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犬小孢子菌的耐药性和应对策略研究进展

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摘　要

犬小孢子菌是浅部真菌病常见的致病菌之一。犬小孢子菌作为一种亲动物性皮肤癣菌，近年来饲养宠物的流行使其发病率逐年上升。随着抗真菌药物的不规范使用，真菌的耐药性逐渐增强。目前，犬小孢子菌的耐药机制主要包括生物膜的形成、药物作用位点的突变、细胞内药物水平的降低、应激反应等，为了应对这一威胁，药物的联合使用、新药的研发以及其他多种抗真菌治疗方法被提出和探讨。未来对犬小孢子菌的耐药机制及抗真菌治疗策略的进一步研究，将为抗真菌药物研发和临床治疗提供参考依据。

关键词

犬小孢子菌，浅部真菌病，耐药性，耐药机制，抗真菌治疗

Research Progress on Antifungal Drug Resistance and Relevant Coping Strategies of *Microsporum canis*

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Abstract

***Microsporum canis* is one of the most common pathogenic fungi of superficial mycoses. As a zoophilic dermatophyte, the morbidity of *M. canis* is increasing with the prevalence of raising pets in recent years. The fungal drug-resistance has gradually increased since the nonstandard use of antifungal drugs. Nowadays, antifungal resistance mechanisms of *M. canis* generally include biofilm**

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formation, modification of the drug target, decreased intracellular drug levels, stress responses and so on. In response to this threat, drug combination, development of new drugs and other antifungal treatments are proposed and discussed. Studying the drug resistance mechanism of *M. canis* and exploring more therapeutic strategies will provide a basis for the development of antifungal drugs and clinical treatment in the future.

Keywords

***Microsporum canis*, Superficial Mycoses, Drug Resistance, Mechanism of Drug Resistance, Antifungal Therapy**

1. 引言

犬小孢子菌(*Microsporum canis*)是一种亲动物性皮肤癣菌，人类多由接触携带真菌孢子或已患病的动物而发生感染，其中在大约 50%的人类感染病例中，无症状动物承担疾病传播者的角色[1]。部分情况下也可以发生人际间传播，但犬小孢子菌多在四次人际间传播后丧失致病性[2]。在动物中，犬小孢子菌感染表现为不同程度的鳞屑、多灶性脱毛和红斑[3]，在人类中多表现为局部、浅表感染，如头癣、体癣、足癣和甲癣，罕见情况下在接受长期免疫抑制治疗和遗传性胱天蛋白酶募集域蛋白 9 (Caspase recruitment domain-containing protein 9, CARD9)基因缺陷的患者中，可出现泛发性和难以控制的深部真菌感染[4] [5] [6] [7]。犬小孢子菌在世界范围内广泛分布，该菌是猫和犬的常见致病菌，发病率为 40%~100%不等[8]。据报道，犬小孢子菌是欧洲、南美洲、北美洲、非洲和亚洲，特别是在印度和中国等国家头癣的常见致病菌之一[9] [10] [11]。据一项关于 2000~2019 年中国成人头癣的回顾性研究显示，犬小孢子菌所致的成人头癣占比达到 21.4%，仅次于紫色毛癣菌(35.7%) [12]。儿童和免疫功能低下的个体是易感人群。该菌有可能通过流浪猫或狗为媒介引起皮肤癣菌病的小规模爆发，自 1995 年起，陆续有多地报道学校[13]、军营[14]、疗养院[15]等人群聚集地曾发生该菌的爆发。

近年来，随着饲养宠物的人越来越多，犬小孢子菌的发病率也逐年上升[16]。我国头癣近 60 年的病原体谱由亲人性真菌向亲动物性真菌转变，其中犬小孢子菌在亲动物真菌致病谱中占据主要地位[17]。

目前常见的针对犬小孢子菌所致的浅部真菌病的治疗除了外用药以外，有口服抗真菌药，如氟康唑、灰黄霉素、伊曲康唑、酮康唑和特比奈芬[18] [19]。犬小孢子菌感染易复发，据统计在接受治疗的患者中有 25%~40%的患者治疗失败[20]，失败的原因可能是由于患者缺乏依从性、药物局部渗透力差、药物生物利用度的变化和耐药现象的出现。在抗真菌治疗的药物策略中，关于药物耐受性的担忧备受关注。

据报道，世界范围内皮肤真菌对唑类药物的耐药现象高达 19% [21]。虽然相比于红色毛癣菌(*Trichophyton rubrum*)与须癣毛癣菌(*Trichophyton mentagrophytes*)，犬小孢子菌耐药的相关报道较少，但部分犬小孢子菌在临床[22]和药敏试验[23] [24] [25]中对抗真菌治疗的效果欠佳，其原因可能与耐药有关。通过评估外排泵调节剂与唑类药物的协同作用，也间接证实了犬小孢子菌可能存在耐药现象[26]。耐药的存在意味着发病率和药物治疗费用的增加，临床上也需要寻求新的抗真菌药物。故本文综述近几年犬小孢子菌对临床上常用的抗真菌药的体外敏感性、分析犬小孢子菌可能的耐药机制，并为犬小孢子菌耐药株的治疗提供策略及思路。

2. 耐药性分析

2.1. 临床耐药性

当临床病例在服用常规剂量的抗真菌药物后 4 周内仍出现持续性感染或复发时，通常认为存在临床耐药性[27]。重要医学真菌如曲霉属和念珠菌属中已记录了对常见抗真菌药物的低敏感性趋势，皮肤癣菌的抗真菌耐药性相关报道较少，多数集中在红色毛癣菌[21] [28]、须癣毛癣菌[29]，虽然临床上某些浅部真菌感染对唑类药物或特比奈芬治疗的治疗效果欠佳，但几乎没有犬小孢子菌对唑类药物的耐药现象的报道。2018 年在中国首次报道了一例从患病猫身上分离鉴定的犬小孢子菌，在临床治疗过程和体外药敏试验中(MIC 值 > 32 μg/ml)均表现出了对特比奈芬的耐药性[22]。

2.2. 抗真菌药物体外敏感实验

致病真菌对抗真菌药物的体外敏感性分析可以比较不同药物对特定真菌杀伤或抑制的能力，这对临床合理选择抗真菌药提供指导[30]。目前针对犬小孢子菌的体外药敏试验参考方法还没有标准化[31]，微量液基稀释法、圆片扩散法、E-test 法等多种方法用于验证该菌在体外对抗真菌药物的敏感性，这也导致不同实验室的体外药敏试验数据之间缺乏一定可比性。无论用何种方法，多个研究佐证在犬小孢子菌的体外药敏试验中，氟康唑抗真菌活性普遍低[23] [24] [28] [30] [31] [32]。酮康唑和克霉唑的最低抑菌浓度(Minimum inhibitory concentration, MIC)范围波动较大，在一项包含 208 株犬小孢子菌的体外药敏试验中，酮康唑和克霉唑的抑菌活性仅次于氟康唑(0.016~32 μg/ml) [33]。灰黄霉素作为几十年来治疗头癣的首选药物之一，虽然在体外药敏试验中大多表现出较好的抗菌活性[33] [34] [35]，也无灰黄霉素耐药犬小孢子菌的临床报道，但是一项对来自伊朗的 16 株犬小孢子菌的研究显示，MIC 值在 0.03~256 μg/ml 之间[36]。此外，伊曲康唑在动物和人类来源的犬小孢子菌中活力均低[24] [26] [37]。上述药物对犬小孢子菌的低敏感性一方面可能是由于这些药物在临床中应用广泛，反复使用后产生的获得性耐药现象[18]，另一方面是野生型菌株对抗真菌药物的先天耐药，根据以上研究结果，上述唑类抗真菌药物不能做为治疗犬小孢子菌感染的最佳选择[25]。伏立康唑和特比奈芬表现出较伊曲康唑和灰黄霉素更好的抗真菌活性[25] [32]，在治疗犬小孢子菌所致浅部真菌病中更有优势。近期新型三唑类抗真菌药物的研发和上市，新一代唑类药物，如卢立康唑(Luliconazole)、拉诺康唑(Lanoconazole)、艾氟康唑(Efinaconazole)和雷夫康唑(Ravuconazole)对犬小孢子菌有较高的抗真菌菌活性[23] [33] [38] [39]，MIC 值不仅更小，而且范围更窄，可能对耐药犬小孢子菌更具应用潜力。

真菌体外抗真菌活性与临床治疗失败之间存在相关性[32]，目前皮肤癣菌的耐药性研究滞后于深部真菌病致病菌，与全球可获得的 MIC 数据相比，包括犬小孢子菌在内的皮肤癣菌抗真菌药敏试验数据有限，这一定程度上也阻碍了体外药敏试验数据在临床中的应用。

3. 耐药机制

3.1. 生物膜的形成

生物膜的形成是微生物耐药机制的重要因素。浅部真菌病中，甲真菌病生物膜的形成被认为是导致该病慢性化、治疗困难和临床复发的主要因素[41]。已发现多种真菌菌种存在生物膜，其中也包括犬小孢子菌。犬小孢子菌的生物膜在扫描电子显微镜(Scanning electron microscopy, SEM)下表现为结构严密的三维菌丝体结构，向各个方向网状生长，且菌丝间有富含多糖的细胞外基质(Extracellular matrix, ECM)覆盖相连[40]。这种细胞外基质作为物理屏障，阻止抗真菌药物的渗透，导致耐药性的发生。此外，生物膜还减少了真菌与宿主免疫系统之间的相互作用，使外排泵的表达活跃，胞内药物浓度下降[42]。在对白念珠

菌生物膜耐药的研究中还发现生物膜会导致 ERG、FKS1 等基因发生突变，改变药物作用靶点，导致交叉耐药[44]。与其他皮肤癣菌属菌种比较，犬小孢子菌生物膜的产生量少，但对抗真菌药物不敏感[43]。一项针对皮肤癣菌生物膜的研究结果显示，抗真菌药物作用下该菌生物膜的代谢活性降低，但只有当药物浓度达到 50 倍的 MIC 值时，生物膜的代谢活性抑制才具有统计学意义($P < 0.05$) [43]。这侧面印证了生物膜的形成是该菌对传统抗真菌药物治疗不敏感的原因之一。犬小孢子菌生物膜引起的耐药机制相关研究有待深入研究。

3.2. 药物作用位点的突变

唑类抗真菌药物主要抑制甾醇 14α-去甲基化酶(Sterol 14α-demethylase, CYP51)的活性，抑制麦角甾醇的生物合成，从而影响真菌细胞膜的通透性导致真菌死亡[45]。ERG 基因在编码包括甾醇 14α-去甲基化酶在内的有关麦角甾醇生物合成的酶中发挥作用[46]。其中，皮肤癣菌的唑类耐药表型通常与 ERG3、ERG6、ERG11 基因的点突变有关[47]。且在耐药的念珠菌属[49]和部分皮肤癣菌[48]中，唑类药物的应用会使 ERG 基因表达上调，故 ERG 基因的过表达很大程度上被认为是与真菌类群无关的耐药因素。近期在一篇通过转录组测序研究酮康唑对犬小孢子菌作用机制的研究中，该菌 ERG6 基因的表达明显上调[50]，这也一定程度上表明 ERG 基因是犬小孢子菌对唑类药物耐药机制之一。

特比萘芬作为广泛应用于浅部真菌病感染的药物，以角鲨烯环氧化酶(Squaleneepoxidase, SQLE)为靶点发挥抗真菌作用[51]。在一项包含 17 株特比奈芬耐药的毛癣菌的研究中，全部菌株都发生了 SQLE 基因的点突变[29]，结合其他报道及研究，皮肤癣菌对特比奈芬的耐药性机制与 SQLE 蛋白 4 个位点(Leu393、Phe397、Phe415 和 His440)之一的错义突变有关[52]。SQLE 蛋白的氨基酸取代可能会引起该酶的构象改变，从而导致药物亲和力下降，产生耐药[29]。可能出于对犬小孢子菌的相关研究及临床重视较少，目前该菌中有关 SQLE 基因突变导致的耐药暂无报道，在特比奈芬作用靶点一致、且目前已有犬小孢子菌对特比奈芬临床耐药报道的前提下，该耐药机制于犬小孢子菌中的发现风险极大。

3.3. 细胞内药物水平的降低

由于药物需要到达细胞靶点才能发挥有效作用，而部分真菌细胞通过药物外排蛋白降低细胞内的药物水平，减少抗真菌药物的胞内积累，从而导致耐药性逐步增加[53]。这些外排泵的表达往往是治疗失败的主要原因[54]。

目前已知的外排泵主要包括两类，分别是利用 ATP 水解作为能量来源的 ATP 结合盒(ATP-binding cassette, ABC)转运蛋白和利用膜电位驱动外排的主要协同转运蛋白超家族(Major facilitator superfamily, MFS) [55]。其中对 ABC 转运蛋白的研究最为广泛。在药物存在的情况下，ABC 转运蛋白会出现过表达，这可能会导致耐药。编码上述转运蛋白类的基因的上调已被证实会引起念珠菌属[56]和马拉色菌属[57]的耐药。在皮肤癣菌中，有数十个基因包含 ABC 转运蛋白的结构域，其中包括 pdr1、mdr1、mdr2、mdr4 基因等[58]，上述基因的异常表达往往与皮肤癣菌对抗真菌药物的敏感与否相关，这些机制的研究大部分集中在毛癣菌属。而在犬小孢子菌中联合应用具有外排泵抑制特性的药物(如异丙嗪、氟哌啶醇)和唑类抗真菌药后，在高 MIC 值的犬小孢子菌中均发现了两类药物间的协同作用，即外排泵抑制剂能够提高唑类耐药的犬小孢子菌对抗真菌药物的敏感性[26]。这也提示外排泵基因可能在上述菌株中过表达，从而导致唑类耐药现象。

特比奈芬耐药犬小孢子菌的耐药机制进一步研究结果显示该耐药菌株 pdr1、mdr1、mdr2 和 mdr4 基因的表达量明显升高，该菌的耐药性与编码 ABC 转运蛋白家族的基因过表达相关[59]。综上所述，外排泵导致的细胞内药物水平的降低是犬小孢子菌不论在唑类还是烯丙胺类抗真菌药物中产生耐药性的重要机制。并且，外排泵具有独立于药物作用机制之外的产生多重耐药的能力。

3.4. 应激反应

真菌在遭受各种明显的环境变化，如药物暴露时，能产生一系列适应性的变化，涉及到基因表达的调节和特定蛋白质的合成，以增强细胞抗损伤能力和在不利条件下的生存能力。这其中，泛素(Ubiquitin, Ub)作为一种在选择性蛋白质降解过程中发挥作用的蛋白，在真菌面临热应激及抗真菌药物时，泛素基因表达强烈、泛素产生增多[60]。Kano 等人[61]经 RT-PCR 技术发现氟康唑作用下，犬小孢子菌泛素基因转录产物增多，反过来抑制泛素－蛋白酶体的活性，又可以使犬小孢子菌对氟康唑的敏感性增加。又于一例氟康唑耐药的紫色毛癣菌(*Trichophyton violaceum*)中发现 Ub1 基因的过表达[62]，表明皮肤癣菌对氟康唑的耐药性很可能与泛素基因过表达有关。

皮肤癣菌已被证明能够分泌多种蛋白质以应对环境和药物暴露应激。其中热休克蛋白(Heat Shock Proteins, Hsp)90 在念珠菌属和曲霉菌属中已被证实可以促进耐药[63]。在皮肤癣菌中，hsp70、hsp90 等热休克蛋白作为毒力因子发挥作用，其中 hsp90 被发现与红色毛癣菌对伊曲康唑和米卡芬净的敏感性有关[64]，但这些蛋白与犬小孢子菌耐药性的相关性尚未得到明确阐述。但据信，应激反应使细胞在药物存在的情况下稳定下来，并使其随着时间的推移发展出更深刻的耐药性机制。

此外，抗真菌药物和细胞毒性药物的长期应用会促进代偿性应激反应，并可能导致细胞解毒、药物外排相关基因的过度表达，从而导致耐药性[55]。其中，犬小孢子菌分泌的过氧化氢酶(Catalase, Ca)和溶血因子(Hemolytic factors, Hz)在高敏感和低敏感菌株中的活性呈现差异[25]。这与红色毛癣菌耐药机制的相关研究一致[65] [66]，说明细胞解毒相关酶有可能在犬小孢子菌的耐药机制中发挥作用。目前对犬小孢子菌酶学的研究大多集中在毒力因子和致病性上，鲜有该菌酶学与耐药性关联和产酶基因方面的研究，未来研究可以多关注于此。

4. 应对策略

4.1. 传统药物或方法的联合应用

目前耐药性真菌在世界范围内日益流行，但是可用的抗真菌药物种类有限，新型药物的研发与临床推广周期长。为了应对这一威胁，替代的非抗真菌药物疗法是很有必要的。其中抗菌光动力疗法(Antimicrobial photodynamic therapy, aPDT)被认为是局部浅表感染、尤其是甲真菌病的一种替代治疗方法[67]。抗菌光动力疗法与抗真菌药物联用不仅可以减少药物剂量和副作用，还具有协同杀伤耐药菌株的能力[68] [69]。但是该方法的较高成本可能成为其推广的阻力。

联合抗真菌药物也是一种很有前途的抗真菌治疗策略[70]。外排泵抑制剂(Efflux pump modulators, EPMs)与抗真菌药物的联合使用在应对耐药菌株上具有很大前景，其可能的作用机制是阻断 MDR1/p 糖蛋白和 ABC 转运蛋白编码基因的过表达[71]，降低 ABC 转运体蛋白的活性从而降低耐药性。

4.2. 新型抗真菌药物和药效团的研发

为了保持对真菌性皮肤病的控制，新型抗真菌药物的开发显得尤为重要。在过去十年里已有多种新型抗真菌药物问世，其中，艾氟康唑(Efinaconazole)和他伐硼罗(Tavaborole)在美国、欧洲和许多其他国家被批准用于甲癣，其副作用较轻，但治愈率较低[72]。卢立康唑(Luliconazole)是一种外用唑类药物，对犬小孢子菌具有较高的体内外抗真菌活性[73]。第三代唑类药物如泊沙康唑(Posaconazole)、伏立康唑(Voriconazole)和艾沙康唑(Isavuconazole)在皮肤癣菌体外药敏试验中的 MIC 值均较低[33]，且犬小孢子菌对其敏感性可与特比奈芬相媲美[74]，但临床使用的报道较局限[75]。

8-羟基喹啉衍生物(8-Hydroxyquinoline derivatives)作为一类具有良好抗真菌活性的药效团[76]，在它基础上以三唑环加以修饰形成的 8-羟基喹啉-1,2,3-三唑衍生物(8-Hydroxyquinoline 1,2,3-triazole)通过损伤

真菌细胞壁对犬小孢子菌等多种皮肤癣菌和酵母菌表现出稳定且广泛的抗真菌活性[77]。同样，新合成的一类噻唑衍生物也对犬小孢子菌表现出了高抗真菌活性和高治愈率[78]。药效团的研发能够推动新药的发展，解决真菌性疾病复发、耐药的治疗难题。

近年来，生物治疗作为新的治疗手段应用于犬小孢子感染在内的真菌感染性疾病的治疗。寡雄腐霉(*Pythium oligandrum*)在体外药敏试验[80]和足癣、甲癣患者[81]中对犬小孢子菌表现出了优异的抗菌活性。枯草芽孢杆菌(*Bacillus subtilis*)的次级代谢产物环脂肽(Cyclic lipopeptides, CLPs)可能通过引起犬小孢子菌细胞内容物的泄漏、抑制菌丝的生长来发挥抑菌作用[79]。球孢白僵菌(*Beauveria bassiana*)产生的生物表面活性剂通过抑制犬小孢子菌生物膜的形成增强该菌的药物敏感性[82]。上述生物治疗能够为皮肤真菌病的局部治疗提供新的选择。

4.3. 免疫接种与抗体耦联

自 1944 年以来，用于人和动物的真菌疫苗研究一直在进行[83]，然而目前还没有可以用于人类真菌感染的标准化疫苗。针对犬小孢子菌的疫苗研究多以该菌细胞壁成分[84]、金属蛋白酶[85] (Metalloprotease, MEP3)和枯草菌素蛋白酶[86] (Subtilisin, SUB3)作为外源性抗原，虽然可以诱导较为强烈的体液和细胞免疫应答，但是都缺乏安全、有效、充分的保护作用。近期发现犬小孢子菌内的锌离子响应转录激活因子(Zinc-responsiveness transcriptional activator, ZafA)蛋白可能具有作为疫苗抗原的潜力[87]。同时，疫苗的研发可以考虑使用新的佐剂、更换给药方式来刺激强烈和持久的细胞免疫反应。

除上述免疫接种外，使用特定抗体作为载体与抗真菌成分耦联，能够在发挥靶向抗真菌作用的同时，避免与邻近未感染组织相互作用而产生不良反应[88]。以犬小孢子菌细胞壁成分为抗原的单克隆抗体与纳米银粒子[89] (Silver nanoparticles, AgNPs)或噻唑类化合物[78]耦联的治疗方法在体外实验中也初获成效。

4.4. 植物提取物与中药治疗

近几年，对天然产物的研究进一步拓展了真菌治疗策略，其中，细叶糙果芹(*Trachyspermum ammi*)精油[90]、伞形大胡椒(*Pothomorphe umbellata*)提取物[91]、蜂胶乙醇提取物[90]、胡椒薄荷(*Mentha* × *piperita*)精油[92]、丁香(Eugenia caryophyllus)精油及其衍生物[93]通过损伤真菌 DNA、抑制蛋白酶活性、抑制生物膜形成、抑制孢子的萌发和菌丝的生长等机制对犬小孢子菌及其他皮肤癣菌产生抗真菌作用，个别成分对耐药株也具有良好的抗真菌活性[94]。上述天然产物的作用机制需要进一步完善，以评估其临床应用价值。

中草药作为中国传统的优势资源，具有来源广、价格低、抗菌谱广、不易产生耐药性的特点[95]，尤其适合浅部真菌病等此类病程长、易复发疾病的长期治疗。苦参、白鲜皮、土荆皮[97]、鸡冠花[98]、香鳞毛蕨[99]等单味中草药对犬小孢子菌具有较强的体外抗真菌活性。此外，中草药复方用于药浴[100]、湿敷治疗或洗剂[96]对浅部真菌病卓有成效，因不同中草药成分间的协同抗真菌作用一定程度上能够延缓真菌耐药的发生，而且对患有艾滋病等免疫缺陷疾病的患者疗效佳[101]。中西结合治疗可以优势互补，降低毒副作用，缩短治疗周期，有临床推广价值。

5. 小结与展望

随着饲养宠物的流行，犬小孢子菌感染作为一种人畜共患性疾病，过去二十年中的发生率明显增加，其中犬小孢子菌及其他皮肤癣菌耐药株的报道屡出不鲜，这与不规范用药以及长期广泛使用数量有限的抗真菌药物密切相关。为了应对这一难题，近年来对犬小孢子菌的耐药机制从基因分析、转录组学到蛋白质的鉴定分析等几个层面研究，并在此基础上探索了新的抗真菌药物和治疗方法。虽然这些药物或药

效团有很多可观的体外药敏数据，但还需要进一步完善临床实验评估及其临床价值。规范使用抗真菌药在一定程度上能够减少耐药株的增加和流行。

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