specific tyrosine phosphatases: new targets for drug discovery?

Alastair J. Barr and Stefan Knapp

Structural Genomics Consortium, University of Oxford, Botnar Research Centre, Oxford, OX3 7LD, UK

Protein tyrosine phosphatases (PTPs) have key roles in a diverse range of cellular processes, and their dysregulation is associated with several human diseases. Many PTPs are recognized as potential drug targets; however, inhibitor development has focused only on a small number of enzymes, most notably PTP1B for type II diabetes and obesity, and MKP1 and CDC25 for cancer. The future challenge of selective-inhibitor development for PTPs will be significantly facilitated by the recent rapid progress in the structural biology of the 'PTPome'. In this article, we focus on the family of mitogen-activated protein kinase (MAPK)-specific tyrosine phosphatases – PTPN5 [also called striatal-enriched phosphatase (STEP)], PTPN7 (also called hematopoietic PTP) and PTPRR (also called PC12 PTP or STEP-like PTP) – and discuss approaches for achieving selectivity for the MAPK-PTPs at the molecular level using recently determined high-resolution X-ray crystal structures. We believe that the development of specific inhibitors would provide a valuable set of experimental pharmacological tools for investigating the physiological role of these phosphatases and exploring their emerging role in human disease.

Introduction

Protein phosphorylation is regulated by the opposing actions of kinases and phosphatases, and provides an important means of regulating protein function. There are at least 107 genes in the human genome that encode protein tyrosine phosphatases (PTPs) [1,2], and the class I cysteine-based PTPs comprise the largest family, with 37 tyrosine-specific 'classical' PTPs (Box 1) and 61 dual-specificity phosphatases. Classical PTPs are multidomain proteins that can be further divided into receptor-like transmembrane (group R1–R8) and non-transmembrane (group NT1–NT9) PTPs. Most receptor-like PTPs, with the exception of the R3, R7 and R8 groups, have two PTP domains: a catalytically active D1 domain and a D2 domain with negligible or no catalytic activity. High-resolution crystal structures of 20 PTP domains have been determined, with a representative member in most of the subgroups (Box 1). The PTP subgroup R7, which is the focus of this article, consists of PTPN5 [also called striatal-enriched phosphatase (STEP)], PTPN7 [also called hematopoietic PTP (HePTP)] and PTPRR [also called PC12 PTP (PCPTP1) or STEP-like PTP (PTP-SL)]. These three tyrosine-specific mitogen-activated protein kinase (MAPK)-PTPs bind to and negatively regulate the activity and cellular localization of members of the MAPK family [3,4]. High-resolution structures of all three human enzymes have recently been determined [5–7], which will facilitate studies aiming to develop specific MAPK-PTP inhibitors by providing insights into the unique structural features of the active sites of these PTPs.

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Available online 21 August 2006.

Overview of MAPK-PTP structure and function

MAPK-PTPs counterbalance the activity of MAPKs in the cytosol and are, therefore, crucial regulators of the cellular response to extracellular stimuli (Figure 1). The structure of the MAPK-PTP domains closely resembles the classical architecture of tyrosine phosphatases [8], comprising extremely twisted mixed β-sheets flanked by α-helices. They can be distinguished, however, by the presence of a kinase interaction motif (KIM) of 16 amino acids that is on the N-terminal side of the phosphatase domain [9]. This motif forms an α-helix that targets MAPK-PTPs to their MAPK substrates. Dual-specificity phosphatases also contain a KIM motif. Recently, the structure of extracellular-signal-regulated kinase (ERK)2 in complex with a peptide from PTPN7 was determined and KIM sequences were compared [10]. This crystallographic study showed that KIM binding induces structural changes in the kinase activation segment that might contribute to substrate specificity. MAPK-PTPs prefer the substrates ERK1/2 and p38 over JNK, and ERK5 is a substrate of PTPRR [11,12]. The substrate specificity of these phosphatases is brought about by a bidentate-substrate-recognition motif consisting of the phosphatase KIM sequence interacting with the MAPK-docking site, and the active site of the phosphatase binding to the phosphorylated activation loop of the kinase [13,14].

MAPKs are activated by phosphorylation of a specific threonine and tyrosine residue (pThr-Xaa-pTyr) in the activation loop, and dephosphorylation of the tyrosine residue is sufficient to inactivate MAPK, blocking its nuclear translocation. It is unknown whether monophosphorylated MAPKs have other biological functions. The activity of MAPK-PTPs is also regulated by phosphorylation at multiple sites by protein kinase (PK)A, PKC and ERK. A well-documented serine phosphorylation site within the KIM domain blocks the interaction of MAPKs with MAPK-PTPs, thereby leading to inactivation of the phosphatase *in vivo* [15–17] (Figure 1).

Box 1. Phylogenetic tree of human tyrosine-specific PTP D1 and D2 domains

Figure I shows a phylogenetic tree of human PTP D1 and D2 domains, with boxes indicating phosphatase domains for which a crystal structure has been determined. The PTPs are grouped into receptor PTPs (groups R1–R8) and non-transmembrane PTPs (groups NT1–NT9), although it should be noted that, for several PTPs, alternative splicing generates both receptor and non-transmembrane forms. The abbreviated Human Genome Organisation (HUGO: http://www.hugo-international.org/) gene symbol nomenclature is used in the tree, and the corresponding common names are provided in Table I (further information about deposited structures is available at http://science.novonordisk.com/ptp/ and http://www.sgc.ox.ac.uk/structures/). PTPRV (also known as osteotesticular PTP) has not been included in the tree because it is a pseudogene in humans, although a functional gene is found in other species.

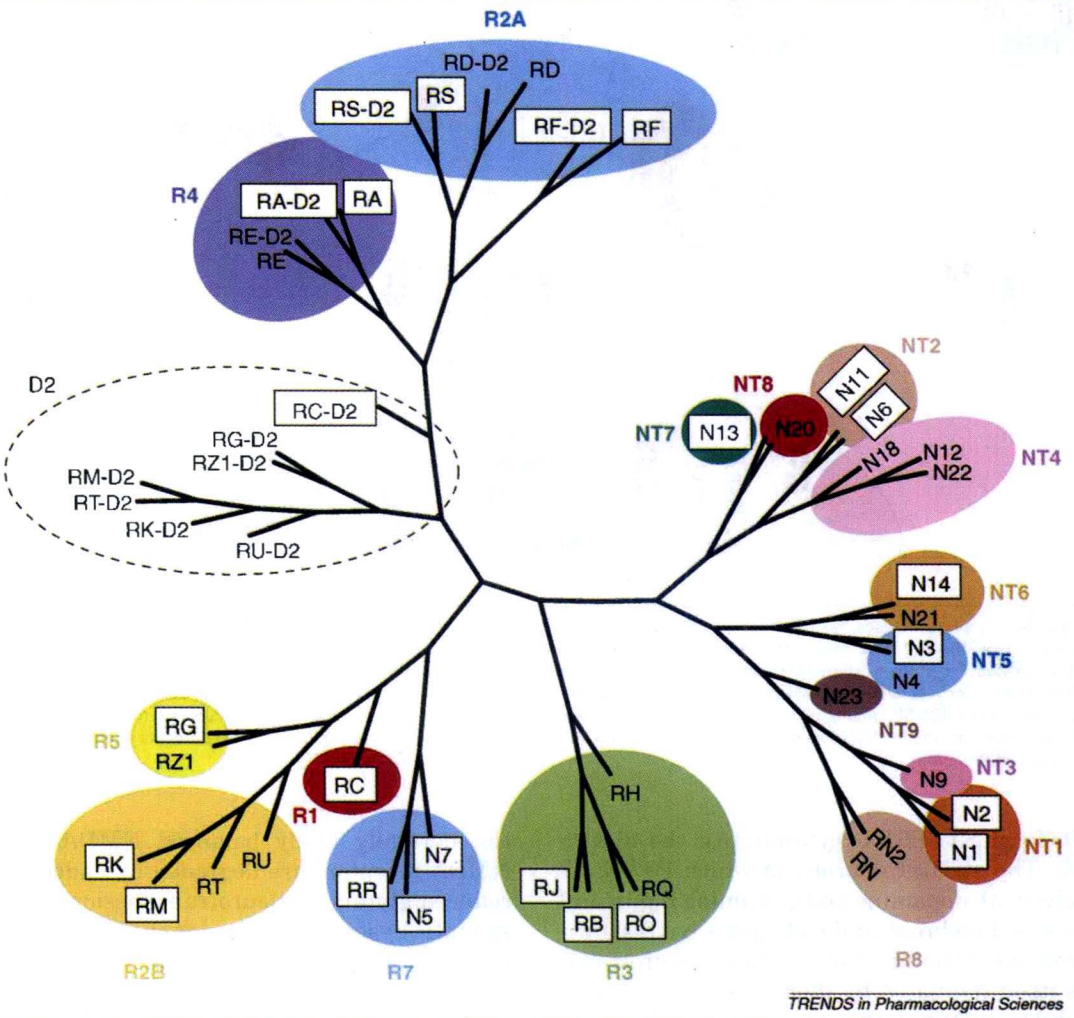

Figure I. Phylogenetic tree of human PTP D1 and D2 domains. The distance between family members in the tree is related to their evolutionary divergence.

Table I. HUGO gene symbol nomenclature for PTPs and their corresponding common names

HUGO name	Protein name	HUGO name	Protein name	HUGO name	Protein name	HUGO name	Protein name
PTPN1	PTP1B	PTPN13	PTPBAS	PTPRD	PTPδ	PTPRO	GLEPP1
PTPN2	TCPTP	PTPN14	PTPD2	PTPRE	PTPε	PTPRQ	PTPS31
PTPN3	PTPH1	PTPN18	BDP1	PTPRF	LAR	PTPRR	PCPTP1
PTPN4	MEG1	PTPN20	PTPTyp	PTPRG	PTPγ	PTPRS	PTPσ
PTPN5	STEP	PTPN21	PTPD1	PTPRH	SAP1	PTPRT	PTPρ
PTPN6	SHP1	PTPN22	LyPTP	PTPRJ	DEP1	PTPRU	PTPλ
PTPN7	HePTP	PTPN23	HDPTP	PTPRK	PTPκ	PTPRZ1	PTPζ
PTPN9	MEG2	PTPRA	PTPα	PTPRM	PTPμ		
PTPN11	SHP2	PTPRB	PTPβ	PTPRN	IA2		
PTPN12	PEST	PTPRC	CD45	PTPRN2	IA2β		

PTPN5

Although the three MAPK-PTPs catalyze the same reaction – the inactivation of MAPKs – their different tissue distributions enable them to have diverse biological roles. PTPN5 is a brain-specific phosphatase that is expressed preferentially in neurons of the striatum, hippocampus and cortex [18]. Alternative splicing of PTPN5 produces several isoforms that are either membrane associated

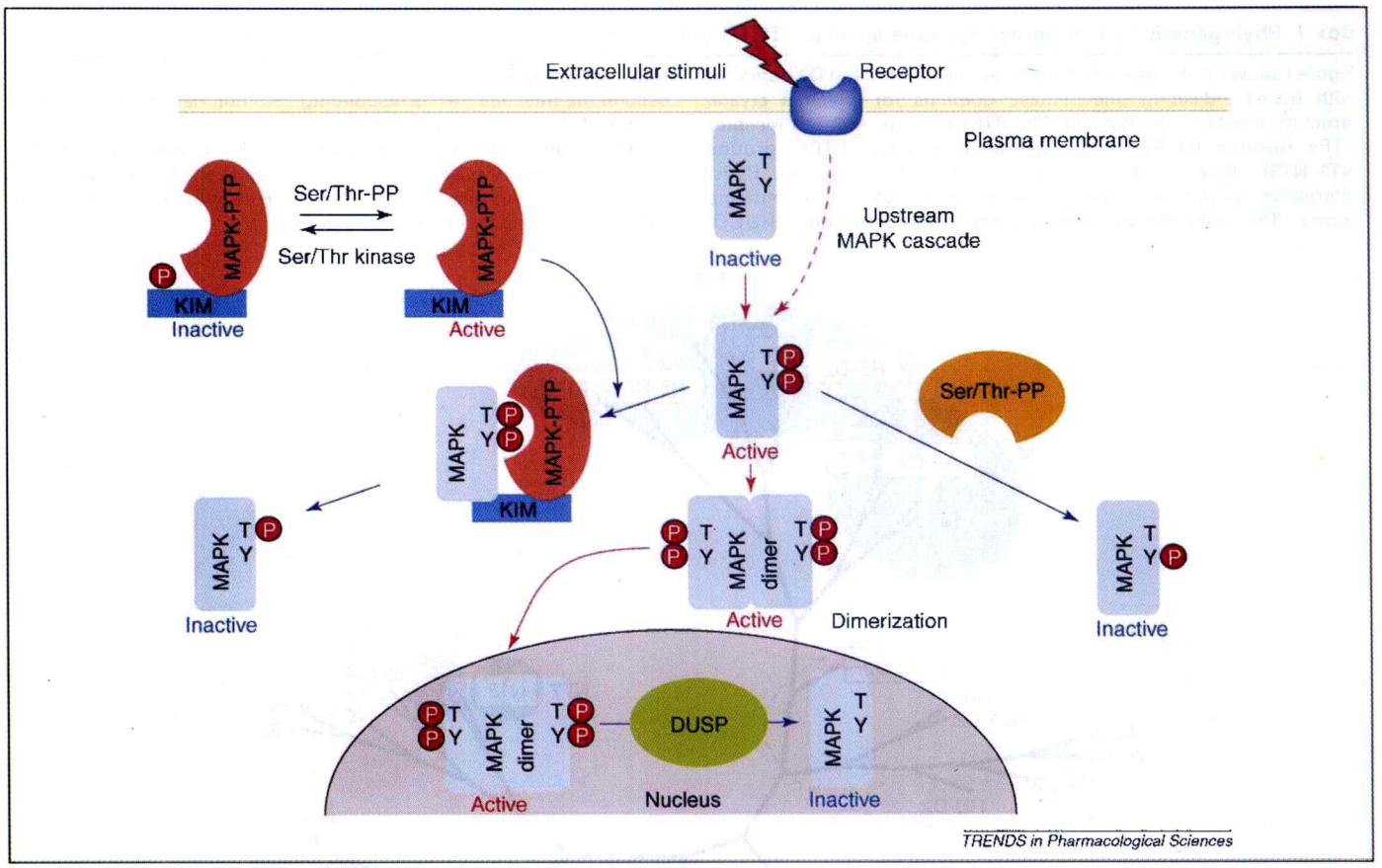

Figure 1. MAPK regulation by phosphatases. MAPKs such as ERK1/2 and p38 are activated by a range of extracellular stimuli. The amplitude and duration of MAPK activation vary depending on the cell type and extracellular stimuli. Activation is mediated by a cascade of upstream kinases (red broken arrow) that leads to phosphorylation of a Thr-Xaa-Tyr motif in the MAPK activation loop. Phosphorylated active MAPKs dimerize and translocate to the nucleus, where they, in turn, phosphorylate nuclear targets. The inactivation of MAPKs is achieved through several routes (blue arrows) by MAPK-PTPs (red), Ser/Thr-phosphatases (Ser/Thr-PP, orange) and dual-specificity phosphatases (DUSP, green), which specifically dephosphorylate pTyr, pThr or both. A subgroup of DUSPs is cytoplasmic (not shown). The activity of MAPK-PTPs is further regulated by phosphorylation–dephosphorylation (black arrows). Phosphorylation of the KIM sequence prevents interaction of MAPK-PTP with MAPK and leads to phosphatase inactivation.

(e.g. the 61-kDa form, STEP61) or cytosolic (e.g. the 46-kDa form, STEP46). The striatal neurons in which PTPN5 is expressed receive both dopamine and glutamine input, and detailed studies by Lombroso and colleagues have shown that PTPN5 regulates the functions of these neurotransmitters and is itself regulated by them, thereby having a key role in cellular processes that are related to learning and memory [19–21]. Intriguingly, these studies also revealed that PTPN5 recognizes substrates other than MAPKs – the src-family kinase fyn and NMDA-receptor subunits – and it remains to be determined whether this activity is also dependent on the KIM domain.

A recent study by Snyder *et al.* [22] reported a novel mechanism linking PTPN5 and soluble amyloid-β protein to the pathology of Alzheimer's disease. In this model, it is the effects of β-amyloid on synaptic function, rather than its deposition in plaques and neurofibrillary tangles, that contribute to neurodegeneration and cognitive decline [17,22,23]. In the brain of Alzheimer's disease patients, levels of the soluble 42-amino acid amyloid-β peptide (Aβ42) accumulate following the cleavage of amyloid precursor protein. The binding of Aβ42 to the α7 nicotinic acetylcholine receptor leads to PTPN5 dephosphorylation by a mechanism that involves protein phosphatase (PP)2B [24] and activation of PTPN5, leading to perturbation of the normally finely balanced NMDA signaling events. NMDA receptors are degraded by endocytosis, leading to reduced glutamate neurotransmission and, consequently, synaptic dysfunction. Snyder *et al.* demonstrated that the introduction of dominant–negative PTPN5 (dnSTEP-Tat) into neurons blocks amyloid-β-induced endocytosis of the NMDA-receptor subunit NR1 [22,23], and it is therefore tempting to speculate that PTPN5 inhibitors would reduce the synaptotoxic effects of amyloid-β.

PTPRR

PTPRR is expressed predominantly in the brain, with the highest levels in the cerebellum [25]. As with PTPN5, multiple isoforms are expressed that have also been detected in many non-neuronal tissues and cell types. Nerve growth factor (NGF) treatment of PC12 cells (rat pheochromocytomas derived from an adrenal tumor of neural crest origin) increases transcription of the gene encoding PTPRR, although longer-term treatment over several days decreases mRNA levels [25,26]. Because the overexpression of PTPRR in PC12 cells suppresses ERK activation by NGF or epidermal growth factor [9,27], it has been speculated that PTPRR functions as a negative regulator of NGF signaling, which is of significance to neurodegenerative disease.

PTPN7

PTPN7 is expressed mainly in the thymus, spleen and leukocytes, and it has a negative role in antigen-receptor signaling in T cells by downregulating MAPK activity [28–30]. The gene encoding PTPN7 maps to chromosome 1q32.1, which is a site frequently associated with preleukemic myeloproliferative diseases, and grossly overexpressed PTPN7 was detected in myeloid cells from a patient with acute leukemia [31,32]. However, it remains to be established whether overexpression has a causative link to the disease.

Achieving MAPK-PTP inhibitor selectivity using a structure-based design approach

The development of selective phosphatase inhibitors is challenging because of the high level of similarity in the active sites of individual PTPs, the highly polarized nature of the pocket and the small active-site cavity. Most reported potent and competitive PTP inhibitors are highly charged phosphomimetics or are peptide based with limited cell permeability and oral bioavailability; however, despite these challenges, successes have been achieved in the design of selective inhibitors (for recent reviews, see Refs [33–35]). Successful strategies have exploited the markedly different structural surface features surrounding the active site, non-conserved individual residues in loops proximal to the active site or allosteric inhibitor sites [36], and on this basis we propose approaches for achieving selectivity for the MAPK-PTPs.

The phosphotyrosine-recognition loop with the motif KNRY defines one boundary of the active-site pocket and is followed by a lysine and threonine residue in MAPK-PTPs (Figure 2). The corresponding residues in PTP1B are Arg47 and Asp48, and the negatively charged aspartate residue, in particular, has been targeted in inhibitor-development studies [37,38]. The threonine residue in the corresponding position of MAPK-PTPs is unique to this subfamily and we believe that this difference in the proximity of the active site could be explored for the development of more-selective inhibitors. The preceding lysine residue is orientated away from the active site in PTPRR and is disordered in the PTPN5 and PTPN7 structures, indicating that the side chain is flexible. Another region with non-conserved residues adjacent to the active site is present in the loop between β-sheets 5 and 6 (Figure 2). This region is poorly defined in both PTPN7 structures (Protein Data Bank codes 2A3K and 1ZCO) but it is well ordered in PTPRR (Protein Data Bank code 2A8B) and PTPN5 (Protein Data Bank code 2BV5). Targeting Asn498 of PTPRR in this loop, which projects over the active site, might provide an approach for increasing inhibitor specificity towards PTPRR and PTPN5.

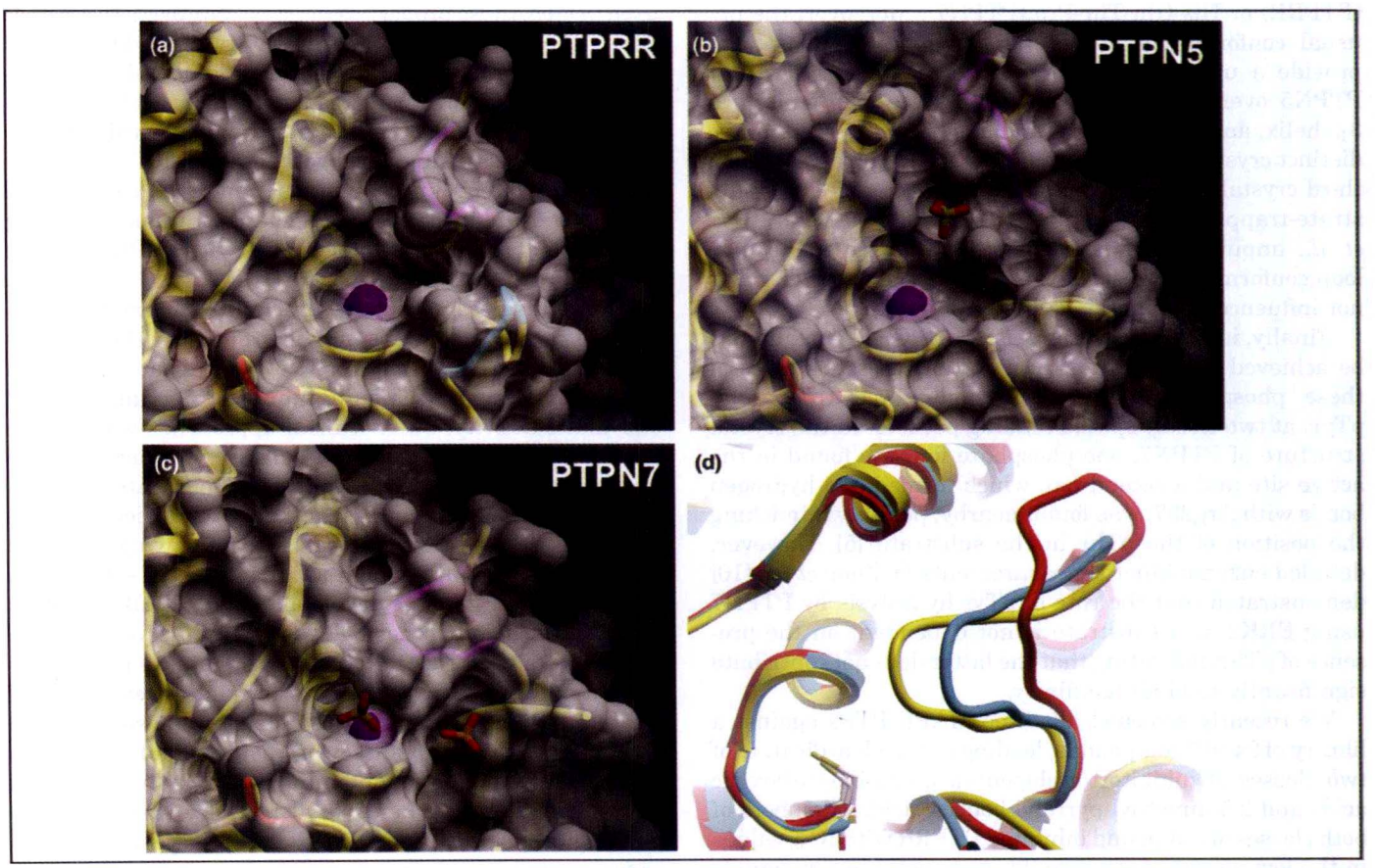

Figure 2. Comparison of the active-site structure of MAPK-PTPs. Features are shown that can be used for designing specific inhibitors. The surface is shown as a semi-transparent layer, with the secondary-structure elements represented as ribbons underneath (yellow). The conserved cysteine residue at the bottom of the active site is shown for orientation (magenta). The backbone of the moveable WPD loop (residues WPDXGXP, magenta) is shown with PTPRR **(a)** and PTPN5 **(b)** in the open conformation and with PTPN7 **(c)** in the closed state. The pTyr-recognition loop is shown in red (residues K and T). The loop between β-sheets 5 and 6 is colored blue in PTPRR. The sulfate moiety in the PTPN5 crystal structure and the phosphate moieties in the PTPN7 structure are shown in a ball-and-stick representation. **(d)** A comparison of WPD-loop conformations by structural overlay in PTPN5 (red), PTPN7 (yellow) and PTPRR (blue).

A third region of non-conserved residues surrounding the active site is located at positions corresponding to Met258 and Gly259 of PTP1B, in which these residues form a gateway or open cleft that has been investigated by introducing inhibitor substituents that cause steric hindrance of certain PTPs that have a bulky residue at this position (e.g. Gln in PTPRA) [37]. Sequence alignments reveal that MAPK-PTPs have two glycine residues in the corresponding positions, indicating that this region also forms an open cleft. However, analysis of PTPRR and other MAPK-PTP structures reveals that this region is occupied by a side chain (e.g. Phe404 in PTPRR) projecting from the α2′-helix, resulting in closure of the cleft. Therefore, bulky inhibitor moieties designed to target this cleft would not bind to MAPK-PTPs. This observation underlines the importance of high-resolution structures compared with sequence comparisons for the design of inhibitors.

Besides the structural features described, we believe that the differences in sequence, conformation and dynamics of the WPD loop are some of the most promising structural elements that can be targeted for the development of more-selective inhibitors of MAPK-PTPs. The amino acid sequence of the WPD loop, which undergoes a large conformational change following substrate binding, is conserved in most PTPs (WPDXGXP) (Figure 2). In MAPK-PTPs, the common His-Gly-Val-Pro sequence is replaced by Gln-Lys-Thr-Pro (PTPN5), His-Lys-Thr-Pro (PTPRR) or His-Gln-Thr-Pro (PTPN7). Moreover, the unusual conformation of the WPD loop in PTPN5 could provide a unique opportunity to achieve selectivity for PTPN5 over other MAPK-PTPs [5]. The loop ends in a 3_{10}-helix, and this conformation has been observed in two distinct crystal forms with a sulfate ion (Figure 2) and in a third crystal with pTyr bound to the active site of a substrate-trapping mutant (PTPN5-Cys472Ser) (A.J. Barr *et al.*, unpublished), indicating that this unusual WPD-loop conformation is stable and, in contrast to PTP1B, is not influenced by peptide substrate binding.

Finally, inhibitor selectivity for MAPK-PTPs might also be achieved by exploiting the fact that the substrates of these phosphatases are bi-phosphorylated (pThr-Xaa-pTyr) at two closely spaced binding pockets. In the crystal structure of PTPN7, one phosphate ion was found in the active site and a second ion, which formed two hydrogen bonds with Arg297, was found nearby, possibly mimicking the position of the pThr in the substrate [5]. However, detailed enzyme-kinetic measurements by Zhou *et al.* [10] demonstrated that the rate of pTyr hydrolysis by PTPN7 using ERK2 as a substrate is not dependent on the presence of pThr, indicating that the latter does not contribute significantly to binding affinity.

We recently screened all three MAPK-PTPs against a library of 24 000 compounds, leading to the identification of two classes of inhibitor: cyclopenta[c]quinoline-carboxylic acids and 2,5-dimethyl-pyrrolyl benzoic acids. Members of both classes of compound inhibited PTPRR with IC_{50} values in the low micromolar range [5]. Although the compounds were small (molecular weights of ~200 Da), they showed surprisingly high selectivity within the MAPK-PTP family. However, PTP1B was also inhibited by these compounds. A docking model of the cyclopenta[c]quinoline inhibitor scaffold in PTPRR indicated that a large portion of the binding pocket is not occupied and that chemical modification by the nitrogen atom of the quinoline ring could present an opportunity for the design of more-potent and more-selective inhibitors [5].

Concluding remarks

Several PTPs are already established drug targets, and progress towards clarifying the functional role of individual PTPs will provide essential information for understanding the role of PTPs in disease. Specific inhibitors are valuable tools with which to study cellular functions of the targeted protein and validate it as a potential intervention point for the treatment of human disease. The availability of high-resolution structural information is a prerequisite for rational inhibitor-design approaches and it is likely that the structure of all PTP family members will be determined in the near future.

One of the main challenges for the design of potent inhibitors is to overcome the small size and polar nature of the active-site pocket. In the case of PTP1B, bidentate inhibitors have been designed that target two surface pockets. This concept could also be applicable to other family members. The polarity of the active site and difficulties in identifying potent pTyr mimetic compounds resulted in phosphatase inhibitors with unfavorable pharmacological properties. To generate inhibitors that can be used *in vivo*, these properties must be improved. In a recent study, the problem of cell permeability was addressed by coupling inhibitors to a cell-penetrating peptide or a lipophilic fatty acid, and converting carboxylic acids to esters [39]. We believe that the inhibitor approach will complement strategies using the overexpression of dominant–negatives or gene knockouts that might be complicated by compensatory biochemical changes induced during development (as discussed for studies with PTPN7$^{-/-}$ mice [28]).

The strategies outlined, together with the crystal structures of catalytic domains, provide routes for the development of MAPK-PTP inhibitors. We believe that, in addition to the conventional screening approach for inhibitors of enzymatic activity, other fruitful approaches will involve modulating the KIM-domain–MAPK interface, virtual screening and screening for allosteric modulators. NMR-based fragment screening – together with medicinal chemistry to link low-affinity fragments occupying adjacent sites, thereby creating high-affinity ligands – has been used successfully for the development of PTP1B inhibitors and is applicable to other PTPs [40,41]. Co-crystallization of inhibitors with this family of phosphatases is urgently needed to provide new insights for the development of inhibitors and to facilitate structure-based design approaches. The drug-discovery potential of PTPs has yet to be fully exploited, and inhibitors of individual PTPs have the potential to be used, at the very least, as pharmacological tools with which to investigate the physiological roles of the enzymes and, at best, as therapeutics.

Acknowledgements

We gratefully acknowledge Brian Marsden and Wen Hwa Lee for assistance preparing the figures, and Structural Genomics Consortium

colleagues and collaborators for their valuable contributions and helpful discussions. The Structural Genomics Consortium is a registered charity (number 1097737) that is funded by the Wellcome Trust, GlaxoSmithKline, Genome Canada, the Canadian Institutes of Health Research, the Ontario Innovation Trust, the Ontario Research and Development Challenge Fund, the Canadian Foundation for Innovation, VINNOVA, The Knut and Alice Wallenberg Foundation, The Swedish Foundation for Strategic Research and Karolinska Institutet.

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To cite this article, use the original reference: Peterson, O.H. & Sutton, R. (2006) Trends Pharmacol. Sci. 27, 113–120

Ca^{2+} signalling and pancreatitis: effects of alcohol, bile and coffee

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Ca^{2+} is a universal intracellular messenger that controls a wide range of cellular processes. In pancreatic acinar cells, acetylcholine and cholecystokinin regulate secretion via generation of repetitive local cytosolic Ca^{2+} signals in the apical pole. Bile acids and non-oxidative alcohol metabolites can elicit abnormal cytosolic Ca^{2+} signals that are global and sustained and result in necrosis. Necrosis results from excessive loss of Ca^{2+} from the endoplasmic reticulum, which is mediated by Ca^{2+} release through specific channels and inhibition of Ca^{2+} pumps in intracellular stores, followed by entry of extracellular Ca^{2+}. Reduction of the cellular ATP level has a major role in this process. These abnormal Ca^{2+} signals, which can be inhibited by caffeine, explain how excessive alcohol intake and biliary disease cause acute pancreatitis, an often-fatal human disease in which the pancreas digests itself and its surroundings.

Pancreatitis lacks specific therapy

Acute pancreatitis is a human disease in which the pancreas digests itself. The incidence of both acute and chronic pancreatitis continues to increase and these disorders cause significant morbidity and mortality **[1,2]**. However, despite much research and many clinical trials, pancreatitis lacks specific pharmacological therapy, even though there are opportunities for prevention or treatment at various stages of the disease **[1]**. The central role of Ca^{2+} signalling in controlling normal pancreatic enzyme secretion, the generation of excessive Ca^{2+} signals by hyperstimulation of cells and the importance of premature activation of digestive enzymes in pancreatitis suggest that pancreatic acinar cell injury and its consequences are due to cytosolic Ca^{2+} overload **[3]**. In this article, we focus on the latest progress in understanding the earliest events in pancreatitis because modification or inhibition of Ca^{2+} signalling mechanisms might improve clinical outcome.

Physiological and pathological Ca^{2+} signals

Intracellular Ca^{2+} is involved in the regulation of virtually all cellular functions. Whereas physiological Ca^{2+} signals are mostly localized and transient, global and sustained elevations of the cytosolic Ca^{2+} concentration {$[Ca^{2+}]_i$} can be fatal **[4–6]**.

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Available online 6 January 2006

The pancreatic acinar cell is a classic secretion model **[7]**; in this cell the regulatory Ca^{2+} signals occur as repetitive local spikes that are mostly confined to the granule-containing apical pole **[6,8]**. Sustained global $[Ca^{2+}]_i$ elevations cause abnormal intracellular enzyme activation, vacuolization and necrosis **[9–13]**, processes that are crucial in the initiation of acute pancreatitis.

Premature digestive enzyme activation

Acinar cells synthesize inactive digestive enzymes, which are stored in apical zymogen granules (ZGs) and secreted into the duodenum where the enzymes are triggered into an activation cascade through conversion of trypsinogen into active trypsin by duodenal enterokinase. In pancreatitis, whatever the precipitant, premature intracellular enzyme activation occurs, contributing to subsequent tissue damage. The identification of mutations in the gene encoding trypsinogen in hereditary pancreatitis **[14]**, which results in mutated trypsinogen that is more readily activated or trypsin that is less readily inactivated, confirms the importance of premature digestive enzyme activation in the pathogenesis of pancreatitis.

Acinar cell injury

Migrating gallstones precipitate acute pancreatitis through biliary reflux into the pancreatic duct and/or pancreatic ductal hypertension **[11,15,16]**. Bile salts are toxic and induce severe experimental pancreatitis **[12]**.

Ethanol excess precipitates both acute and chronic pancreatitis, although it is the non-oxidative metabolites of ethanol that induce primary acinar cell injury, rather than ethanol itself or acetaldehyde **[13]**. Acinar cells contain high concentrations of ester synthases, which shuttle ethanol into combination with fatty acids that accumulate as fatty acid ethyl esters; these esters are subsequently hydrolysed and oxidised. Furthermore, fatty acids are likely to mediate acinar cell injury in hyperlipidaemia **[13]**. In addition to enzyme activation, acinar cell injury is characterized by vacuoles in the apical secretory granular pole **[9]**, and by the colocalization of lysosomes and ZGs **[17]**. The lysosomal component reduces the pH of these subcellular compartments to less than 5, below which cathepsin B cleaves trypsinogen to release active trypsin **[18]**. The cytoskeleton is disrupted and secretory polarity is lost, with activation of nuclear factor κB (NF-κB), cytokine expression and/or cell death pathways **[19,20]**.

Paradoxically, neutrophil infiltration and activation increase intrapancreatic digestive enzyme activation and