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瘢痕疙瘩的临床研究现状

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摘　要

瘢痕疙瘩是一种特殊的病理性瘢痕，在临床上极难治愈，具有治疗抵抗和治疗后高复发的特征。目前关于其发病机制临床上主要集中在两个学说，“炎症学说”和“肿瘤学说”。瘢痕疙瘩的发病特点和诊疗手段是整形外科的热点话题，这种特点表现在人种、性别、年龄、遗传、部位、诱因等特异性。关于其治疗方案也是多种多样，各有其优缺点。本文主要对目前瘢痕疙瘩的发病机制、发病特点以及治疗方式的研究进展进行综述。

关键词

瘢痕疙瘩，发病机制，流行病学，治疗

Clinical Research Status of Keloid

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Abstract

Keloid is a special pathological scar, which is very difficult to cure clinically. It has the characteristics of treatment resistance and high recurrence after treatment. At present, its pathogenesis is mainly focused on two theories, “inflammation theory” and “tumor theory”. The pathogenesis and diagnosis and treatment of keloid is a hot topic in plastic surgery. This characteristic is manifested in the specificity of race, gender, age, heredity, location, inducement and so on. There are also various treatment schemes, each with its advantages and disadvantages. This paper mainly reviews the research progress of the pathogenesis, characteristics and treatment of keloid.

Keywords

Keloid, Pathogenesis, Epidemiology, Treatment

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1. 引言

瘢痕是各种皮肤损伤所引起的正常皮肤组织外观形态和组织病理学改变的统称，是人体创伤修复过程中必然的产物。在伤口愈合过程中，各种外界或自身因素所导致的胶原的合成代谢与降解代谢之间的平衡被破坏即可形成病理性瘢痕，包括增生性瘢痕和瘢痕疙瘩。临床上根据瘢痕形态不同，分为增生性瘢痕、瘢痕疙瘩、萎缩性瘢痕和瘢痕癌；根据瘢痕颜色、质地、感觉的不同，分为未成熟和成熟的瘢痕。瘢痕疙瘩主要表现为类似良性肿瘤的特征，可进行性生长，不断侵蚀周边正常组织，高出皮肤表面、超出原始损伤范围，一般呈蟹足状，质地较硬，可伴有瘙痒或疼痛。不仅影响美观，而且会引起不适的症状，严重者甚至影响皮肤、关节等功能，甚至会导致患者的心理问题，瘢痕疙瘩的防治亟需提上日程。目前其详细的发病机制尚不明确，发病特点也是不尽相同，治疗方式并不统一，以下将对瘢痕疙瘩的研究现状做个简单的探讨。

2. 瘢痕疙瘩的发病机制

2.1. 炎症学说

皮肤发生损伤时，受损皮肤会立即开始修复，而这个修复的过程便包括五个阶段，即止血、炎症、增殖、再上皮化和重塑[1]，炎症学说主要认为机体修复过程中的炎症反应失衡导致机体的异常修复，进而形成了病理性瘢痕，包括增生性瘢痕和瘢痕疙瘩。参与瘢痕形成的炎症细胞包括巨噬细胞、淋巴细胞、肥大细胞和中性粒。而在瘢痕疙瘩组织中，巨噬细胞、T 细胞和肥大细胞都有不同程度的增加[2] [3]。除此之外，瘢痕疙瘩组织中存在大量炎症因子，包括 IL-6、IL-8、IL-18、趋化因子样因子-1 (CKLF-1)、环氧化酶(COX-1)产生的前列腺素(COX-1) [4] [5]，在瘢痕疙瘩患者的外周血中，IL-8 水平也比正常人高 7 倍[6]。NF-kB 家族成员是调节许多关键炎症基因的转录因子，NF-kB 通路在瘢痕疙瘩成纤维细胞中被激活，其下游基因较正常皮肤的成纤维细胞上调，瘢痕疙瘩组织中成纤维细胞的 NF-kB 蛋白水平和 NF-kB 结合活性也较高[7] [8]。STAT-3 信号通路是多种细胞因子的下游，是细胞增殖、迁移、分化、凋亡、炎症以及纤维化的调节器。在瘢痕疙瘩组织中，该信号通路被激活，降低 STAT-3 的表达或抑制其磷酸化可显著减少胶原的合成和瘢痕疙瘩成纤维细胞的增殖和迁移[9] [10]。

2.2. 肿瘤学说

瘢痕疙瘩不会自发消退，会持续生长，侵犯周围正常组织，呈一种类肿瘤的发病特征，而其组织病理学特点也与肿瘤有相当多类似之处。有研究发现，多种生长因子如 TGF-β、IGF-I (Insulin-Like Growth Factors-I)、PDGF (Platelet Derived Growth Factor)、EGF (Epidermal Growth Factor)等在瘢痕疙瘩组织中存在过表达和分泌，且瘢痕疙瘩组织对某些生长因子的敏感度也较正常组织明显增强[11] [12] [13]，使得瘢痕疙瘩的侵袭性增加。瘢痕疙瘩组织中抑癌基因 P53 的失活[14]以及 ASY、PEA 15、AVEN、ADAM12 等凋亡相关基因的异常表达[15] [16]充分显示其类肿瘤特性，为其不受控制的增值提供了理论基础。除此之外，相较于正常皮肤，瘢痕疙瘩较正常皮肤可能具有更强的血管形成能力[17] [18]。肿瘤的局部浸润和远处转移的特点与上皮间充质改变(Epithelial-Mesenchymal Transition, EMT)和上皮细胞极性丧失有重要的关系，而我们在瘢痕疙瘩组织中也发现了粘附相关基因的表达较正常皮肤降低，间充质标志物和 EMT 标志物的 mRNA 水平升高

[19]，在体外实验中，一些细胞因子成功诱导了瘢痕疙瘩角质形成细胞发生 EMT [20]。能量代谢异常是肿瘤细胞的特征，在瘢痕疙瘩组织中也存在异常的能量代谢过程[21] [22] [23]，包括高乳酸含量、高 ATP 含量以及高耗氧率，这种异常的能量代谢是否与瘢痕疙瘩打发生发展有关，尚需进一步证实。

3. 瘢痕疙瘩的发病特点

3.1. 人种

肤色较深的人种相对于肤色较浅的人种更容易患瘢痕疙瘩[24]，西班牙裔、非裔美国人和亚洲人都形成瘢痕疙瘩疤痕的风险都比较高，其中非洲人后裔的患病率最高；据估计，这一比例为 4%~6%，非裔美国人种的患病率约为 10% [25] [26] [27]。但据报道，扎伊尔成年人口中这一比例高达 16%，亚裔和西班牙裔血统的人相对来说不那么容易感染，白人的患病率最低，在英格兰低至 0.09% [28] [29]。然而关于瘢痕疙瘩的种族特异性的机制尚不清楚，在目前的研究中，多数猜测与种族遗传有关。

3.2. 性别

一些报告称，女性患瘢痕疙瘩的可能性比男性高[30]，这可能与男女之年内分泌的差别有关系[31]，也不排除女性对于外观的要求较男性高，从而更愿意去寻求医疗帮助[32]，而且，相对来说，女性穿耳洞的几率也高于男性[33]。鉴于妊娠期瘢痕疙瘩的高发病率，也有学者猜测，这可能与性激素有一定关系[31] [34]。

3.3. 年龄

瘢痕疙瘩可发生在任何年龄，但不同年龄的发病风险有差异[35]。年轻人的发病风险普遍较高，主要集中在 10~30 岁左右[30] [36]。具体造成这一区别的机制尚不清楚，有学者研究提出[31] [34]，这可能与内分泌变化有关，青春期、妊娠期等时期内分泌较活跃可能对瘢痕疙瘩的发生发展起到某些潜在作用，而瘢痕疙瘩的发病在青春期呈峰值，在妊娠期也有较高发病率的特征也支持这一点。

3.4. 遗传

瘢痕疙瘩具有遗传易感性，近年来的研究已经证实了瘢痕疙瘩与遗传有关[31] [37]。有些家庭的多个成员几代人都患有瘢痕疙瘩。在这些家族中，瘢痕疙瘩倾向于以常染色体显性遗传模式在家族内部差异性表达，表现为不完全外显的特征。有研究证明，有家族史的人患病风险会增加，而且与散发性瘢痕疙瘩患者(即无瘢痕疙瘩家族史)相比，家族性瘢痕疙瘩患者往往在多个身体部位出现瘢痕疙瘩，并且有多个家族成员在相同的不同部位出现瘢痕疙瘩的情况，而且可能患上多个瘢痕疙瘩，程度也更重[36]。

3.5. 部位

不同部位发生瘢痕疙瘩的风险也不同，同一个人同样的受伤方式，在不同的部位可能同时出现正常瘢痕和瘢痕疙瘩[38]。其好发部位主要分布在耳垂、颈部、胸骨、上背部、肩部和上肢，尤其是耳垂和前胸[35]，这可能与这些部位的张力过高以及运动时产生一定的拉力有关[39]。除此之外，皮脂腺密度高、胶原蛋白增加和 M1 巨噬细胞数量减少都是瘢痕疙瘩易感皮肤的特征[38] [40]。

3.6. 诱因

创伤通常是瘢痕疙瘩疤痕形成的必要先决条件，因为必须对皮肤受到某种形式的刺激才能激发瘢痕疙瘩的形成，但是不同的受伤方式形成瘢痕疙瘩的可能性不同，所形成的瘢痕疙瘩的特点也有区别[41] [42]。除此之外，痤疮、毛囊炎、水痘、带状疱疹和化脓性汗腺炎等炎症性皮肤病也可能导致瘢痕疙瘩的形成[43]。

4. 瘢痕疙瘩的治疗

4.1. 非侵入疗法

4.1.1. 压力疗法

在过去45年中，压力疗法不仅是治疗瘢痕疙瘩疤痕的一种选择，也是烧伤疤痕的一线治疗手段[44] [45]。压力服装疗法可以缓解瘙痒和疼痛，但其缺点是成本高，而且由于服装造成的明显不适，患者依从性差[46] [47]。瘢痕疙瘩患儿可采用压力疗法治疗，因为与其他侵入性疗法相比，压力疗法副作用很小[26]。

4.1.2. 硅胶薄膜材料

硅胶薄膜硅胶材料也是治疗瘢痕疙瘩的首选[35] [48]。研究表明，使用硅胶敷料后，瘢痕疙瘩的改善率高达90% [49]，明显降低了术后瘢痕疙瘩的发病率[44] [50]，硅酮材料所制成的薄片和凝胶，也起到同等的功效[51]。但是有个明显的缺点是，大多数硅胶辅料都非常昂贵。

4.1.3. 洋葱提取物

洋葱提取物的主要成分是槲皮素，它有抗炎、抗菌的作用，除此之外，还对胶原蛋白有一定的抑制作用[52]。槲皮素通过抑制成纤维细胞的增殖和胶原的生成，来起到抑制病理性瘢痕发生发展的作用[53]。除此之外，它还具有抗组胺作用，而组胺会增加成纤维细胞的胶原生成[54] [55]。但是，它对瘢痕疙瘩的治疗作用有待于进一步验证[25]。

4.2. 局部注射治疗

4.2.1. 皮质类固醇激素注射治疗

目前的国际指南建议将皮质类固醇注射作为预防和治疗瘢痕疙瘩的一线疗法[41] [56]。既可以单独使用，也可以与其他疗法结合使用[57]。皮质类固醇通过减少成纤维细胞增殖、减少胶原合成、改变细胞外基质成分(如糖胺聚糖)和抑制炎症发挥作用[57] [58]。病灶内皮质类固醇注射可改善疤痕的柔韧性，减少疤痕的体积和高度，并导致瘙痒和疼痛等相关症状的快速临床改善[26] [27] [59]。尽管注射治疗过程比较痛苦，但治疗效果有目共睹，但有效率在50%到100%之间，复发率在9%到50%之间[26] [60]。通过将注射与手术、5-氟尿嘧啶和冷冻疗法等其他治疗相结合，可以改善结果[27] [58]。其副作用包括疼痛、皮肤萎缩、色素减退、色素沉着过度和毛细血管扩张[60] [61]。

4.2.2. 5-氟尿嘧啶

5-氟尿嘧啶作为瘢痕疙瘩的一种治疗方案已经使用了25年多，但其使用仍存在争议[62]。5-氟尿嘧啶是一种含氟嘧啶类似物，也是一种经典的化疗药物。它作为一种细胞毒性剂发挥作用，可以抑制瘢痕组织中的细胞增殖[26] [62] [63]，并已被证明在不引起组织坏死的情况下可以抑制成纤维细胞增殖和促进成纤维细胞凋亡。它还可以抑制转化生长因子-β (Transforming Growth Factor-β, TGF-β)诱导的I型胶原表达[63]。临床上常将病灶内5-氟尿嘧啶单独使用，与皮质类固醇联合使用，或作为术后辅助治疗，其有效性在临床已经得到证实，有研究证明，5-氟尿嘧啶联合皮质类固醇对于瘢痕疙瘩的治疗中，有效率最高可达95~100% [64] [65]。5-氟尿嘧啶的副作用包括疼痛、烧灼感、紫癜形成、暂时性色素沉着、皮肤红斑和溃疡等。病灶内5-氟尿嘧啶治疗是安全的，目前尚未出现贫血、白细胞减少或血小板减少等全身并发症的报告[66]。

4.2.3. 博莱霉素

博莱霉素是一种具有抗菌和抗病毒活性的细胞毒性化疗药物[66] [67]。它诱导细胞凋亡并减少TGF-β1诱导的胶原合成[67] [68]。其副作用包括疼痛、注射部位的浅表溃疡和结痂、暂时性色素沉着和皮肤萎缩。

目前低剂量皮下注射博莱霉素尚未出现任何全身毒性，如肺毒性、肾毒性、皮肤毒性、肝毒性或骨髓毒性[68]。

4.2.4. 丝裂霉素 C

丝裂霉素 C 具有抗肿瘤和抗增殖活性[45]，它可以抑制 DNA、RNA 和蛋白质的合成。它还抑制成纤维细胞增殖，防止细胞分裂，从而减少体外和体内的瘢痕形成[68]。使用丝裂霉素 C 来治疗瘢痕疙瘩也逐渐开始应用于临床。

4.3. 手术治疗

手术治疗是中、大型瘢痕疙瘩的一线治疗方法。但就目前的治疗效果来看，手术的复发率非常高，有效减少创周皮肤的张力可以降低瘢痕疙瘩的复发率，合理分布创缘的张力可以减少拉力不均造成的病理性瘢痕，制定合适的手术方案对于瘢痕疙瘩的预后来说影响很大。一般来说，伤口闭合时应尽量减少张力和缝线，放松皮肤张力线，留下外翻的伤口边缘，如果因张力过大而导致瘢痕挛缩，则可能需要 Z 形成形术、W 形成形术或各种局部皮瓣[69]。

4.4. 冷冻疗法

冷冻疗法会导致瘢痕疙瘩组织的细胞损伤和坏死。它可以通过接触、喷雾或病灶内注射来给药。病灶内冷冻疗法将寒冷区域集中在病灶内，因而对正常皮肤的影响最小；它很简单，适用于所有类型的疤痕，比接触/喷雾疗法更有效[70]。冷冻疗法与皮质类固醇注射相结合是瘢痕疙瘩最常用的传统治疗方法。其最常见的副作用是色素减退，其次是水泡、局部疼痛和色素沉着[25] [26]。

4.5. 放射疗法

放射治疗常作为外科手术的辅助手段，研究发现，放射治疗和手术相结合是治疗严重瘢痕疙瘩最有效的方法[27]，在 30 个月的随访中，复发率降低了 55% [25]。它可能通过抑制成纤维细胞的增殖、阻止成纤维细胞的重新增殖或抑制血管生成来发挥作用[71]。放疗的副作用包括急性皮肤反应，如早期的脱皮、脱毛、色素沉着和红斑，而亚急性和晚期并发症包括疤痕、永久性色素沉着、萎缩、脱皮、毛细血管扩张、皮下纤维化和数周后的坏死。不建议对孕妇、儿童(12 岁以下)或放射敏感部位(如甲状腺)的瘢痕疙瘩进行放射治疗。放射治疗的致癌风险抑制是人们所担心的问题，但是目前的研究表明，在放疗后瘢痕疙瘩疤痕上发生癌症几率并不高[72]。

4.6. 一些新兴的治疗方法

4.6.1. A 型肉毒毒素

在伤口愈合过程中，肉毒毒素可以减少肌肉的收缩[73]。事实上，张力高是瘢痕疙瘩疤痕的原因之一。在一项前瞻性非对照研究中，皮损内注射肉毒杆菌毒素可改善瘢痕疙瘩，并比皮质类固醇注射更有效地减少了瘢痕疙瘩的体积[66] [74]。然而，关于肉毒杆菌毒素的治疗效果，有研究出现了与其相反的结果[75] [76]，因此，关于使用 A 型肉毒毒素治疗瘢痕疙瘩，需要进行更大规模的随机对照研究来确认其疗效。

4.6.2. 咪喹莫特

咪喹莫特是一种免疫反应调节剂。作为一种 T 淋巴细胞样受体激动剂，它增加促炎细胞因子肿瘤坏死因子-α、干扰素-α 和白细胞介素 1、6、8 和 12 的产生。此外，它还可以诱导瘢痕疙瘩组织中凋亡基因的表达[76]。荟萃分析结果表明，瘢痕疙瘩手术后接受咪喹莫特乳膏辅助治疗的患者的瘢痕疙瘩复发率约为 24.7% [77]，这较单纯手术治疗复发率降低了很多，虽然如此，但目前其治疗效果仍然存疑[78] [79]。据报道，其副作用包括疼痛、色素沉着和其他局部皮肤反应如刺激、红斑、糜烂和结痂[57]。

4.6.3. 干扰素

干扰素是具有抗增殖、抗纤维化和抗病毒作用的一种细胞因子[67]。其能增加胶原蛋白的分解[46]。尽管干扰素对瘢痕疙瘩有很好的疗效，但其治疗费用昂贵，且治疗效果仍存在争议[27] [76]。此外，干扰素注射过程比较痛苦，可能需要同时进行局部麻醉[27]。不良反应包括全身流感样症状(73.7%)，以及注射部位的疼痛和炎症[57]。

除此之外，瘢痕疙瘩的治疗药物还有 TGF-β、血管紧张素转换酶抑制剂、钙通道阻滞剂、他克莫司、阿莫西芬等，但其属于新兴的治疗方式，尽管有些药物在临床上已经取得了很客观的治疗效果，但目前应用尚未普遍，尚缺乏更大规模的随机对照研究来确认其疗效，且其副作用也常常让人望而却步[80]。

5. 总结

上述概述了瘢痕疙瘩的研究现状，包括发病机制、发病特点和治疗方式。瘢痕疙瘩所造成的创伤除带给患者组织功能的影响之外，也带来了无尽的心理压力，在临床上，其难治性及高复发率的特征也给临床医师带来巨大的挑战，目前暂没有作为金标准的明确的治疗方法可以使治疗有效率达到 100%，这就需要临床上结合患者的实际情况，做出最优方案，尽可能降低其复发，并且降低患者的治疗痛苦，除此之外，结合瘢痕疙瘩的发病机制及发病特点，对瘢痕疙瘩的高危人群做出针对性的预防措施也是至关重要。

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