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文献综述 REVIEW

促进大肠癌血管新生相关因素研究进展

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Angiogenesis-promoting factors in colorectal cancer

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Abstract

Colorectal cancer (CRC) is one of the common malignant tumors, accounting for about 10% and 9.4% of malignancies in males and females, respectively. The number of patients who die from CRC reaches 700000 each year. In addition, there are about 1.4 million new patients every year. Angiogenesis is involved in a variety of physiological and pathological processes and is an important pathological marker for many diseases such as tumor, ischemia, atherosclerosis, inflammation, wound healing, and tissue regeneration. Angiogenesis plays a crucial role in the occurrence, development, and metastasis of CRC. In this review, we summarize our current knowledge of tumor-associated angiogenesis, the factors that promote angiogenesis in CRC, and future directions in this field, with an aim to provide a theoretical basis for better understanding the role of angiogenesis in the pathogenesis of CRC.

Key Words: Colorectal cancer; Angiogenesis; Promoting factors

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摘要

大肠癌(colorectal cancer, CRC)是胃肠道常见的恶性肿瘤, 占全球男性和女性恶性肿瘤约10%和9.4%, 每年因大肠癌死亡的患者可达70万人, 每年新增患者数约为140万人, 呈逐年增加趋势. 血管新生参与多种生理病理过程, 是很多疾病(肿瘤、局部缺血、动脉粥样硬化、炎症性疾病等)以及创口愈合、组织再生的重要病理学标志. 血管新生在CRC的发生、发展与转移中发挥重要作用. 对于促进大肠癌血管新生相关因素的研究有利于寻找或者研发更有效的抑制CRC血管新生的药物, 从而达到抗肿瘤的效果. 本文

就肿瘤相关血管新生、促CRC血管新生因素、结论三个方面进行综述, 为我们更好地认识血管新生在CRC发病过程中的作用提供理论依据.

关键词: 大肠癌; 血管新生; 血管新生促进因素

核心提要: 血管新生与大肠癌(colorectal cancer, CRC)的发生、发展与转移密切相关, 探究CRC中促进血管新生的相关因素, 有助于寻找和开发更有效的抑制CRC中血管新生的药物, 为CRC的诊治提供新的策略.

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0 引言

血管新生, 指在各种诱导和抑制因素的共同作用下, 从原有血管萌生出新血管的过程. 其过程涉及细胞、可溶性分子以及细胞外基质等[1]. 具体机制为[2]: 组织微环境变化激活内皮细胞, 引起细胞间及基底膜结构重塑, 周皮细胞分裂, 从而使边缘化的内皮细胞得以伸出伪足, 迁移出细胞外基质; 柄细胞紧随顶端细胞, 不断增殖使新生血管得以延长, 形成管腔, 并募集周皮细胞稳固血管结构.

血管新生与肿瘤生长之间的关系由Hanahan等[3]于1971年首次提出, 当肿瘤组织生长达到1-3 mm后, 其生长需要充足的血管供应, 因此需要形成新的血管向细胞提供氧分与营养, 并运输代谢物, 以保证肿瘤组织的正常生长. 至此以后就形成了靶向血管新生来治疗肿瘤的假说. 在过去近40年中, 大量研究支持了此假说. 但是经过多年对各种肿瘤的抗血管生成药物的研究得出结论: 仅仅使用抗肿瘤血管生成药物无法达到预期治疗肿瘤的效果; 在大多数情况下必须将它们与细胞毒性药物或者靶向药物联用才能发挥积极效果. 肿瘤血管新生过程同样受正向和负向调节因子的共同作用, 处于一种动态平衡中, 一旦这种平衡被破坏, 机体将开启活跃的血管新生. 正向调节因子多为蛋白或者细胞因子[4], 通过直接或间接作用引起血管内皮生长因子(vascular endothelial growth factor, VEGF)表达上调, 从而促进新血管的形成, 主要包括生长因子类和其他调节因子; 负向调节因子主要包括蛋白质片段、可溶性介质和抑癌基因等[5]. 近年来, 相关研究发现骨形成蛋白家族(bone morphogenetic proteins, BMPs)、轴突导向分子、miRNAs和内皮细胞代谢也参与肿瘤血管新生的调节[6]. 本文就促进大肠癌血管新生的相关因素作一综述.

1 生长因子类

血小板衍生生长因子D (platelet-derived growth factor-D, PDGF-D)在肿瘤的发生发展中发挥重要作用, 研究表明, 在结直肠癌中, PDGF-D表达上调并与临床病例特征呈正相关, 促进肿瘤生长、迁移和血管生成. 此外, PDGF-D可通过Notch1和Twist1信号通路促进肿瘤上皮细胞向间充质细胞转化[7]. VEGF与VEGF受体(VEGF receptor, VEGFR)是血管生成的关键因素, 贝伐单抗是一种靶向VEGR的人源化抗体. VEGF中内分泌腺源性VEGF是一种克隆血管生成因子, 可选择性的作用于内分泌腺细胞的内皮, 可导致血管新生, 促进CRC细胞增殖和肝转移[8]. 胰岛素样生长因子(insulin-like growth factor, IGFs), 在CRC组织内IGF-I和IGF-II表达水平明显升高. IGF-I来源于肝脏, 可促进细胞增殖, 抑制肿瘤细胞凋亡[9,10]. Hakam等[11]研究发现, IGF-I可诱导VEGF生成, 促进CRC血管生成. 随后, Reinmuth等[12]研究证实, 阻断IGF-I受体可抑制CRC生长和血管生成.

2 细胞因子

炎症介质白介素(interleukin, IL) 8属于CXC家族成员, 其有特定的氨基酸序列ELR (Glu-Leu-Arg). 对HCT116和Caco2大肠癌细胞系研究发现, 过表达IL-8可促进癌细胞增殖、转移以及血管新生, 并降低对奥沙利铂的敏感性[13]. 对表达人*IL-8*基因的小鼠模型研究发现, IL-8可动员髓样细胞, 通过与其受体CXCR1、CXCE2作用加剧炎症反应, 促进*IL-8*转基因小鼠CRC的发生发展[14]. 同时Wang等[15]研究证实, 由骨髓来源的间充质干细胞分泌产生的IL-8可诱导人脐静脉血管内皮细胞的增殖和迁移形成血管, 并促进肿瘤细胞的生长. Kuniyasu等[16]研究发现由大肠癌细胞分泌的IL-15可能通过抑制p21Waf1、Bax, 上调细胞周期素E、细胞核抗原和VEGF的表达, 促进AKT的磷酸化从而引起癌旁粘膜的增生、血管新生并最终导致肿瘤转移. 同时, 前列腺素(prostanoid, PG) E2结合其受体可刺激肿瘤细胞迁移、增殖和血管新生从而促进肿瘤生长[17]. Dufour等[18]研究发现, PGE2可通过mTORC1介导CRC细胞生长以及VEGF表达, 促进肿瘤血管新生.

缺氧是肿瘤血管生成的主要驱动因素, 缺氧诱导因子(hypoxia-inducible factors, HIFs)家族在这一过程中发挥重要作用. Yoshimura等[19]通过检测临床直肠癌样本中HIF1和HIF2的表达量、病理分期、微血管密度、环氧化酶-2 (cyclooxygenase-2, COX-2)并随访患者预后, 发现HIF2在肿瘤血管生成中发挥重要作用, 而且HIF1和HIF2的组合性表达与直肠癌的进展与预后密切相关. 同时, 肿瘤细胞在缺氧情况下Notch信号通路激活, Orai1表达升高, 通过SOCE/NFATc3介导肿瘤转移和血管生成[20].

3 蛋白质类

与其他肿瘤类似, CRC癌组织的生长及血管新生主要通过两种途径完成: COX诱导PG生成途径以及NO诱导途径[21]. COX是PGE合成的限速酶. COX分为COX-1、COX-2两类, COX-1在多种细胞中组成型表达, 维持细胞功能; COX-2可由生长因子、炎症因子以及肿瘤启动子诱导产生. 在乳腺癌与CRC中COX-2可通过上调PGE引起血管新生, 并促进肿瘤的转移[22]. 已有研究证实[23], 在人CRC中基质金属蛋白(matrix metalloproteinase, MMP) 1, MMP-2, MMP-3, MMP-7, MMP-9, MMP-13表达升高. MMPs属于锌内肽酶家族, 目前已发现约16种结构域类似的MMP[5]. 大多数MMP为无活性的酶原, 在细胞外被激活后可降解细胞外基质, 破坏基底膜, 从而促进肿瘤细胞的侵入. 随着基底膜的破坏, 肿瘤内血管内皮细胞可侵入邻近组织的基质并形成新的毛细血管. 与其他MMP不同, MMP-12的表达与CRC患者存活率正相关, 可能与其对血管生成的抑制作用相关[24]. 目前研发的口服低分子量MMP抑制剂虽对动物模型有效, 但是在III期临床试验中未能延长晚期癌症患者的存活期[25].

血管生成素(angiopoietin, Ang)是血管内皮细胞重要的调节剂. Ang-1和Ang-2可通过与内皮细胞特异性受体Tie-2结合而介导内皮细胞稳定性的改变. 研究证实, 将HT29癌细胞注射进入裸鼠后, Ang-1和Ang-2表达上调; 但是Ang-2在新生血管的形成中发挥更为重要的作用[26]. Ang-1可通过增加血管周围组织粘附力而提高内皮细胞的稳定性, 抑制血管生成. 相反, Ang-2可破坏内皮细胞的稳定性, 作为血管生成的起始因子, 引发内皮细胞的有丝分裂, 从而促进肿瘤血管新生[27].

一氧化氮(nitric oxide, NO)可由三种不同的一氧化氮合成酶(nitric oxide synthase, NOS)产生, 其中机体组成性表达神经和内皮NOS, 合成瞬时水平NO; 而炎症可诱导诱导型一氧化氮合成酶(inducible nitric oxide synthase, iNOS)表达, 产生持续高浓度NO[28]. 相关研究发现, CRC组织中iNOS蛋白和基因表达上调, 与VEGF表达以及微血管密度(microvessel density, MVD)正相关[29].

过氧化物酶(peroxiredoxin 1, Prdx1)属于PrdxS家族成员, 参与调节细胞信号传导和细胞分化. 研究证实, Prdx1可促进MMP-2、MMP-9以及VEGFA的表达, 增加HT29癌细胞迁移侵袭能力, 促进人脐静脉内皮细胞血管新生[30]. 壳多糖酶3样蛋白1 (chitinase 3-like 1, CHI3L1)属于壳多糖家族, 既往研究认为, 血清CHI3L1水平升高是晚期肿瘤患者预后不良的重要标志. 在CRC研究中, CHI3L1可促进癌细胞增殖、巨噬细胞募集和血管新生[31]. 解旋酶DHX32属于DEAH家族, 可与β-连环蛋白相互作用, 使VEGFA在转录水平表达上调, 促进CRC微血管的形成, 其表达水平与人CRC中的微血管密度和患者的不良预后正相关[32]. 组织蛋白酶S是一种半胱氨酸蛋白酶, 可促进肿瘤内皮细胞的增殖和肿瘤侵袭. 在HCT116异种移植小鼠模型中, 组织蛋白酶S拮抗剂Fsn0503可显著性抑制肿瘤侵袭和内皮细胞毛细血管的形成[33]. 细胞质磷脂酶A2α是COX介导PG产生的限制性底物, 可促进花生四烯酸产生, CRC细胞质中细胞质磷脂酶A2α表达量与微血管密度和VEGF表达正相关[34]. p38/MAPKAP激酶2激酶通过促进M2巨噬细胞极化和肿瘤血管生成促进肿瘤进展[35].

肿瘤坏死因子-α诱导蛋白8通过上调PDK1表达和磷酸化, 促进VEGFR2介导的血管生成[36]; 核糖体蛋白S24 (ribosomal protein S24, RPS24)通过RPS24c/MVIH/PGK1途径促进CRC血管生成[37]. 前动力蛋白2 (prokineticin 2, PROK2)是维持机体组织稳态不可或缺的部分, Kurebayashi等[38]通过检测6种CRC细胞系中PROK2表达水平, 并将*PROK2*基因转染至低表达细胞系中, siRNA转染至高表达细胞系中. 相对于低表达PROK2细胞系, *PROK2*基因转染组血管新生及肿瘤生长显著性增加; siRNA干扰后肿瘤生长和血管生成被抑制. 同源异型蛋白Six1在多种肿瘤中高表达, 与肿瘤的生长和转移相关. Xu等[39]研究显示, Six1通过MAPK信号途径, 上调VEGF, 刺激巨噬细胞特异性集落刺激因子、趋化因子, 募集肿瘤相关巨噬细胞, 从而促进肿瘤的生长与转移. Gabs家族蛋白是一类高度保守的支架蛋白. 在CRC中, Gab2通过上调MEK/ERK/c-Myc途径介导VEGR表达, 促进肿瘤生长及血管生成[40]. 人CD24是一种重要的糖基磷脂酰肌醇锚定膜蛋白, Wang等[41]通过分析CRC中CD24的表达量与MVD的相关性, 并通过使用CD24沉默技术, 发现CD24以Hsp90依赖性方式诱导CRC血管新生, 并可激活STAT3信号通路介导VEGF转录表达. 妊娠特异性糖蛋白9属于妊娠特异性糖蛋白(pregnancy-specific glycoprotein, PSG)家族. Yang等[42]通过检测CRC患者及健康对照组血清PSG9水平, 分析PSG9水平与MVD相关性, 并通过使用免疫共沉淀技术, 发现患者血清学PSG9升高与不良预后及MVD正相关, 同时PSG9 与SMAD4形成复合物, 促进多种血管生成相关基因的表达. 人UTP14a在CRC细胞中上调PDGFA的转录和分泌[43]. Dickkopf相关蛋白2在转移性结直肠癌中高表达的分泌蛋白, 可以通过经典的VEGF/VEGFR途径刺激血管生成, 此外也可通过加速癌细胞需氧糖酵解以及自分泌或自噬等方式刺激CRC血管生成[44]. G蛋白中GNA13通过增加核因子κB (nuclear factor kappa-B, NF-κB)依赖的趋化因子CXCL1, CXCL2和CXCL4表达水平促进肿瘤生长和血管生成[45].

T细胞内抗原含有3个识别RNA的结构域(RPM1, RPM2, RPM3). CRC的血管生成能力及其对抗血管生成

药物的敏感性由VEGF同型表达决定. T细胞内抗原的可变剪接可以调节VEGF的同型特异性表达, 改变CRC的血管生成特性及其对抗血管生成药物的抵抗性[46]. G蛋白偶联受体120可通过诱导促血管生成介质如VEGF, IL-8和COX-2衍生的PGE2的表达和分泌. 激活PI3K/Akt-NF-κB信号通路, 活化增强CRC细胞的运动性并诱导上皮细胞向间质细胞转化; G蛋白偶联受体120与CRC组织中E-钙粘蛋白表达呈负相关[47]. 同源性核糖体合成调节蛋白是核糖体合成的必需因子. CRC组织中同源性核糖体合成调节蛋白表达明显升高, 同源性核糖体合成调节蛋白高表达与CRC患者存活率负相关, 敲除同源性核糖体合成调节蛋白后G2/M细胞周期停滞、凋亡并抑制CRC细胞增殖, 血管生成减少[48]. T细胞免疫球蛋白结构域和粘蛋白结构域4通过激活血管生成并通过PI3K/AKT/mTOR信号通路募集与肿瘤相关的巨噬细胞来促进结直肠癌的生长[49].

4 基因

*p53*和*K-ras p53*是一种抑癌基因, 大肠癌中p53突变最常见于第5-8外显子; *K-ras*基因是最常见的癌基因, 作为大肠癌转化基因, 以12位密码子突变最常见. 钟等人发现大肠癌组织中*p53*和*K-ras*基因突变率及VEGF和MVD表达水平正相关, 说明*p53*和*K-ras*基因在调控CRC血管形成方面发挥重要作用[50]. Michael等人将携带正常*p53*基因的腺病毒转染CRC细胞, 研究发现VEGF表达下调, 从而抑制肿瘤血管生成[51]. Cai等[52]发现, 果蝇眼睛同源缺失体(drosophila eyes absent homologue 1, EYA1)在CRC细胞中过表达, 可通过PI3K信号途径诱导HIF-1α和VEGF-A, 促进肿瘤生长和血管生成. 染色质重构复合物核心催化亚基(brahma-related gene 1, BRG1)是高度保守的SWI/SNF染色体重塑复合物的成员之一, 具有抑癌基因的特征. 研究发现, BRG1与VEGF-A在CRC中过表达成正相关, 促进结直肠癌血管生成, BRG1可作为抗结直肠癌的药物的新靶点[53]. 转录因子NRF2是细胞氧化应激反应的重要修饰物, 在人CRC细胞中使用RNAi敲除NRF2后可抑制异种移植小鼠体内肿瘤生长, VEGF表达下调, 血管生成减少[54]. 转录因子EST易位突变体5(ETS translocation variant 5, ETV5)可以直接结合到PDGF-BB的启动子区域[55]; SIX4通过与HIF-1α配合促进VEGF-A的表达[56].

5 RNA

miRNA是短的(长度约22个核苷酸)内源性非编码RNA, 在转录后水平上负调节靶基因的表达[57,58]. miRNAs以时间和组织特异性方式对细胞进行调节[57]. 既往研究证实, 多种miRNAs可调节血管生成因子的表达或干扰血管生成信号通路[59,60]. exomiR-1229和exomiR-25-3p水平与CRC血管生成密切相关[61,62]. CRC等多种癌细胞可合成岩藻糖基转移酶(fucosyltransferase, FUT)家族聚糖, Liang等[63]研究表明: miR-125a-3p过表达可通过PI3K/Akt信号通路下调FUT5和FUT6, 最终抑制CRC细胞的增殖, 迁移, 侵袭和血管生成. miR-181a抑制SRC激酶信号传导抑制因子1, 使SRC从无活性状态转变为活性构象并促进VEGF的分泌, 导致血管生成[64]. 近期研究发现miR-143表达在CRC患者的血液样本和肿瘤标本中都被下调, 并与临床分期和淋巴结转移密切相关. 胰岛素样生长因子-I受体是miR-143的新型直接靶标, 其表达水平与人CRC标本中的miR-143表达呈负相关. miR-143的过表达抑制细胞增殖, 迁移, 肿瘤生长和血管生成, 并以IGF-IR依赖性方式增加对奥沙利铂治疗的化学敏感性[65]. miR-6868-5p/转录因子FOXM1平衡失调促进CRC血管生成[66]. 此外, 越来越多的研究研究表明长非编码RNA在肿瘤相关血管新生中发挥重要作用. lncRNA 可参与信号转导, 与蛋白质相互作用并且竞争内源性RNA改变靶基因的表达, 诱导内皮细胞形成毛细血管[67].

6 其他调节因子

硫化氢(hydrogen sulfide, H_2S)既往研究表明, H_2S可发挥舒张血管, 促进生物能量产生及血管生成. H_2S可由胱硫醚β合酶(cystathionine β synthase, CBS)介导产生, 在对CRC患者与健康对照配对研究中, 结肠癌中CBS表达上调, H_2S生成量增加; 沉默CBS可抑制肿瘤细胞增殖、迁移和侵袭, 减少内皮细胞迁移, 降低新生血管密度. 因此, H_2S可促进肿瘤生长和增殖, 并促进血管生成与血管舒张, 为肿瘤细胞提供血液与营养[68]. 先天性角化病1 (dyskeratosis congenita 1, DKC1)通过直接激活HIF-1α转录来调节CRC血管生成和转移[69]. 单核细胞在肿瘤中, 单核细胞可与癌细胞相互作用后分化成肿瘤相关的巨噬细胞. Honda等[70]研究使用人结肠癌细胞系DLD-1和人单核细胞系THP-1共培养后发现DLD-1细胞中IL-1β, MMP-1, MMP-2和MMP-3的表达增加. 说明与单核细胞相互作用后人结肠癌细胞的分化可能与血管生成和转移有关. 脂肪酸代谢脂肪酸合成酶(fatty acid synthase, FASN)是脂肪合成的关键酶, 与CRC的转移相关, 敲除FASN的CRC细胞可抑制VEGFR2及其下游信号的传导, 抑制内皮细胞增殖、迁移和血管形成[71]. 间充质干细胞可早期整合到肿瘤基质中并且分泌细胞因子, 进而促进肿瘤细胞分泌的促血管新生因子, 增加血管生成和肿瘤生长[72].

7 结论

多年来, 对于肿瘤新生血管的研究使我们对CRC血管新生有了更深层次的认识. 随着研究的深入, 除VEGR/VEGR外, 更多影响CRC血管新生的因素被发现, 为我

表 1 大肠癌相关血管新生促进因素汇总

分类	名称	作用靶点	Ref.
生长因子类	PDGF-D	Notch1, Twist1	[7]
	VEGF	VEGFR	[8]
	EG-VEGF		[8]
	IGFs	VEGF	[9-12]
细胞因子	白介素8	动员髓样细胞；CXCR1, CXCE2	[13-15]
	白介素15	抑制p21Waf1、Bax; 上调细胞周期素E, 细胞核抗原和VEGF	[16]
	PGE2	PGE2R; mTORC1;VEGF	[17,18]
	HIFs	Notch；Orai1；SOCE/NFATc3	[19,20]
蛋白质类	COX	PGE; PG; NO	[21,22]
	MMP	细胞外基质, 基底膜	[24,25]
	Ang	Tie-2	[26,27]
	一氧化氮	VEGF; MVD	[28,29]
	过氧化物酶	MMP-2; MMP-9; VEGFA	[30]
	壳多糖酶3样蛋白		[31]
	解旋酶DHX32	β-连环蛋白; VEGFA	[32]
	组织蛋白酶S		[33]
	细胞质磷脂酶A2α	PG；花生四烯酸	[34]
	p38/MAPKAP激酶2激酶	M2巨噬细胞极化	[35]
	肿瘤坏死因子-α诱导蛋白8	上调PDK1表达和磷酸化, 促进VEGFR2	[36]
	核糖体蛋白S24	RPS24c/MVIH/PGK1途径	[37]
	前动力蛋白2		[38]
	同源异型蛋白Six1	MAPK信号途径	[39]
	Gabs家族蛋白	MEK/ERK/c-Myc途径	[40]
	CD24	Hsp90；STAT3信号通路	[41]
	妊娠特异性糖蛋白9	与SMAD4形成复合物	[42]
	Dickkopf相关蛋白2	VEGF/VEGFR途径; 需氧糖酵解以及自分泌或自噬	[44]
	T细胞内抗原	VEGF	[46]
	G蛋白偶联受体120	VEGF, IL-8, PGE2; PI3K/Akt-NF-κB	[47]
	同源性核糖体合成调节蛋白		[48]
	T细胞免疫球蛋白	PI3K/AKT/mTOR	[49]
基因	P53和K-ras		[50,51]
	果蝇眼睛同源缺失体	PI3K信号途径诱导HIF-1α和VEGF-A	[52]
	染色质重构复合物核心催化亚基		[53]
	转录因子NRF2	VEGF	[54]
	转录因子EST易位突变体5	PDGF-BB	[55]
RNA	exomiR-1229; exomiR-25-3p		[61,62]
	miR-125a-3p	PI3K/Akt信号通路下调FUT5和FUT6	[63]
	miR-181a	SRC激酶信号传导抑制因子1	[64]
	miR-143	IGF-IR	[65]
	miR-6868-5p/转录因子FOXM1平衡失调		[66]
	lncRNA		[67]
其他调节因子	H2S, DKC1, FASN 间充质干细胞		[68-72]

PDGF: 血小板衍生生长因子; VEGF: 血管内皮生长因子; EG-VEGF: 内分泌腺源性血管内皮生长因子; IGFs: 胰岛素样生长因子; HIFs: 缺氧诱导因子; COX: 环氧化酶; MMP: 基质金属蛋白; Ang: 血管生成素; lncRNA: 长链非编码RNA; DKC1: 先天性角化病1; FASN: 脂肪酸合成酶.

们抑制血管新生提供更多作用靶点. 同时, 我们也认识到传统VEGR/VEGR抑制剂治疗失败的可能因素. CRC作为常见的肠道肿瘤, 其肿瘤细胞的生长、转移与血管新生密切相关, 若能有效抑制肿瘤血管生成, 将对肿瘤的控制发挥巨大作用. 以上综述总结了近年来CRC血管新生正向调节因素(表1), 为研发靶向抑制CRC血管新

生药物提供基础理论依据.

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