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Characterization of different biodegradable scaffolds in tissue engineering[J]. Molecular Medicine Reports，2019，19(5)：4043-4056

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Characterization of different biodegradable scaffolds in tissue engineering

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Abstract

The aim of the present study was to compare the characteristics of acellular dermal matrix (ADM), small intestinal submucosa (SIS) and Bio-Gide scaffolds with acellular vascular matrix (ACVM)-0.25% human-like collagen I (HLC-I) scaffold in tissue engineering blood vessels. The ACVM-0.25% HLC-I scaffold was prepared and compared with ADM, SIS and Bio-Gide scaffolds via hematoxylin and eosin (H&E) staining, Masson staining and scanning electron microscope (SEM) observations. Primary human gingival fibroblasts (HGFs) were cultured and identified. Then, the experiment was established via the seeding of HGFs on different scaffolds for 1, 4 and 7 days. The compatibility of four different scaffolds with HGFs was evaluated by H&E staining, SEM observation and Cell Counting Kit-8 assay. Then, a series of experiments were conducted to evaluate water absorption capacities, mechanical abilities, the ultra-microstructure and the cytotoxicity of the four scaffolds. The ACVM-0.25% HLC-I scaffold was revealed to exhibit the best cell proliferation and good cell architecture. ADM and Bio-Gide scaffolds exhibited good mechanical stability but cell proliferation was reduced when compared with the ACVM-0.25% HLC-I scaffold. In addition, SIS scaffolds exhibited the worst cell proliferation. The ACVM-0.25% HLC-I scaffold exhibited the best water absorption, followed by the SIS and Bio-Gide scaffolds, and then the ADM scaffold. In conclusion, the ACVM-0.25% HLC-I scaffold has good mechanical properties as a tissue engineering scaffold and the present results suggest that it has better biological characterization when compared with other scaffold types.

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Study of tissue engineered vascularised oral mucosa-like structures based on ACVM-0.25% HLC-I scaffold *in vitro* and *in vivo*

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Abstract

Purpose: To explore the feasibility of constructing tissue-engineered vascularised oral mucosa-like structures with rabbit ACVM-0.25% HLC-I scaffold and human gingival fibroblasts (HGFs), human gingival epithelial cells (HGECs) and vascular endothelial-like cells (VEC-like cells).

Method: Haematoxylin and Eosin (H&E) staining, immunohistochemical, immunofluorescence, 5-ethynyl-2'-deoxyuridine (EdU) staining and scanning electron microscope (SEM) were performed to detect the growth status of cells on the scaffold complex. After the scaffold complex implanted into nude mice for 28 days, tissues were harvested to observe the cell viability and morphology by the same method as above. Additionally, biomechanical experiments were used to assess the stability of composite scaffold.

Results: Immunofluorescence and Immunohistochemistry showed positive expression of Vimentin, $S100A_4$ and CK, and the induced VEC-like cells had the ability to form tubule-like structures. *In vitro* observation results showed that HGFs, HGECs and VEC-like had good compatibility with ACVM-0.25% HLC-I and could be layered and grow in the scaffold. After implanted, the mice had no immune rejection and no obvious scar repair on the body surface. The biomfechanical test results showed that the composite scaffold has strong stability.

Conclusion: The tissue-engineered vascularised complexes constructed by HGFs, HGECs, VEC-like cells and ACVM-0.25% HLC-I has good biocompatibility and considerable strength.

Keywords: Tissue engineering; human gingival epithelial cells; human gingival fibroblasts; vascular endothelial-like cells.

类人胶原带白联合天然、人工合成及纳米材料作为组织工程支架材料的应用进展[J]. 医学综述, 2017, 23(07):1258-1261

类人胶原蛋白联合天然和人工合成及纳米材料作为组织工程支架材料的应用进展

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摘要: 动物来源胶原材料在组织工程修复中的应用已十分广泛 ,而类人胶原蛋白(HLC)作为天然生物材料中的一种 ,是传统动物来源胶原材料的改良。HLC 具有细胞相容性好、无免疫原性等特点 ,可以作为组织工程支架材料应用于组织工程修复组织器官损伤 ,并受到广泛关注。然而 ,低生物力学强度及不可控的生物降解速率使 HLC 在应用时受到一定程度的限制。为克服这些缺陷 ,将 HLC 与其他天然生物材料、人工合成材料及纳米材料联合使用 ,使得复合材料既无免疫源性 ,同时又具备了良好的细胞相容性、一定的机械强度和可控的生物降解速率 ,以便为组织工程修复组织和器官缺损提供更为优良的支架材料。

关键词: 类人胶原蛋白; 组织工程; 天然生物材料; 人工合成材料; 纳米材料

Application Progress of Human-like Collagen Combining with Natural , Synthetic and Nano Materials as Tissue Engineering Scaffolds

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Abstract: Animal collagen material is widely used as a scaffold in tissue engineering repair. As a kind of natural biological material ,human like collagen (HLC) is the improvement of traditional animal derived collagen material. Due to its good biocompatibility , no immunogenicity , it can be used as scaffold material for tissue engineering to repair organ tissue damage , and receive extensive attention. However ,several factors such as low mechanical strength and uncontrollable biodegradation rate may limit the application of HLC. In order to overcome these defects , HLC combined with natural materials ,synthetic materials or nano materials as tissue engineering scaffolds for reconstruction tissue and organ have favorable cell compatibility ,low immunogenicity and mechanical strength as well as controllable biodegradation rate.

Key words: Human-like collagen; Tissue engineering; Natural biological material; Synthetic material; Nano material

组织工程包括种子细胞、支架材料和细胞因子三个基本要素 ,其中组织工程支架材料是组织工程三要素中至关重要的一个部分 ,它的存在为组织工程化组织器官的构建提供了三维空间[1]。组织工程支架材料的选择直接关系到支架置入体内的效果。而对于支架材料的选择: ①要具备良好的生物相容性 ,这就要求支架材料能够为种子细胞提供良好的吸附界面 ,有利于种子细胞的黏附生长和细胞增殖; ②要求支架材料具备较高的生物安全性 ,即支架材料应无细胞毒性、无免疫原性、无致瘤性 ,且不会对机体产生致畸作用; ③要求支架材料具备整合细胞因子的功能 ,这是因为细胞因子能够激活细胞中各种特异基因的表达 ,进而维持种子细胞在支架材料表面的正常表型; ④要求支架材料具有一定的孔隙率、生物力学强度 ,并在置入后具有可控的生物降解速率[2-4]。天然生物材料 ,如类人胶原蛋白(human-like collagen ,HLC)与种子细胞的亲和力强 ,能够有效促进种子细胞在支架材料表面的黏附生长和细胞增殖[5]。然而 ,低生物力学强度和不可控的生物降解速率限制了 HLC 在组织工程中作为支架材料的应用[5]。在实际应用中 ,常将 HLC 与天然生物材料、人工合成高分子材料及纳米材料等联合使用 ,以更好地提高材料的机械强度和生物降解速率。现就 HLC 联合天然生物材料、人工合成高分子材料及纳米材料作为组织工程支架材料的应用

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老年人隐裂牙全冠修复适应症的选择 [J]. 中华老年口腔医学杂志, 2018, 16(03):169-172

·论著·

老年人隐裂牙全冠修复适应症的选择

宋海清

【摘要】目的：探讨隐裂牙冠修复的适应症，对本经牙髓治疗的隐裂牙保守治疗提供依据。方法：将满足条件抽取的40例老年患者40颗未进行牙髓治疗的隐裂牙作为研究对象直接进行冠修复，在六个月后观察其症状有无缓解，从裂纹陈旧度、病情轻重、疼痛持续时间三个方面进行因素分析，并进行适应症的讨论。结果：40例40颗患牙冠修复后总缓解率60%，不同裂纹陈旧度、不同疼痛持续时间、不同病情轻重的缓解率差异具有显著性(P< 0.05)。结论：裂纹陈旧度新、疼痛时间短、疼痛程度低的活髓隐裂牙相对裂纹程度旧、疼痛时间长、疼痛程度重的活髓隐裂牙更适宜直接进行冠修复。

关键词：牙隐裂；冠修复；疼痛时间；裂纹陈旧度
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The choice of indications of crown restoration on cracked tooth in the elderly

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[Abstract] Objective: To explore the indication of the repair of the crown prosthesis and to provide the basis for the conservative treatment of the untreated teeth. **Methods:** Forty cracked teeth of 40 elderly patients who were not treated with dental pulp were used as the research object. After six months, the symptoms of the teeth were observed whether the symptoms were relieved, and the severity and severity of the crack were observed. The duration of pain was analyzed in three aspects, and indications were discussed. **Results:** The total response rate of the 40 case is 60%. There were significant differences in the remission rate of different crack old degree, different pain duration and different severity of the disease ($P<0.05$). **Conclusion:** New crack oldness, time is short, low degree of pain, live pith of cracked tooth good curative effect, the relative degree of crack old, long pain, pain degree heavy live pith cracked tooth crown restoration is more suitable for direct.

Key words: tooth cracked; crown restoration; the time of pian; crack oldness

牙隐裂是指本经治疗的牙齿表面由于某些因素的长期作用，而出现的临床不易发现的细微裂纹，是中老年患者较常发生的一种牙体慢性损伤。初期肉眼无法分辨，以至很多活髓牙隐裂未得到及时诊治，最终引起牙髓炎、牙髓坏死或局部牙周炎，严重者可引起劈裂(斜折或纵折)而导致拔牙[1]，故临床医生应给予足够的重视。

目前，临床上虽然针对不同的隐裂程度制定了不同的治疗方法，但是采用保守治疗的方法，例如对患牙直接进行冠修复，保存活髓的较少，而且适应症模糊，研究也较欠缺。完善的治疗固然是比较好的选择，但是对于老年人而言，多次复诊和治疗给他们造成了诸多不便和经济负担。为了探讨老年人隐裂牙活髓进行直接冠修复的适应症，对满足适应症的隐裂牙及早进行冠修复，以隔绝外界刺激，消除隐裂牙的薄弱部分，避免牙髓被激惹引发牙髓炎或根尖周炎从而保存患牙牙髓，恢复咀嚼功能，建立新的咬平衡，避免牙折或裂沟处产生龋坏，阻止隐裂进一步加深，最终减轻患者就诊次数、疼痛及经济负担，提高患牙的生存率，遂开展此研究，结果如下。

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1. 研究对象和方法

1.1 研究对象 选择来我院诊治并未进行牙髓

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治疗的 40 例老年患者 40 颗隐裂患牙为研究对象，其中男性 22 例 22 颗患牙，占 55.0%；女性 18 例 18 颗患牙，占 45.0%。年龄 60-87 岁，平均年龄 72.15±2.96 岁。总体年龄聚集在 66-75 岁(占 42.5%)和 76-82 岁(占 37.5%)。

1.1.1 选择标准　选择有以下情况的患牙：①患牙有咬合不适，偶在某部位有短暂撕裂样疼痛病史，可自行缓解；②肉眼可见裂纹，碘酊染色；③冷热(-)，无自发痛等牙髓炎症状；④叩(-)，无根尖炎症状，x-ray 未见根尖周暗影；⑤排除牙纵折，牙本质过敏等。

1.1.2 病例　在 40 颗患牙中，上颌第一前磨牙(B4)1 例，占 2.5%；上颌第二前磨牙(A5+B5)4 例，占 10%；上颌第一磨牙(A6+B6)15 例，占 37.5%；下颌第一磨牙(C6+D6)16 例，占 40%；上颌第二磨牙(A7+B7)2 例，占 5.0%；下颌第二磨牙(C7+D7)2 例，占 5.0%。裂纹陈旧度新 25 例，占 62.5%；陈旧度旧 15 例，占 37.5%。疼痛时间≤10s 14 例，占 35.0%；疼痛时间 10s-20s 14 例，占 35.0%；疼痛时间 20s-30s 2 例，占 5.0%；疼痛时间＞30s 10 例，占 25.0%。病情轻 12 例，占 30.0%；病情中 15 例，占 37.5%；病情重 13 例，占 32.5%。

1.2 方法

1.2.1 治疗方法　对 40 颗患牙冠修复(在 2%甲哌卡因局麻下进行常规牙体预备、取模、灌模，用造牙粉制作临时冠，丁香油粘固粉粘固，一周后无自发痛，无叩痛则粘固烤瓷全冠)。

1.2.2 研究方法　记录 40 颗患牙的裂纹陈旧度、病情程度以及疼痛持续时间①裂纹陈旧度：裂纹颜色浅，不明显定义为裂纹程度新；裂纹颜色深，肉眼可见明显裂纹定义为裂纹陈旧度旧；②病情程度：疼痛时间≤10s、裂纹陈旧度新为病情轻度；疼痛时间≥10s 疼痛时间≤30s、裂纹陈旧度新或疼痛时间≤10s、裂纹陈旧度旧为病情中度；疼痛时间＞30s、裂纹陈旧度新或疼痛时间≥10s 裂纹陈旧度旧为病情重度。③疼痛持续时间(≤10s、10s-20s、20s-30s、＞30s)三个方面，在六个月后观察症状有无缓解。对结果的缓解率进行统计分析并探讨冠修复的适应症。④症状缓解：咬合不适及疼痛的症状均消失，患牙牙髓电活力测试结果正常。

2. 结果

2.1 SPSS 卡方检验　此次抽取的样本中总体的有 24 例症状缓解，缓解率为 60.0%，16 例未缓解在冠修复一月后出现根尖周炎或牙髓炎的症状，其中 3 例拍摄 x-ray 可见根尖周有暗影，给予常规牙髓治疗后症状消失。在调查对象中，有 25 例是裂纹陈旧度为新的患牙，其中 20 例(80.0%)症状缓解，缓解率优于裂纹陈旧度旧的 15 例患牙(26.7%)。病情程度轻的共有 20 例，程度中等的有 11 例，病情重的有 9 例。轻、中、重的缓解率分别为 100%、45.5%和 33.3%。疼痛持续时间为≤10s 的缓解率最高(85.7%)，其次为 10s-20s(57.1%)，＞30s(40.0%)，20s-30s 的缓解率最低(0.00)。运用 SPSS19.0 统计软件可得出缓解率在裂纹陈旧度、病情程度、疼痛时间三个方面差异均具有统计学意义($P<0.05$)见表 1。

表 1　不同观察项目对患者症状缓解情况

观察项目	症状		总计(例)	X2	P^*
	缓解(例)	未缓解(例)			
裂纹陈旧度				11.1	0.001
新	20(80.0%)	5(20.0%)	25		
旧	4(26.7%)	11(73.3%)	15		
总计	24	16	40		
病情轻重				14.747	0.001
轻	14(100%)	0(0%)	14		
中	5(45.5%)	6(54.5%)	11		
重	5(33.3%)	10(66.6%)	15		
总计	24	16	40		
疼痛时间				8.571	0.036
≤10s	12(85.7%)	2(14.3%)	14		
10s-20s	8(57.1%)	6(42.9%)	14		
20s-30s	0(0.00)	2(100%)	2		
＞30s	4(40.0%)	6(60.0%)	10		
总计	24	16	40		

* 表示有统计学意义

2.2 SPSS19.0 非条件多因素 Logistic 回归分析　在单因素分析的基础上，缓解或未缓解为结果变量(0、1)，选取病情轻重、疼痛时间、裂纹陈旧度为自变量，进行非条件多因素 Logistic 回归分析。结果显示：病情轻重的 P 值(Sig)=0.022<0.05，说明病情轻重与冠修复后病情缓解与否的关系有统计学意义。疼痛时间与缓解与否的关系有统计学意义($P=0.036<0.05$)，疼痛时间每增加一个层次，其症状不能缓解的可能性是分别是第一个层次的

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2.107倍(95%CI：1.049~4.235)；裂纹陈旧度与缓解与否的关系有统计学意义($P=0.032<0.05$)，裂纹陈旧度旧的发生症状未缓解的可能性是裂纹陈旧度新的41.081倍(95%CI：1.369~1233.063)(见表2)。

表2　不同影响因素对症状缓解的非条件多因素Logistic回归分析

影响因素	OR值	95%CI
病情轻重	0.036	(0.002，0.621)
疼痛时间	2.107	(1.049，4.235)
裂纹陈旧度	41.081	(1.369，1233.063)

3. 讨论

3.1 牙隐裂的病因有以下三点　①咬力的因素：牙隐裂是临床上常见的牙体非龋性疾病，常见于磨牙和前磨牙，以第一磨牙比较多见，可能由于萌出时间比较早，承担的咬力比较大，容易出现病理性磨耗，导致牙隐裂②牙体因素：牙齿的沟裂处是牙结构的薄弱环节，是牙齿发育时期的钙化结合区，不仅本身抗裂强度差，而且是牙承受正常咬力时应力集中的部位；②牙尖斜度大，水平分力大[3]；③增龄性改变：中老年人牙齿的牙髓血管细胞成分减少，牙本质弹性变脆[1]。隐裂牙的牙冠表面常无明显龋坏或深的牙周袋，牙面上也探不到过敏点[4]。

3.2 牙隐裂的诊断　表浅的隐裂常无明显的症状，较深时则遇冷热刺激敏感，或有咬合不适感。深的隐裂因已达到牙本质深层，多有慢性牙髓炎的症状，有时也可急性发作，并出现定点性咀嚼剧痛。一般可用尖锐的探针检查，如隐裂不明显，可涂以碘酊，使渗入隐裂染色面将其显示清楚。有时将探针置于裂隙处加压或用力摇动，可有疼痛感。沿裂隙磨除，可见裂纹已达牙本质深层。将棉签置于可疑牙的牙尖上，嘱患者咬合，如出现短暂的撕裂样疼痛，则可能该牙已有隐裂。

3.3 牙隐裂的治疗　临床上对于隐裂仅达牙本质界，着色浅而无继发龋坏者，用酸蚀法和釉质粘接剂光固化处理；有继发龋或裂纹着色深，已达牙本质浅层，中层，沿裂纹备洞，氢氧化钙糊剂覆盖，氧化锌丁香油粘固剂暂封2~4周后无症状则换光固化复合树脂，直接树脂粘接修复具有牙体结构保存好、操作简单、省时的优点，但存在聚合收缩引起微渗漏[5]，易磨损、抗力有限、术后敏感等缺点[6]；正确判断牙髓活力是最终修复成功的关键，Opdam等[7]建议在暂时修复体佩戴后观察足够时间，确认牙髓状况后行最终修复。但是暂时冠修复存在增加诊疗费用、延长治疗时间的不足，其制作不规范可对牙周组织造成破坏，影响修复进程，牙体预备过程中尚存在进一步加深裂纹的风险。对活髓患牙而言，牙体预备、暂时冠粘接、边缘渗漏等过程可对患牙造成额外刺激，增加细菌感染和激惹牙髓的几率[8]，暂冠佩戴时间越长风险越大。面较深的裂纹或已有牙髓病变者，在治疗牙髓的同时调整牙尖斜面，彻底去除致裂力量。并在牙髓治疗开始时做带环保护牙冠，以避免咀嚼等原因发生牙体自裂纹处劈裂开，治疗完毕后做冠修复[9]。但很多的研究表明，隐裂并不是静止的状态，即使做了彻底的根管治疗，如果致病因素未去除，隐裂可能会进一步的发展，沿着裂沟薄弱区加深、加长[10]。综上，对于早期隐裂牙应该及早进行冠修复。冠修复的优点在于①可以保存患牙活髓，不但能隔绝外界的不良刺激，不论是物理刺激还是化学刺激，而且能够有效的抵抗咬验力及侧向验力②对于比较浅的裂纹，还可在牙体预备时磨除隐裂纹，消除其发展和龋坏的可能③全冠修复使患者在进食食物时不再有咬验痛，恢复了患者的咀嚼功能，提高咀嚼效率，从而提高生活质量[11]。但是并不是每一颗隐裂牙都适合直接进行冠修复，需要对其进行多方面的分析及判断，以免冠修复后出现牙髓炎或根尖炎的症状后只能去冠做治疗。这样不仅加重了患者的痛苦及经济负担，也降低了患牙的生存质量。

此次对适应症的研究过程中有16例患牙冠修复后两周出现了咬合痛，经仔细询问病史，其中一位患者曾偶有患牙自发疼痛史，就此判断患者就诊时可能已经由于长期刺激而引起了慢性牙髓炎。从单因素方面可得出：

研究中裂纹陈旧度新的患牙有80.0%症状缓解且未出现牙髓炎或根尖炎的症状，较缓解率为26.7%的裂纹陈旧度旧的患牙来说缓解率高，且两者的差异具有显著性($P<0.05$)，可见裂纹陈旧度新是活髓隐裂牙冠修复的相对适应症。裂纹陈旧度新的患牙由于受外界物理或化学刺激时间不长，未激惹牙髓，冠修复后缓解率高。

研究中病情轻重程度分为三个等级，其缓解率分别是轻(100.0%)、中(45.5%)、重(33.3%)。经过统计分析可知三者的缓解率差异具有显著性

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($P<0.05$)。病情中、重的患牙的牙髓由于有不同程度的受到激惹，冠修复后较病情轻的患牙易出现咬合痛，从面对于病情中、重的患牙最好的治疗方法是先进行彻底地牙髓治疗后再冠修复。

从研究结果中可以看出疼痛时间在≤10s 的范围里缓解率是最高的，为 85.7%。这类患牙的牙髓基本没收到外界刺激的激惹，或者为可复性牙髓炎，可以进行直接冠修复。10s-20s 的患牙可结合裂纹陈旧度等方面具体分析再决定可否进行直接冠修复。面对于 >20s 的患牙不建议直接冠修复。

根据非条件多因素 Logistic 回归分析可看出裂纹陈旧度的新旧以及疼痛时间的长短对于冠修复后症状缓解与否关系密切，裂纹陈旧度越新、疼痛时间越短的隐裂牙，经过活髓直接进行冠修复后症状缓解有很大的提高。

4. 结论

综上所述，针对老年患者的隐裂牙，及早进行的冠修复能缩短就诊时间，增加患者满意度。另外，就适应症而言，裂纹陈旧度、病情轻重、疼痛时间都是未经治疗的活髓隐裂牙直接冠修复的影响因素，裂纹陈旧度新、病情轻、疼痛时间≤10s 的患牙直接进行冠修复的病情缓解率较裂纹陈旧度旧、病情中重程度、疼痛时间 >10s 的患牙高，是本次研究得出的老年人隐裂牙冠修复的适应症。

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Novel therapies for malignant pleural effusion: Anti-angiogenic therapy and immunotherapy (Review) [J] International Journal of Oncology,58(3) :359-70

Novel therapies for malignant pleural effusion: Anti-angiogenic therapy and immunotherapy (Review)

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Abstract. Patients with a variety of malignancies can develop malignant pleural effusion (MPE). MPE can cause significant symptoms and result in a marked decrease in quality of life and a poor prognosis. MPE is primarily considered as an immune and vascular manifestation of pleural metastases. In the present review, the existing evidence supporting the applicability of anti-angiogenic therapy and immunotherapy for the treatment of MPE was summarized. Patients with MPE have benefited from anti-angiogenic agents, including bevacizumab and endostar; however, no relevant prospective phase III trial has, thus far, specifically analyzed the benefit of anti-angiogenic therapy in MPE. Immunotherapy for MPE may be sufficient to turn a dire clinical situation into a therapeutic advantage. Similar to anti-angiogenic therapy, more clinical data on the efficiency and safety of immunotherapy for controlling MPE are urgently required. The combined use of anti-angiogenic therapy and immunotherapy may be a promising strategy for MPE, which requires to be further understood.

Contents

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Key words: malignant pleural effusion, anti-angiogenic therapy, immunotherapy, vascular endothelial growth factor, review

1. Introduction

Tumor cells that have metastasized to the pleural space may result in malignant pleural effusion (MPE), which can develop in patients with various types of tumor, including breast, lung and hematological tumors (1,2). Dyspnea, chest pain and coughing are common symptoms of MPE (1). A significant decrease in quality of life (QoL) and a poor prognosis can be observed in patients with MPE (1).

Currently, the popular approaches for MPE management include pleuroscopy with subsequent chemical pleurodesis and thoracostomy (2). However, these treatment methods only provide symptomatic relief, with poor and unsatisfactory results (2). Furthermore, adverse effects such as chest pain, fever and dyspnea are often observed (3).

At present, the pathogenesis of MPE is not fully understood, but it is associated with impaired pleural fluid drainage (4). When metastatic cancer infiltrates the thoracic lymph nodes and pleura, the normal cycle of fluid secretion and absorption is interrupted, and the fluid is finally collected (4,5). MPE is the build-up of fluid in the pleural space, which contains immune cells, cancer cells and proteins (5). Cytokines and chemokines, including interleukin (IL)-10 (6), IL-6 (5), transforming growth factor (TGF)β (7) and vascular endothelial growth factor (VEGF) (8), are abundant in MPE. These factors serve an important role in MPE formation and can be used as therapeutic targets that enable MPE treatment. Among them, VEGF, which can prompt the formation of new blood vessels, is a key mediator of MPE pathogenesis (9). Several therapeutic strategies for MPE have focused on this protein (4,8,9). Furthermore, the pleural space in MPE is regarded as a tumor-tolerogenic milieu, which has a complex connection with immunosuppressive factors (10). However, this tumor-tolerogenic milieu can be reversed by immunotherapy, which has the potential to stimulate tumor-specific immune responses in the pleural space (10). Therefore, immunotherapy has been an area of special interest for MPE treatment (10).

MPE is primarily considered as an immune and vascular manifestation of pleural-metastasized cancer (11,12). Therefore, in the present review, the existing evidence supporting the applicability of anti-angiogenic treatment and immunotherapy for the treatment of MPE was summarized,