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非编码 RNA 及其在组织工程中的潜在应用

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摘要

组织工程是医学科学中一个相对较新但发展迅速的领域。非编码 RNA(ncRNA) 是不编码蛋白质的功能性 RNA 分子，它们可以调节细胞的行为、改变组织的生物学环境。虽然以对 ncRNA 作为治疗靶点尚未进入临床实践，但 ncRNA 在组织工程中的应用已经吸引了越来越多的关注，而且对 ncRNA 的调节作用和释放方法的深入探讨可以促进其在组织工程中的应用。本文简要介绍了 ncRNA 在神经、皮肤、肝脏、血管和肌肉的调控作用和可能的释放方法及其潜在的治疗应用价值。

1. 引言

组织工程是生物医学日益发展的研究领域，在再生医学中具有广阔的应用前景。它结合工程学和生命科学的基本原理，开发生物替代物修复受损的组织和器官，帮助其恢复功能。组织工程的本质是利用活细胞、生物相容性材料、生化因素(如生长因子)和物理因素(如循环机械加载)，去构建一个仿生的组织样结构 [1]。组织工程的活细胞一般来自供体组织，但供体细胞常常有限，因此干细胞或祖细胞可以被用作替代细胞[1]。组织工程的种子细胞往往具有重要作用，细胞微环境要让种子细胞能够发挥生物学作用，因此对细胞的调控往往是必要的。

ncRNA是一大群RNA，尽管它们不编码蛋白质，但它们在各种细胞过程中具有多重功能。根据它们的生物学功能，ncRNA可分为基础型和调控型，前者包括核糖体RNA(rRNA)、转运RNA(tRNA)、核仁小分子RNA(snoRNA)、小核RNA(snRNA)、向导RNA(gRNA)和端粒酶RNA，而调控ncRNA可分类为微小RNA(miRNA)、小干扰RNA(siRNA)、长链非编码RNA(lncRNA)、

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Piwi蛋白相互作用的RNA(piRNA)、启动子相关的RNA(PAR)和增强子RNA(eRNA)[2–4]。

ncRNA是一类可以在组织工程中发挥重要调控作用的分子靶点。ncRNA在组织工程中的应用，包括用ncRNA改变内源性细胞活性、调控组织工程中干/祖细胞的细胞学行为及影响内源的或种植的细胞的命运。与此同时，miRNA、siRNA和lncRNA是目前主要的具有潜在应用价值的ncRNA。miRNA是一类小RNA，它们可以通过下调或上调靶基因的表达来调控广泛的细胞功能，包括增殖、迁移、分化、凋亡等，因此它们已引起人们的广泛关注[5–7]。lncRNA是一类重要的真核转录因子，可以通过染色质重塑、选择性剪接及与蛋白质相互作用等来调节蛋白质的活性和定位，或作为结构成分调控基因的表达[8,9]。此外，lncRNA可以通过争夺miRNA与靶基因的结合影响miRNA对靶基因的调控。lncRNA几乎影响基因调控的每一步，尤其在等位基因表达的表观遗传调控中具有广泛的研究[10,11]。

2. ncRNA 在组织工程中的应用

ncRNA在组织工程中的应用备受关注，在下面的内容中，我们概述了各种ncRNA在神经组织工程、肝组织工程、皮肤组织工程、肌肉组织工程和血管组织工程中的潜在应用。

2.1. 神经组织工程

神经系统包括中枢神经系统(CNS)和周围神经系统(PNS)。在临床实践中，神经系统损伤是常见的，神经组织的再生能力有限，因此神经组织工程为神经疾病和神经损伤带来了福音。神经组织的再生能力差的原因之一是由于神经系统疾病和神经损伤后的不利于再生的微环境导致的，因此神经组织工程的一个重要问题是改善这种不利于再生的微环境，从而加速神经再生。

在神经组织工程，种子细胞被植入损伤处神经，它们可以产生生长因子或细胞外基质(ECM)，从而促进神经再生。神经细胞和神经胶质细胞是神经组织工程使用最多的细胞类型，此外，神经干细胞由于其具有自我更新和分化成成熟的神经细胞的能力，也被广泛应用于神经组织工程。因此ncRNA在组织工程的应用主要集中在神经干细胞、神经细胞、神经胶质细胞(表1)[12–200]。

2.1.1. 神经干细胞

(1)神经干/祖细胞。神经干细胞自我更新和分化的能力是神经干细胞应用于组织工程的关键。miR-25、miR-124/124a、miR-200和miR-106b-25可以调控神经干细胞向神经元的分化，miR-9、let-7d可以促进其向神经元和星形胶质细胞的分化[16,17]。miR-34a能显著增加

表1 ncRNA在组织工程中的潜在应用

Cell type and function	ncRNAs
Nerve	
Neural stem/progenitor cells	
Promote proliferation	miR-25 [12]; miR-137 [13]; miR-184 [14]; miR-195 [15]
Induce differentiation	miR-9, siRNA-TLX [16]; let-7d [17]; miR-137 [13]; miR-184 [14]; miR-195 [15]; miR-34a [18]; lncRNA-BDNF-AS, siRNA-BDNF-AS [19]
Mesenchymal stem cells	
Induce differentiation	miR-9 [20]; miR-124 [21]
Reduce differentiation	miR-128 [22]
Neuronal cells	
Inhibit cell death	miR-223 [23]; miR-181c [24]; miR-592 [25]; miR-424 [26]; miR-23a-3p [27]; miR-23a/b, miR-27a/b, siRNA-Apaf-1 [28]
Promote cell death	miR-134 [29]; miR-200c [30]; miR-30a/b [31–33]; miR-124 [34]; miR-711 [35]
Regulate degeneration and apoptosis	miR-20a [36]; miR-29b [37]; miR-146a, siRNA-miR146a [38]
Promote neurite outgrowth	miR-7 [39]; miR-21 [40]; miR-222, siRNA-PTEN [41]; miR-8 [42]; miR-431 [43]; miR-145 [44]; lncRNA-uc.217 [45]; miR-138, siRNA-SIRT1 [46]
Microglial cells	
Inhibit inflammation	let-7c [47]; miR-124, siRNA-C/EBP-α [48]
Promote pro-inflammation	miR-155 [49]
Inhibit activation	let-7c-5p [50]
Astrocytes	
Promote proliferation	miR-17-5p [51]
Inhibit inflammation	miR-146a [52]
Promote activation and differentiation	miR-181 [24]

Table 1 (*continued*)

Cell type and function	ncRNAs
Inhibit proliferation and migration	lncRNA-SCIR1 [53]
Schwann cells	
Inhibit proliferation and migration	miR-182 [54]; let-7 [55]; miR-1 [56]
Promote proliferation and migration	miR-221, miR-222 [57]
Inhibit migration	miR-9 [58]
Promote migration	miR-132 [59]
Regulate dedifferentiation and proliferation	miR-34a [60]
Regulate myelination	miR-140 [60]; miR-29a [61]
Regulate fibrinolysis	miR-340 [62]
Liver	
Stem/progenitor cells	
Reduce differentiation	let-7b [63]; let-7f [64]
Induce differentiation	miR-1246, miR-1290, miR-148a, miR-30a, miR-30a, miR-424 [65]
Induce/reduce differentiation	miR-122, siRNA-FoxA1 [66–68]
Reduce differentiation and engraftment	miR-199a-5p, siRNA-SMARCA4, siRNA-MST1 [69]
Hepatocytes	
Promote proliferation	miR-21 [70–72]; miR-211 [73]; lncRNA-URHC [74]
Inhibit proliferation	miR-26a [75]; miR-33 [76]; miR-127, siRNA-Bcl6 [77]; miR-378 [70]; lncRNA-H19 [78]
Regulate cholesterol metabolism	lncRNA-HC [79]
Promote migration	lncRNA-HOTAIR [80]
Inhibit apoptosis and inflammation	lncRNA-TUG1 [81]
Cholangiocytes	
Inhibit cell function	miR-506 [82]
Skin	
Epithelial stem cells	
Inhibit proliferation, induce differentiation	miR-203 [83–86]
Induce differentiation	miR-27b, miR-224 [87]; miR-574-3p, miR-31 [88]
Inhibit proliferation	miR-34, siRNA-P63 [89]; miR-720 [90]; miR-210, siRNA-E_2F_3 [91]
Improve proliferation, reduce differentiation	miR-125b, siRNA-$FGFR_2$ [92,93]
Inhibit proliferation, induce differentiation	miR-24, siRNA-PAK4 [94]
Keratinocytes	
Improve migration	miR-205 [95–97]
Inhibit migration, improve proliferation	miR-483-3p [98]
Inhibit migration	miR-198 [99]
Improve migration, inhibit migration	miR-21 [100,101]
Improve migration and proliferation	miR-31, siRNA-EMP-1, siRNA-TGF-β [102]
Regulate apoptosis	lncRNA-p21 [103]
Fibroblasts	
Inhibit proliferation	let-7, miR-125 [104]
Improve proliferation	miR-29 [104]; miR-21 [105]; miR-22 [106]; lncRNA-H19 [107]
Induce senescence	miR-152, miR-181a [108]; miR-141 [109]; miR-143 [110]; miR-519a [111]
Improve migration	miR-21 [112]
Induce epithelial-mesenchymal transition	miR-34 [113]; let-7 [114]
Reduce epithelial-mesenchymal transition	miR-200 [113]
Reduce transdifferentiation	miR-146a [115,116]; miR-7 [117]
Decrease extracellular matrix deposition	miR-29 [118,119]; miR-150 [120]; miR-19a [121]
Increase extracellular matrix deposition	miR-92a [122]
Increase mechano-transduction	miR-21 [123–125]
Control collagen stabilization	lncRNA-TSIX, siRNA-TSIX [126]
Melanocytes	
Inhibit apoptosis	miR-17 [127,128]
Muscle	
Myoblasts	
Induce differentiation	lncRNA-MD1 [129]; miR-1 [130]; lncRNA-MyoD [131]; lncRNA-Dum [132]; lncRNA-MUNC [133]; lncRNA-YY1 [134]; miR-29 [135]; miR-181 [136]; lncRNA-H19 [137]; miR-322, miR-503 [138]
Promote proliferation	miR-133 [130]
Promote proliferation and reduce differentiation	lncRNA-sirt1 AS [139]; lncRNA-Malat1 [31,140]; lncRNA-31 [141]
Reduce differentiation	miR-23a, siRNA-Myh [77]
Promote proliferation and migration	miR-486 [142]

Table 1 (*continued*)

Cell type and function	ncRNAs
Skeletal muscle satellite cells	
Induce differentiation	miR-206 [143]; miR-214, siRNA-Ezh2 [144]; miR-27b [145]
Inhibit proliferation and induce differentiation	miR-1, miR-206 [146]
Skeletal muscle stem cells	
Inhibit differentiation	miR-669a/q [147]
Induce cell-cycle arrest	miR-195, miR-497 [148]
Cardiac progenitor cells	
Control the balance between differentiation and proliferation	miR-1 [149]
Inhibit proliferation and induce differentiation	miR-133a [150]; miR-1, miR-499 [151]
Enhance cardiac remodeling and reduce survival	miR-208a [152,153]; miR-28b [154]
Inhibit apoptosis	miR-138 [155]
Cardiomyocytes	
Inhibit apoptosis	miR-21 [156]; miR-214 [157]; miR-24 [52]; lncRNA-MHRT [158]
Regulate differentiation and remodeling	miR-21, miR-129, miR-212 [159]
Promote hypertrophy	miR-22 [160]
Promote muscle growth	miR-486 [142]
Induce proliferation	miR-199a, miR-590 [161]; miR-17-92 [162]
Inhibit hypertrophy	lncRNA-H19 [163]
Promote apoptosis	lncRNA-NRF [164]
Cardiac fibroblasts	
Inhibit proliferation	miR-101 [165]
Promote proliferation	lncRNA-H19 [166]
Induce reprogramming to cardiomyocytes	miR-1, miR-133, miR-208, miR-499 [167]
Vascular	
Endothelial cells	
Inhibit proliferation	miR-34a [168]; miR-19a [169]; miR-200c, siRNA-ZEB1 [170]
Promote proliferation and/or migration	miR-126-5p [171]; miR-210 [172]; miR-424 [173]; lncRNA-H19 [81]
Induce senescence and reduce angiogenesis	miR-34a [168]; miR-217 [174]; miR-17-92 [175]; miR-503 [176]; siRNA-ROBO4 [177]
Inhibit migration and angiogenesis	miR-101, siRNA-EZH2 [178]
Promote angiogenesis	miR-17-5p, miR-18a, miR-31, miR-155 [179]; miR-210 [172]; miR-424 [173]; lncRNA-H19 [81]; miR-126 [180]
Promote apoptosis and senescence	miR-200c, siRNA-ZEB1 [170]; PINC [181]
Inhibit proliferation, migration, and apoptosis	miR-503 [176]; miR-155, siRNA-RhoA, siRNA-MYLK [182]
Regulate inflammation	miR-92a, siRNA-KLF4 [183]; miR-663 [184]; miR-10a [185]; miR-712, miR-502, siRNA-TIMP3, siRNA-RECK [186]
Smooth muscle cells	
Induce differentiation and inhibit proliferation	miR-143, miR-145 [187]; lncRNA-MYOSLID [166]
Inhibit proliferation, migration, and apoptosis	miR-503 [176]
Promote migration	miR-712, miR-502, siRNA-TIMP3, siRNA-RECK [186]; miR-24, siRNA-Trb3 [188]
Promote proliferation	miR-24, siRNA-Trb3 [188]; miR-221, miR-222, siRNA-Kip1, siRNA-Kip2 [189]; miR-34a [190]
Promote proliferation and inhibit apoptosis	miR-21 [191]
Inhibit proliferation and promote apoptosis	lncRNA-HIF1A-AS1 [33]; lncRNA-p21 [192]
Reduce elastin levels	miR-29a [193]
Regulate phenotype	siRNA-Jagged1 [194]
Fibroblasts	
Reduce elastin levels	miR-29a [193]
Stem cells	
Induce differentiation	miR-145 [195]; miR-200c, miR-150, siRNA-ZEB1 [196]; miR-1 [197]; miR-10a [198]
Reduce differentiation	siRNA-NOX4, siRNA-TGF-β [199]
Endothelial progenitor cells	
Inhibit survival and migration	miR-15a, miR-16 [200]

$NeuN^+$细胞的数量，并增强神经元的成熟和神经干细胞分化的神经元的轴突延长。此外，它对于确保分化成熟的细胞的细胞增殖也具有调控功能。miR-25、miR-137、miR-184和miR-195可以增强神经干细胞的增殖，而这有利于获得足够的细胞去恢复组织的结构和功能[12–15]。miR-137、miR-184和miR-195也可以通过促进神经干细胞的分化而增加神经元和星形胶质细胞的数量[13–15]。

(2)间充质干细胞(MSC)。MSC是多能干细胞，定位于骨髓间质室。骨髓间充质干细胞容易获得，而且可以通过体外培养进行大规模扩增，因此被广泛应用于细胞疗法来治疗各种疾病。miR-9和miR-124能促进MSC分

化为成熟的功能性神经元，而miR-128负性调控MSC分化为神经元样细胞[16,21,22]。

2.1.2. 神经细胞

神经损伤后，神经元细胞死亡是影响恢复的因素之一，因此保护神经元免于细胞死亡是非常重要的。miR-223、miR-181c、miR-592、miR-424、miR-23a-3p、miR-23a/b和miR-27a/b能保护神经元免受缺血性脑损伤后导致的细胞死亡 [23–28]，而miR-134、miR-200c、miR-30a/b、miR-124和miR-711则促进神经元细胞的死亡[29–32,34,35,201]。脊髓损伤中，miR-20a通过靶向*Ngn1*引起运动神经元的变性[36]，miR-29b通过减少*Bad*、*Bim*、*Puma*和*Noxa*的表达来调节神经元的凋亡[37]。周围神经损伤中，miR-21和miR-222的过表达能减少细胞凋亡，增强背根神经节(dorsal root ganglion, DRG)的神经元活性[40,41]。miR-146a介导了DRG神经元在高糖状态下的凋亡[38]。

损伤神经元轴突的再生长是周围神经再生的关键，miR-21和 miR-222通过靶向Sprouty2和PTEN分别促进神经轴突生长[40,41]。miR-8、miR-431、miR-145和miR-138在神经轴突生长中具有调节作用[42-44,46]。此外，lncRNA-uc.217在DRG神经元周围神经损伤后调控轴突生长[45]。

2.1.3. 神经胶质细胞

(1) 小胶质细胞。小胶质细胞在中枢神经系统中具有重要作用，let-7c在缺血性脑损伤中抑制小胶质细胞的活化[47]。miR-124能够在神经损伤中，通过小胶质细胞降低炎症反应，从而防止继发性损伤[48]。miR-155 能调控M1、M2表型的比例，进而调节小胶质细胞介导的神经毒性反应和促进轴突再生[49]。

(2) 星形胶质细胞。星形胶质细胞是一种特异的神经胶质细胞，在中枢神经系统中起支持、代谢和平衡功能。有髓鞘轴突的损伤会导致轴突变性和髓鞘碎片堆积，其中包含各种各样的轴突生长抑制因子。通过小胶质细胞和星形胶质细胞清除这些抑制因子可以促进轴突再生，另外，星形胶质细胞也通过介导不同的信号通路影响免疫应答。miR-17-5p通过靶向细胞周期抑制剂p21和RB1促进星形胶质细胞增殖[51]。miR-181影响星形胶质细胞炎症因子的分泌，调节星形胶质细胞的活化和分化[24]。miR-146a通过调节星形胶质细胞细胞因子的释放，具有抗炎作用，表明miR-146a可以预防继发性损伤，从而促进组织修复[52]。

(3) 施万细胞。施万细胞是周围神经系统的主要神经胶质细胞，在周围神经再生中具有重要作用。施万细胞能产生各种生长因子，如神经生长因子(NGF)、脑源性神经营养因子(BDNF)等[202]。此外，施万细胞具有吞噬能力，能够清除髓鞘碎片，这些特性使施万细胞成为神经组织工程中应用最广泛的支持细胞。另外，施万细胞能在轴突损伤后去分化成未成熟的状态，去分化后，施万细胞能够通过增殖来增加细胞数目，从而发挥促进神经再生的作用。此外，施万细胞迁移到受伤部位也是其发挥功能所必需的。因此，在再生的准备期提高施万细胞增殖和迁移的能力，可以促进神经再生。miR-182在坐骨神经损伤早期，通过靶基因*FGF9*和*NTM*抑制施万细胞的增殖和迁移[54], 而miR-221和miR-222 通过靶向*LASS2*促进施万细胞的增殖和迁移[57]。miR-9通过靶向*CTHRC1*调控施万细胞的迁移，进而又可以调节Rac1 GTP酶的活性[58]。miR-132可以促进施万细胞的迁移，从而影响周围神经再生[59]。miR-34a在周围神经损伤后，通过靶向*Notch1*与Cyclin D1可以调节施万细胞的分化和增殖[60]。

NGF是神经营养因子中第一个被发现的成员，可以促进周围神经系统神经元的存活和轴突的生长，也能够影响中枢神经系统神经元功能的完整性。许多研究表明，NGF对神经再生具有明显的促进效果，但由于其一些副作用和控制释放的复杂性，NGF尚没有被临床应用。let-7可以通过靶向NGF，抑制NGF蛋白的翻译，从而显著调节施万细胞的增殖和迁移，结果表明let-7的抑制剂可以增加原代培养的施万细胞NGF的分泌，进而影响共同培养的DRG神经元的轴突生长。此外，let-7也可以抑制施万细胞的凋亡，这可能是神经损伤的一种早期应激反应[55]。此外，NGF能调节miR-221/222的表达，表明let-7可以通过靶向调控NGF，NGF进一步调控miR-221/222的表达，进而调控施万细胞的增殖、迁移等表型，这可能也是let-7调控施万细胞表型的一条调节旁路。此外，miR-1可以靶向调控神经营养因子BDNF，进而调节施万细胞的增殖和迁移[56]。

施万细胞在周围神经系统中能够形成髓鞘，这对于周围神经系统来说是重要的生物学事件，miR-140通过靶向转录因子EGR2，可以调节施万细胞的髓鞘化[60]，而miR-29a通过靶向PMP22调节施万细胞的髓鞘化[61]。

周围神经损伤后，损伤部位会发生髓鞘崩解，髓鞘碎片和过度的炎症反应会阻碍再生轴突向靶器官的延

长。miR-340在坐骨神经再生过程中，通过靶向具有降解基质分子和细胞粘连能力的丝氨酸蛋白酶tPA，从而调节纤溶活性，进而影响碎片清除和轴突再生[62]。

2.2. 肝组织工程

肝脏是人体最大的器官之一，急性或慢性肝病严重威胁着生命健康。近几年，在急救护理和肝脏移植方面的进步使得肝病患者的存活率有了实质性的提高，然而可用的移植肝脏数量不能满足持续增长的市场需求[203,204]。由于取自脑死亡捐献者的肝脏或者是取自活人捐献者的肝脏数量有限，因此生物工程肝脏可能是肝病治疗最有前景的肝脏来源[205]。

肝脏组织工程的目的是临时或最终支撑或取代病变的肝脏。研究表明，在一些生理、病理过程中，肝脏的一些ncRNA具有差异表达[206–210]。ncRNA能够促进肝细胞的增殖和诱导干细胞向肝细胞的分化。miR-21和miR-378均能够在切除2/3肝脏后，通过抑制Btg2和鸟氨酸脱羧酶的活性促进DNA的合成[70]。miR-21能够通过靶向周期蛋白D1来促进细胞周期由G1期向S期转化，从而调控肝脏再生[71]。miR-33的抑制能够显著促进肝脏增生[76]。miR-26a和miR-127也能够调控肝细胞的增殖[75,77,211]。

ncRNA已被用于调控干细胞或其他祖细胞向肝细胞的分化，在肝脏组织工程中具有潜在应用价值。miR-122的过表达能够提高肝细胞分化[66,212]，而且miR-122的表达量在小鼠胚胎干细胞向肝细胞转化的过程中逐渐增加[68]。let-7能够调控脂肪组织来源的间充质干细胞特异因子的分泌[63]。并且，针对肝病治疗使用一系列miRNA比单个miRNA可能效果更好，例如，7个miRNA(miR-1246、miR-1290、miR-148a、miR-30a、miR-424、miR-542-5p和miR-122)的过表达能够诱导人间充质干细胞向有功能的成熟的肝细胞转化，而单个miRNA不能启动这个肝分化的过程[65]。

与肝细胞系统相比，胆道得到的关注较少，组织工程方法模拟胆的功能需要一个更为复杂的支架微体系结构，从而有助于促进细胞之间的相互作用，这是胆物质代谢和运输的基础[213,214]。miRNA在调控胆管上皮细胞增殖方面的报道较少[215], 一些研究揭示了在胆管癌中的特异性miRNA的作用。比如，miR-31在胆管癌中的过表达能改变RAS/MAPK信号通路[216]，miR-138通过直接靶向RhoC，从而能够调控胆管癌的增殖、细胞周期和迁移[217]。miR-506能够调控AE2的表达，抑制miR-506的表达能够在原发性胆汁肝硬化中促进AE2功能的发挥[82]。此外，miR-125b/let-7a在胆管细胞中的表达调控也许能够成为肝病治疗的有效手段 [218]。

2.3. 皮肤组织工程

在过去的数年里，皮肤损伤临床干预的需求不断增加。组织工程是获得皮肤替代物的一个可行方法，工程皮肤发展的关键点是控制细胞的行为，而ncRNA的出现和应用能够克服组织工程皮肤设计的一些障碍。通过ncRNA调控细胞的表型和功能，为生物工程皮肤替代物提供了一个可行且精确的方法，如miRNA可以在皮肤组织工程中被过表达或抑制[219]。而ncRNA与皮肤组织工程的结合，有助于为临床提供一个安全有效的皮肤组织工程[220]。

上皮干细胞是皮肤组织工程常用的细胞类型，上皮干细胞具有皮肤特异性，这使其成为皮肤组织工程的理想选择细胞。miRNA可以控制上皮干细胞的增殖以及向角质细胞的分化[221]。miR-203对皮肤和其他复层上皮组织干细胞的干性维持具有重要的调节作用[222–224]。此外，miR-203、miR-720和miR-574-3p通过直接靶向p63，可以调节上皮分层的形成，维持基底细胞的增殖[89, 90]。

从上皮干细胞分化而来的角质细胞为皮肤提供了一个屏障。miR-205能调节角质细胞的迁移[95,96]，miR-198和miR-21通过调节角质细胞的迁移，被发现与慢性伤口愈合相关[99]。miR-31能够促进角质细胞的迁移和增殖[102], miR-483-3p在角质细胞重新上皮化的最后一步抑制它的生长 [225]。

成纤维细胞是皮肤组织的重要细胞。在血清饥饿导致细胞处于静止状态的成纤维细胞中，let-7具有重要的调控功能[104]，miR-22能够通过调控细胞周期的几个关键基因促进成纤维细胞的增殖[106]。Faraonio等[226]报道了在双倍体成纤维细胞中，24个miRNA如何调控细胞的衰老变化[226]，在这些miRNA中，miR-210、miR-376a、miR-486-5p、miR-494和miR-542-5p能够促进DNA损伤并且加速衰老，而miR-21能够调控成纤维细胞的迁移，这对皮肤组织工程的构建是非常重要的[100,101]。

有报道称黑色素细胞能够融入表皮和真皮的皮肤替代物中[227]。研究表明，一些miRNA能够影响黑色素瘤的发生发展[228–230]。miR-17能够在Dicer酶切割后通过靶向Bim抑制黑色素瘤细胞的凋亡[127]。miR-137、miR-182和miR-340能够调控黑色素瘤细胞中的小眼畸形相关的转录因子[231–233]。

2.4. 肌肉组织工程

在人体中，肌肉是力量的象征，它能够带动身体工作，比如心脏的肌肉负责输送动、静脉血液，骨骼肌协调人体的姿势和动作。肌肉损伤和退化在全球成人疾病和死亡中占有一定的比重[234]。

横纹肌障碍的临床护理不总是有效的，因此，肌肉组织工程和基于干细胞的治疗得到了广泛的探讨。组织工程利用具有生物活性的分子或细胞与具有良好生物相容性的生物支架材料结合，形成分子或细胞复合物，然后将该复合物植入受损的横纹肌处，从而达到修复创伤和重建功能的目的[235,236]。ncRNA能够调控种子细胞的表型以及调控外源和内源性干细胞的适应[129]，因此ncRNA(主要是miRNA)被广泛用于骨骼肌、心肌的发育调控以及调节肌肉祖细胞的再生潜能(表1)。

研究表明，肌肉相关miRNA，如 miR-1、miR-133和miR-206，在调节肌肉的形成和再生中能够发挥重要作用[237]。miR-1通过靶向HDAC4促进体外培养的成肌细胞分化，miR-133通过抑制Srf的表达刺激成肌细胞的增殖[130]。miR-206能够提高杜氏肌营养不良患者的骨骼肌再生[143]以及减慢肌萎缩侧索硬化症的形成[238]。此外，lncRNA-MD1作为竞争性抑制剂，抑制miR-133和miR-135与靶基因MAML1和MEF2C的结合，从而进一步影响成肌细胞的分化[129]。

目前，肌肉组织工程的种子细胞大多是干细胞，干细胞为退化的肌肉组织提供祖细胞，分化成合适的成肌细胞，帮助恢复肌肉功能。Sato等[148]研究表明在营养缺陷小鼠中，miR-195和 miR-497在骨骼肌干细胞(MuSCs)能靶向细胞周期相关基因，从而提高肌肉再生能力。

miRNA在心肌组织中也扮演着重要的角色，在新生小鼠、大鼠心脏以及成年小鼠心肌梗死后，miRNA能够刺激心肌细胞增殖[161]。在心脏祖细胞(CPCs)的扩张和终末分化中，miRNA能够进行时空特异性调控。例如，miR-1靶向*Hand2*抑制心脏祖细胞的扩张，而miR-1缺陷型小鼠的胚胎因为严重的心脏畸形，死于胚胎10.5天[149]。有报道称在心脏应激反应中，miRNA能够调控胎儿对应激的异常反应，miR-21、miR-129、miR-212能够引起新生大鼠心肌细胞的肥大和胎儿心脏基因的重编程[159]。在骨骼肌中，miR-22和miR-133a通过调控心肌细胞中关键的表观遗传调控因子影响心脏的肥厚性重塑[239]。

总之，肌肉组织工程可以用适合ncRNA调控的骨骼肌干细胞、分化后的心肌细胞或心肌干细胞等种子细胞，与仿生支架结合，形成组织移植物，从而增加骨骼肌肌肉和心脏肌肉的再生能力[240]。

2.5. 血管组织工程

血管系统遍及全身，负责介导气体交换、营养物质输送和代谢产物排泄，还能够递送免疫系统中的细胞和介质[241,242]。血管组织工程是指利用干细胞或其他细胞和分子为种子细胞结合生物支架，来制备、重建和再生血管，从而恢复、维持或改善血管的组织功能[241]。在血管组织工程中，ncRNA可以增强以细胞为基础的组织工程血管中细胞的数量或表型，可以促进干细胞分化成血管细胞，然后种植于支架中，ncRNA还可以改善组织工程血管中的细胞功能，也可以抑制抗血管生成的分子表达[243,244]。

血管主要是由内皮细胞(ECs)和平滑肌细胞(SMCs)组成，因此内皮细胞和平滑肌细胞是血管组织工程的主要种子细胞，ncRNA在血管组织工程中的应用主要集中在对这两种细胞的调控。内皮细胞覆盖在血管系统的整个内层，从而确保血管内环境的稳定，并在发育和出生后的血管形成中起重要作用[241]。miR-34a和miR-217促进内皮细胞的衰老，因此这些miRNA的抑制剂能够减缓内皮细胞衰老，促进血管生成[168,174]。 miR-424、miR-17-5p、miR-18a、miR-31和miR-155能保护血管的完整性和促进血管生成[173,179]。miR-210和miR-126-5p能促进内皮细胞的增殖[171,172]。而且，ncRNA可以单独或与生长因子(GFs)结合来改善血管组织工程中的内皮覆盖和功能发挥。

平滑肌细胞处于血管壁的中间层，能够调控血管收缩和松弛，调节血压和血流分布，参与损伤后血管的重塑[245–247]。在血管损伤后，平滑肌细胞通过去分化来促进血管修复，并且修复完成后，平滑肌细胞会恢复到收缩的表型状态 [246]。miR-221、miR-222和miR-24促进平滑肌细胞的增殖，miR-143和miR-145则刺激平滑肌细胞的分化。

miRNA还能够调节干细胞向血管细胞的分化及调节血管祖细胞的功能。例如，研究报道，miR-1、miR-10和miR-145可以调节干细胞向各种血管细胞的分化 [195]。

总之，ncRNA能够调控组织工程里的种子细胞，并通过调节种子细胞的表型和功能，从而具有潜在的治疗

应用前景。更多关于ncRNA在组织工程中潜在的调控作用参见表1。

3. 应用方法

ncRNA向组织工程种子细胞的递送是极其重要的，需要低毒性、高转染效率和适合的释放途径[248]。本文根据已有的一些文献报道，对ncRNA在组织工程中的递送方法进行简要综述(图1)。

3.1. 病毒转导

病毒载体介导的ncRNA递送的主要优势在于其转染效率高。常见的病毒载体包括逆转录病毒、慢病毒、腺病毒以及腺相关病毒，在组织工程中，逆转录病毒和慢病毒的使用相对广泛。

逆转录病毒载体可以有效地用于各种分裂细胞的转染，如神经干/祖细胞，但对于静止细胞的转染效果不稳定[249]。与逆转录病毒载体不同，慢病毒载体能够转染不分裂细胞[250–253]，在组织工程的细胞转染中有着广泛的应用。不过逆转录病毒载体和慢病毒载体存储不稳定、病毒滴度不高。腺病毒载体可以转染分裂细胞和不分裂细胞，因此也有大量应用，并且同其他病毒载体比较，它的病毒滴度高，但由于其免疫原性和毒性而在使用上受到限制[254, 255]。腺相关病毒载体属于小病毒科，能够在细胞核中稳定存在，能够数月或数年维持基因的高表达水平[254]，因此，在现有ncRNA病毒载体递送中，腺相关病毒载体可能是最安全和有效的。

病毒转染的效率高，病毒基因组能够整合到宿主基因组从而维持转染细胞中的ncRNA持续高表达，但是基因组整合会导致不可控制的插入突变，因此病毒介导的ncRNA递送在治疗应用中也受到一定限制[256–258]。

3.2. 非病毒转导

通过非病毒载体递送比利用病毒转导有自己的优势：免疫原性低、发生突变的概率低以及能够递送大量的治疗药物[256]。因此研究者更喜欢使用非病毒载体转导技术。

脂质体转染因其生物相容性、可重复性以及易于大量生产的优点而被广泛用于ncRNA递送[259]。迄今为止，脂质体转染试剂的种类很多，比如Lipofectamine®，siPORT™，HiPerFect，Oligofectamine™，MaxSuppressor™，DharmaFECT®，SilentFect™和NeuroPorter™，虽然这些脂质体在结构上有差异，但是它们具有一些共同的特征[256]，如它们表面带正电荷，能够与核酸的磷酸根通过静电作用将RNA分子包裹入内，形成RNA-脂复合体，然后被表面带负电荷的细胞膜吸附，通过膜的融合或细胞的内吞作用进入细胞质中，再进一步进入细

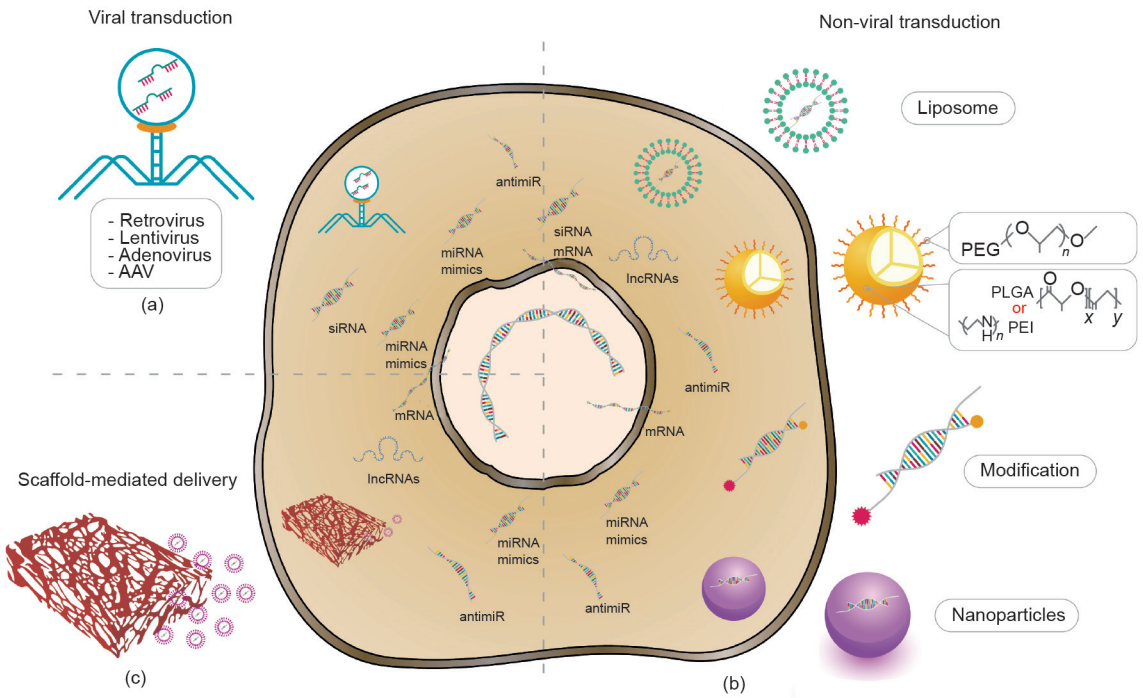

图1. ncRNA递送入细胞示意图。(a)ncRNA可以被不同的病毒载体通过病毒转导进入细胞；(b)非病毒转导包括：脂质体、高聚物、化学修饰、纳米粒子，在这些载体的协助下，ncRNA主要通过内吞作用进入细胞；(c)支架介导的递送，ncRNA在基质被降解后，通过支架上的非病毒载体释放进入细胞。

胞核内转录表达[260]。不过，在体实验时，脂质体的递送系统对细胞有毒性以及会有非特性吸附，而且这种毒性随基因的改变会反过来影响预期的结果[261]。

多聚体也常用作ncRNA递送载体用于基因治疗，如poly(lactide-*co*-glycolide)(PLGA)和polyethylenimine (PEI)[262]。PLGA因其安全性、良好的生物相容性和可降解性被广泛地应用于药物递送。此外，还可以通过进一步优化PLGA纳米颗粒的表面修饰来控制它们的药效学[248]。基于PLGA的纳米颗粒是ncRNA有效递送的潜在方法。PEI是另一个被广泛用于ncRNA递送的载体，它是水溶性和带正电荷的。带正电荷的PEI能够通过静电作用结合带负电荷的ncRNA。纳米复合物内吞到细胞以后，复合物的强缓冲效应导致内体肿胀和不稳定，从而将包裹ncRNA的纳米颗粒释放到胞质中[262–265]。

一些化学修饰能够增强ncRNA的稳定性和亲和力，这使得其在组织和细胞中难以被核酸酶降解，从而提高了稳定性和递送效率，如化学修饰2′-OH为2′-*O*-methyl, 2′-*O*-methoxyethyl 或 2′-*O*-fluorol可以增加ncRNA的稳定性和亲和力[266]。此外，胆固醇修饰也能增加ncRNA的细胞摄取，很多文献已报道胆固醇修饰的ncRNA能够通过静脉注射或局部注射直接进入细胞。

3.3. 支架介导的递送

支架介导的递送也是组织工程和再生医学中常用的药物递送方法。对于细胞植入、增殖、分化以及在受损部位的迁移，仿生支架为组织修复和再生提供了合适的微环境[240]。支架的形貌特征不仅可以确保基因的持续递送，还能够增加额外的物理信号以调节细胞行为和基因的转染效率[256]。此外，支架介导的递送可以改善局部治疗，因此可以直接增强靶组织中的剂量。支架结构也可以影响和调控细胞的表型。例如，纤维支架，特别是规则排列的纤维，可以调节施万细胞的成熟[256,267]。许多研究已经证明利用组织工程支架递送ncRNA是调节基因表达的一种新的方法[220]。

4. 结语和展望

4.1. 基于 ncRNA 治疗的潜在风险

ncRNA的治疗应用，不同于传统的药物设计，近几年在组织工程和再生医学领域开始崭露头角，但其在组织工程和再生医学上的应用也存在着巨大的挑战和风险。比如，miRNA可以同时靶向多个基因是一个优势，但这也导致了miRNA精确靶向变得模糊不清。在临床应用中，miRNA的多种调控功能和调控机制需要被很好地阐述和验证，而miRNA在组织工程细胞活动中具有广泛的调控，它的多种效应需要被谨慎地考虑[268]，如miR-221和miR-222不仅可以通过调控*LASS2*影响施万细胞的增殖和迁移，还可以通过靶向$p27^{kip1}$调控恶性胶质瘤细胞的疯长 [57,269]。

而lncRNA应用的挑战更大，lncRNA可以调控一系列细胞的活动，包括增殖、分化、迁移、凋亡等，但关于这些调控功能的作用机制的阐述仍不够清楚[270]。并且lncRNA是具有组织特异性的调控蛋白表达的RNA，在特异性的组织或亚细胞器中，当它通过靶向调控非编码RNA进而调控蛋白质表达时，这种调控关系更加复杂，会产生额外的、待进一步阐述的问题。

对于分子机制被清楚解读的ncRNA，其向细胞的准确导入也是极大的挑战，而准确导入的相关机制还没有被很好地阐明，导致常常不能到达预期的效果，这也是一个需要解决的问题。

4.2. 未来展望

组织工程可以产生生物替代品，通过支架材料提供支架，种子细胞附着在支架材料上发挥功能，以取代受损的组织或器官。ncRNA可以调控种子细胞的一些表型，有潜在的向组织工程应用的可能性。目前，能看到siRNA在组织工程中的应用报道，但其他ncRNA的应用，比如miRNA，才刚刚开始。

ncRNA在组织工程中的应用需要对ncRNA对不同细胞的作用效果有好的理解。此外，保护ncRNA免遭降解并使它们到达目标组织或器官的输送系统，也是一个需要克服的主要问题。为了实现这些目标，需要来自包括医学、生物学和工程学等不同研究领域的专家密切合作。

总之，ncRNA在组织工程应用方面的研究尚处于起步阶段，但以ncRNA为基础的治疗方法正在迅速扩展，随着能够把ncRNA安全转入种子细胞中，ncRNA在组织工程中的应用可以为组织工程策略提供新的视野。鉴于对ncRNA生物学作用的进一步理解和ncRNA转导方法的不断改进，我们相信，在不久的将来，ncRNA在组织工程和再生医学中的应用将陆续出现。

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Compliance with ethics guidelines

Shiying Li, Tianmei Qian, Xinghui Wang, Jie Liu, and Xiaosong Gu declare that they have no conflict of interest or financial conflicts to disclose.

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