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Shijie Huaren Xiaohua Zazhi

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目　次

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消　　息

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Contents

Volume 30 Number 8 April 28, 2022

Contents

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Volume 30 Number 8 April 28, 2022

COVER

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述评 EDITORIAL

微环境参与消化系统肿瘤放化疗抵抗机制新进展

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New progress in the mechanism of microenvironment-driven chemoradiotherapy resistance in digestive system tumors

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Abstract

Tumor microenvironment (TME) is the cornerstone of the survival of tumor cells. It generally presents unique physical and chemical characteristics such as hypoxia, immunosuppression, metabolic reprogramming, and matrix stiffening, which not only offer suitable soil to support tumorigenesis and progression, but also resist the effects of radiotherapy and chemotherapy. Here, we summarize new progress in the mechanism of hypoxia, immunosuppression, metabolic reprogramming, and matrix stiffness-driven chemoradiotherapy resistance in digestive system tumors, and discuss the new intervention strategy against matrix stiffness-driven chemoradiotherapy resistance, which underlines the contribution of physical and chemical characteristics of tumor microenvironment in drug resistance.

Key Words: Tumor microenvironment; Digestive system tumors; Chemoradiotherapy resistance

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摘要

肿瘤微环境(tumor microenvironment, TME)是肿瘤细胞赖以生存的基石, 其独特的缺氧、免疫抑制、代谢及机械力学环境不仅为肿瘤进展提供合适的物化"土壤", 同时在肿瘤放化疗抵抗中也发挥重要作用. 本文归纳总结了缺氧、免疫抑制、代谢异常和基质硬度参与消化系统肿瘤放化疗抵抗最新研究进展, 同时对靶向力学微环境逆转肿瘤放化疗抵抗新策略进行了探讨, 阐明肿瘤微环境物化特征改变在肿瘤药物抵抗中的重要作用.

关键词: 肿瘤微环境; 消化系统肿瘤; 放化疗抵抗

核心提要: 本文对微环境的主要组分进行简述, 总结缺氧、免疫、代谢和力学微环境参与消化系统肿瘤放化疗抵抗机制的研究及靶向力学微环境逆转肿瘤放化疗抵抗进展.

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0 引言

肿瘤微环境概念最早可追溯至1863年Virchow提出的“肿瘤起源于慢性炎症”和1889年Paget提出的“种子和土壤”假说, 作为“种子”的肿瘤细胞所处周边环境被认为是“土壤”[1]. 2011年, Hanahan和Weinberg总结了肿瘤的十大恶性特征, 明确了“微环境”因素在肿瘤发生发展中的重要作用[2]. 肿瘤细胞与其所处的微环境是一个功能整体, 肿瘤细胞能够教育重塑肿瘤微环境(tumor microenvironment, TME), 而TME通过不断重塑改造以形成更利于肿瘤生存的生态条件. 肿瘤微环境是一个复杂的综合体, 主要由肿瘤细胞、间质细胞、浸润免疫细胞、细胞因子、趋化因子、组织蛋白酶、血管淋巴管和细胞外基质等构成, 各组分与肿瘤细胞相互影响、共同进化, 驱动肿瘤生长和进展, 同时在调控肿瘤治疗敏感性方面也发挥举足轻重的作用[3]. 消化系统肿瘤发病率和死亡率在全球均位居前列, 放疗和化疗在消化系统肿瘤的非手术治疗中占据主导地位, 放化疗抵抗则是肿瘤患者治疗失败的主要原因. 因此, 肿瘤放化疗抵抗机制研究一直是消化系统肿瘤治疗领域研究热点, 以往研究多集中于肿瘤细胞自身突变积累与DNA损伤修复机制异常等方面探索[4,5]. 近来癌症治疗整体概念的出现, 肿瘤不再被认为仅仅是肿瘤细胞自身的病理改变, 而是微环境甚至系统调控失常的病理表现, 其中微环境生化和力学特征改变导致的肿瘤恶性生物学特征增强, 成为肿瘤治疗失败的“帮凶”[6]. 与生理状态下的生化、病理和力学特征不同, 实体肿瘤微环境具有缺氧、免疫抑制、代谢异常及基质变硬四个显著特征, 本文从上述微环境四个特征出发, 归纳总结微环境参与消化系统肿瘤放化疗抵抗新机制及靶向TME逆转抵抗的治疗新策略.

1 缺氧微环境参与消化系统肿瘤放化疗抵抗的机制

缺氧是肿瘤微环境常见特征, 造成肿瘤微环境缺氧的主要原因为, 肿瘤细胞快速生长而消耗大量营养和氧气, 新生血管不能及时有效建立, 肿瘤细胞通透性升高使液体外渗造成血液黏滞等, 因此微环境内存在供氧和耗氧不平衡[7]. 缺氧常引发肿瘤细胞发生系列复杂病理改变以适应低氧环境调节, 这种改变主要由缺氧诱导因子(hypoxia inducible factor, HIF)介导[8]. 研究显示缺氧微环境不仅显著影响肿瘤细胞侵袭转移[9]、干性[10]等恶性特征, 而且可调控免疫抑制[11]、代谢重编程[12]及放化疗抵抗[13].

缺氧微环境导致的放化疗抵抗主要包括以下几种途径: 缺氧促进肿瘤细胞DNA损伤修复, 导致肿瘤细胞耐药基因表达增加以及抑制肿瘤细胞凋亡. 肿瘤细胞DNA损伤是放射线治疗和细胞毒性化疗药物杀伤肿瘤的共同作用机理, 而缺氧可触发肿瘤细胞DNA损伤修复[14]. 将结直肠癌细胞在1%氧含量环境中培养, 测序发现其许多长链非编码RNA上调, 其中以LUCAT1上调最为显著, 体内外实验显示缺氧通过HIF-1α/LUCAT1/PTBP1轴抑制DNA损伤标志物γ-H2AX表达, 使癌细胞对5-氟尿嘧啶和奥沙利铂耐药, 此外, 结直肠癌患者LUCAT1上调也提示化疗疗效不佳、预后不良, 表明缺氧与化疗疗效存在一定的相关性[15]. 也有研究显示, 将缺氧食管鳞癌细胞来源外泌体处理正常氧环境的癌细胞, 能够增强此细胞的DNA损伤修复, 诱导放射抗性, 而敲减缺氧外泌体miRNA-340-5p, 可逆转正常氧癌细胞的放疗抵抗[16], 提示缺氧癌细胞不仅自身对放疗产生抵抗, 还可通过外泌体等细胞间通讯方式, 诱导周围正常氧癌细胞的放射抗性. 多药耐药基因1(multidrug resistance 1, MDR1)编码的P-糖蛋白是药物代谢过程中关键转运体, MDR1基因激活是肿瘤产生耐药的重要原因[17]. 有报道在氯化钴模拟的缺氧环境中, 肝癌细胞HIF-1α蛋白水平升高、对缺氧耐受增加, 同时MDR1表达上调, 导致肝癌对曲古抑菌素A、索拉菲尼和5-氟尿嘧啶等多药耐药[18], 提示缺氧可调控耐药相关基因、导致肿瘤耐药. 凋亡抵抗也是肿瘤耐药的重要途径, 缺氧信号显示可强化肿瘤细胞的抗凋亡通路[19]. 研究发现[20], HIF-1α可调控p53和NF-κB而减少细胞凋亡、降低胃癌细胞的化疗敏感性. 细胞膜碳酸酐酶Ⅸ(carbonic anhydrase Ⅸ, CAⅨ)在缺氧环境中可被异常激活而导致HIF-1α上调, 使癌细胞产生放疗抵抗, 抑制CAIX表达则能够下调HIF-1α、促进食管癌细胞凋亡及增加其放疗敏感性[21]. 以上证据表明, 缺氧可通过诱导肿瘤细胞DNA损伤修复、调控耐药相关基因和抑制凋

亡等适应性生存方式, 抵抗放疗和化疗药物损伤, 从而使肿瘤产生对治疗的耐受性.

2 免疫抑制微环境参与消化系统肿瘤放化疗抵抗的机制

肿瘤免疫抑制微环境主要由免疫抑制细胞和免疫抑制因子组成, 是肿瘤发生、进展及转移的重要调控因素, 免疫抑制微环境强弱不仅显著影响免疫治疗效果[22], 也调控肿瘤放化疗敏感性. FoxP3$^+$调节性T细胞(regulatory T cell, Treg)是经典免疫抑制细胞, 研究显示结直肠癌对奥沙利铂的耐药与Treg细胞扩增相关, 其机制为结直肠癌细胞来源外泌体miR-208b作用于Treg细胞, 促进其增殖及免疫抑制功能增强[23]. 也有研究发现进展期直肠癌患者术前新辅助放疗疗效与外周血中Treg细胞比例相关, PD-1阳性Treg细胞比例较高者放疗效果不佳[24]. 微环境中肿瘤相关巨噬细胞(tumor-related macrophage, TAM)包括M1型和M2型, 其中M2型巨噬细胞主要发挥免疫抑制功能, M2型巨噬细胞免疫抑制功能强化可增强胃癌和结直肠化疗耐药[25,26]. 除了抑制肿瘤免疫, 该类细胞可释放外泌体传递非编码RNA和嘧啶类物质至肿瘤细胞, 导致肿瘤细胞恶性生物特征改变[27]. 研究发现M2型巨噬细胞来源外泌体能够促进胃癌[28]和胰腺癌[29]化疗耐药; 并且通过释放嘧啶类物质在药物摄取和代谢水平竞争性抑制化疗药物, 降低胰腺癌吉西他滨治疗敏感性[30]. 髓源性抑制细胞(myeloid-derived suppressor cell, MDSC)是另一类重要的免疫抑制细胞, 不仅抑制T细胞特异性免疫反应、促进微环境内炎症反应和血管生成[31], 而且参与消化系统肿瘤肝、肺预转移龛形成[32]. 小鼠结肠癌组织和直肠癌患者外周血均存在MDSC细胞扩增, 并伴随精氨酸酶1(arginase 1, Arg1)活性增加和L-精氨酸耗竭; Arg1阳性MDSC细胞在削弱T细胞和M1型巨噬细胞抗肿瘤免疫的同时, 可强化M2型巨噬细胞免疫抑制功能, 导致肿瘤免疫状态失衡、放射敏感性受损[33]. MDSC细胞向M1型巨噬细胞分化抑制状态也导致化疗耐药, 使用Toll样受体激动剂R848上调M1型巨噬细胞的分化比例, 能够显著增加结直肠癌对奥沙利铂的敏感性[34]. 除调控免疫功能, MDSC细胞也通过旁分泌信号增强肿瘤细胞干性. 有报道MDSC细胞对肝内胆管癌干性的增强并不依赖于其免疫抑制功能, 而是由MDSC细胞分泌LTB4蛋白作用于癌细胞膜BLT2受体所致, 干扰LTB4-BLT2通路则减弱肝内胆管癌细胞干性、并逆转吉西他滨耐药[35]. 可见, 微环境免疫特征能够影响消化系统肿瘤放化疗敏感性, 除强化免疫抑制功能的因素外, 免疫抑制细胞与癌细胞互作所致肿瘤增殖、转移和干性增加, 也进一步阻碍了治疗效果.

3 代谢微环境参与消化系统肿瘤放化疗抵抗的机制

代谢重编程是肿瘤标志特征之一, 肿瘤细胞常表现为葡萄糖、谷氨酰胺、脂质、氨基酸代谢增加和乳酸累积[36]. 正常细胞一般倾向于通过氧化磷酸化获得能量, 而癌细胞即使在有氧条件下, 也以糖酵解为主要代谢途径, 即Warburg效应[36]. 与肿瘤细胞代谢特征相似, TME中免疫细胞亦表现为糖酵解水平升高, 肿瘤细胞和免疫细胞糖酵解所致乳酸累积共同促进肿瘤增殖、转移、血管生成及免疫逃逸[37]. 结直肠癌组织糖酵解相关基因表达与患者预后相关性分析显示, 组织水平糖酵解速率与晚期转移性结直肠癌患者化疗疗效呈负相关[38]. 已有大量研究表明, 肿瘤细胞糖酵解活性增强参与消化系统肿瘤化疗抵抗[39,40]. MDSC细胞在分化和激活过程中糖酵解活性增强[31], 所致乳酸累积进一步促进MDSC细胞浸润和免疫抑制功能强化, 从而导致胰腺癌放疗抵抗[41]. 肿瘤糖酵解活性增强常伴随谷氨酰胺分解增加, 谷氨酰胺分解能够在表观遗传水平调控结直肠细胞对化疗药物的敏感性[42], 其机制为提高肿瘤细胞DNA甲基化水平以促进WNT信号通路活化和肿瘤干性增加. 除葡萄糖和谷氨酰胺代谢, 脂代谢重编程也是肿瘤细胞能量代谢失控的重要特征[43]. 胃癌间充质干细胞(mesenchymal stem cell, MSC)通过促进脂肪酸氧化(fatty acid oxidation, FAO)增加胃癌细胞干性和化疗抵抗[44], 揭示了脂代谢对肿瘤治疗敏感性的调控. 铁死亡是近年来新发现的细胞程序性死亡方式, 主要由细胞膜脂质过氧化诱导[45]. 食管鳞癌组织中Nrf2与SLC7A11表达上调与患者TNM分期及放疗疗效呈负相关, 体外实验进一步证实其介导的放疗抵抗机制与其抑制细胞铁死亡有关[46]. 氨基酸代谢亦影响肿瘤治疗敏感性, 胰腺癌细胞中长链非编码RNA(long noncoding RNA, lncRNA)能够通过上调L型氨基酸转运蛋白(L-type amino acid transporter 2, LAT2), 促进胰腺癌对吉西他滨耐药[47]. 金属离子代谢参与调控恶性肿瘤进展是代谢微环境研究新方向, 有报道细胞内铜离子蓄积可加重肝癌放疗抵抗[48], 而铜螯合剂可靶向铜代谢而促进细胞铁死亡, 逆转肝癌放疗抵抗. 以上证据表明, 微环境糖、脂质、氨基酸和金属离子代谢紊乱参与肿瘤治疗抵抗, 代谢微环境重编程是限制消化系统放化疗疗效的关键因素.

4 力学微环境参与消化系统肿瘤放化疗抵抗的机制

肿瘤的发生进展不仅伴随微环境生化特征的改变, 也影响微环境力学特征的改变, 包括胞外基质硬度增加[49]、机械挤压周边组织[50]及增加组织渗透压和静水压[51]等.

作为实体瘤最显著力学特征, 基质硬度增加显示可正向调控肿瘤生长、侵袭、转移、上皮间充质转化(epithelial-mesenchymal transition, EMT)和干性增强等恶性特征[52-55]. 此外, 基质硬度增加也促进微环境内血管新生[56,57]及免疫细胞浸润、极化和功能改变[58,59]. 基质硬度不仅可驱动肿瘤发展转移, 也可削弱肿瘤放化疗的敏感性[60], 但硬度力学信号诱导肿瘤放化疗抵抗及相关调控机制研究目前报道十分有限.

在消化系肿瘤中, 硬度力学信号参与肿瘤放化疗敏感性的研究以肝癌为主. 研究表明基质硬度增加可削弱肝癌细胞奥沙利铂治疗敏感性, 可能与高基质硬度激活integrin β1/Akt/mTOR/SOX2信号通路增强肝癌细胞干性有关[55]. 也有报道显示, 基质硬度上调integrin β1、局部粘着斑激酶(focal adhesion kinase, FAK)、ERK和STAT3等, 降低肝癌细胞对顺铂敏感性[61]. 硬度力学信号同样可激活肝癌细胞miR-17-5p/PTEN/PI3K/Akt/MMPs通路, 削弱二甲双胍对肝癌细胞侵袭转移的抑制作用[62]. 机械硬度增加也可促进EMT和Yes相关蛋白(Yes-associated protein, YAP)/转录共激活因子PDZ结合基序(transcriptional co-activator with PDZ-binding motif, TAZ)活化, 介导胰腺癌对紫杉醇治疗抵抗[63]. 利用海藻酸钠凝胶微球建立不同硬度包围的肝癌细胞微球模型, 分别用顺铂、5-氟尿嘧啶和紫杉醇处理, 结果显示高硬度环境(105 kPa)中肝癌细胞存活率明显高于低硬度(21 kPa)和中硬度(70 kPa)环境, 提示高硬度环境明显增强肝癌化疗耐药, 可能与硬度诱导的内质网应激反应有关[64]. 将结直肠癌细胞与成纤维细胞三维共培养形成肿瘤球体以模拟体内肿瘤微环境, 发现其硬度水平较对照基底显著升高, 对5-氟尿嘧啶和瑞格菲尼的耐受性也增加[65], 提示力学微环境参与调控结直肠癌化疗耐药. 近期, 有研究从DNA损伤修复角度揭示了基质硬度介导细胞放化疗抵抗新机制. 研究显示[66], 相较于低硬度基底生长的对照细胞, 高硬度基底生长的正常细胞和肿瘤细胞对基因毒性化疗药物和放射线抗性明显增强, 对其机制解析发现基质硬度可促进DNA损伤因子RNF8泛素化修饰、招募BRCA1和53BP1至损伤结合位点, 而加速DNA损伤修复, 提示调控DNA损伤修复可能是硬度力学参与消化系统肿瘤放化疗抵抗的关键因素. 尽管力学微环境在肿瘤进展中扮演的角色被逐渐重视, 但其驱动的放化疗抵抗目前仍处起步阶段, 其相关机制的阐明尚需研究的进一步积累.

5 靶向TME提高肿瘤放化疗疗效的新策略—调控力学微环境

越来越多的证据显示[67], 将治疗策略扩展到肿瘤微环境, 而不仅仅是肿瘤细胞本身, 能够实现更强的抗肿瘤效率. 已有实验和临床研究证实[68], 改善微环境缺氧、抑制血管生成、调控肿瘤代谢和肿瘤免疫在治疗肿瘤和增加放化疗敏感性中意义重大, 许多抗血管生成药物和免疫药物也已被批准而广泛应用于临床, 在此不再赘述. 而改善肿瘤力学微环境是近年提高肿瘤放化疗疗效的新角度, 尽管研究报道有限, 但其临床应用前景广阔.

赖氨酰氧化酶(lysyl oxidase, LOX)和赖氨酰氧化酶样蛋白(LOX-like, LOXL)是促微环境基质胶原交联、组织硬度增加的关键分子[69], LOX家族蛋白在增强胃癌[70]、肝癌[53,54]、结直肠癌[71]和胰腺癌[72]等肿瘤恶性特征中的研究已较为深入. 抑制LOX家族蛋白靶向基质硬度在肿瘤治疗领域也取得一定进展. 研究显示, LOX表达增加与肿瘤化疗耐药有关, 小鼠胰腺癌[73]移植瘤模型中, LOX上调可减弱吉西他滨治疗敏感性, 将LOX活性抑制剂β-氨基丙腈(BAPN)与化疗药物联用, 可通过促进药物渗透、改善药物分布均匀性而提高化疗疗效. 新型小分子抑制剂如LOX/LOXL2双重抑制剂PXS-S1A, LOXL2特异抑制剂PXS-S2A及LOXL2/LOXL3双重抑制剂PXS-5153A, 显示可减弱肿瘤细胞增殖、迁移和血管新生能力, 提示可能成为放化疗增敏剂[74]. 干扰肿瘤细胞对硬度力学信号的感知应答是调控力学微环境的另一途径, 通过抑制integrin整合素家族、FAK、Rho相关激酶(Rho-associated kinase, ROCK)和YAP/TAZ介导的硬度传导信号可能逆转肿瘤耐药[75]. 目前一些靶向整合素的单抗药物如单英妥木单抗(Intetumumab)、阿比妥珠单抗(Abituzumab)和小分子抑制剂如E-7820、ATN-161等已进入临床试验阶段[76]. 值得注意的是, 阿比妥珠单抗联合化疗在治疗转移性结直肠癌Ⅰ期临床试验中展示出良好安全性和耐受性, 尽管Ⅱ期临床试验结果证实其总体疗效并未优于标准化疗方案, 但integrin αvβ6高表达患者可明显获益[77]. 提示基于integrin αvβ6表达对结直肠癌患者分层, 可能使靶向整合素药物在应用中获得更好的临床效果. 作为FAK抑制剂, 地法替尼(Defactinib)与RAF/MEK抑制剂VS-6766联用在RAS/RAF突变的实体瘤临床试验中取得突破性进展[78]. 消化系肿瘤临床前研究表明, 地法替尼与紫杉醇联用在治疗胰腺癌细胞和原位胰腺癌小鼠模型中具有协同作用[79], 提示抑制FAK可能增加化疗敏感性. 法舒地尔(Fasudil)能够改善脑血管痉挛, 近期研究发现法舒地尔能够抑制ROCK信号通路, 并提高小鼠胰腺癌吉西他滨和白蛋白紫杉醇化疗疗效[80]. 此外, 通过干预细胞骨架动力[81]、选择性剪切机制[82]和核刚度[83]等来减弱硬度力学信号,可能也有益于提高实体肿瘤治疗疗效. 因此, 靶向力学微环境逆转肿瘤放化疗抵抗新策略无疑为肿瘤放化疗增敏临床应用提供新希望.

6 展望

本文从肿瘤微环境缺氧、免疫抑制、代谢异常和基质硬度四个角度, 对其参与消化系统肿瘤放化疗抵抗及相关机制进行了归纳总结, 同时对靶向力学微环境逆转肿瘤放化疗抵抗临床前景进行了探讨, 显示基质硬度在肿瘤进展和放化疗抵抗中的重要作用. 然而, 微环境力学物理特征的研究目前较为有限, 尚有许多问题亟待解决, 如力学信号与微环境生化信号如何协同参与放化疗抵抗？不同癌种力学信号调控放化疗抵抗机制是否存在共性？关键力学感应分子筛查及干预对肿瘤放化疗抵抗的逆转效果？力学信号主要通过改变何种肿瘤恶性特征而影响治疗疗效？此外, 硬度关联体内外理想模型的匮乏同样制约相关机制的深入开展, 随着三维类器官模型, 激光捕获微切割, 单细胞多组学测序及人工智能等前沿技术的进展, 鉴定相同癌种不同局部微环境特征, 及不同癌种共性微环境特征成为可能, 有望对临床肿瘤放化疗抵抗逆转带来突破性改变.

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• 消息 •

书 讯

本刊讯 由池肇春教授主编的《腹痛的诊断、鉴别诊断与治疗》已由人民卫生出版社出版发行.

腹痛是消化系统最常见的症状之一, 可引起腹痛的疾病很多, 容易发生误诊或漏诊, 以致患者得不到及时的诊治. 本书由全国著名消化内科及相关学科专业学者共同执笔, 为近年在腹痛诊疗方面的最新代表作. 精装, 图文并茂, 内容新颖实用, 全书2014千字, 分上下两篇, 上篇为总论, 包括腹痛的病理生理学、腹痛的病因与发病机制、腹痛的临床诊断、腹痛的内镜与影像诊断与鉴别诊断、腹痛的实验室诊断、腹痛的治疗等11章. 下篇为各论, 分别介绍腹痛疾病的鉴别诊断与治疗. 从第12章至第15章分别介绍腹腔脏器炎症、阻塞、扭转、穿孔、破裂、血管疾病、心肺疾病、妇科疾病、急性中毒等引起急性腹痛的鉴别诊断与治疗. 从第17章至第29章分别介绍胃肠、胰, 肾、感染、肿瘤引起的慢性腹痛鉴别诊断与治疗. 从第30章至第36章分别介绍肝胆系统疾病和系统疾病引起腹痛的鉴别诊断与治疗. 最后一章为经典案例53例, 分别介绍了不同案例的诊治体会、经验与教训.

全书以症状鉴别诊断为中心, 与治疗并重, 均作了全面与详尽的阐述, 是一部有关腹痛诊治的新作, 有较高的学术水平和参考价值, 可为消化内科、普外科、小儿科、感染科、肿瘤科、影像科和妇产科等学科医师学习与参考. 每册定价188元 , 购书热线 010-59787592, 010-59787584, 010-65264830, 人卫智慧服务商城(人卫社官方购书网站)、当当、京东、天猫等网店均可搜索购书, 欢迎选购.

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