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microRNA deregulation in keloids: an opportunity for clinical intervention?

Xin Yu*, Zheng Li†, Matthew T. V. Chan‡ and William K. K. Wu‡,§

**Department of Dermatology, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing 100042, China, †Department of Orthopaedic Surgery, Peking Union Medical College Hospital, Chinese Academy of Medical Science and Peking Union Medical College, Beijing 100730, China, ‡Department of Anaesthesia and Intensive Care, The Chinese University of Hong Kong, Hong Kong 999077, China and §State Key Laboratory of Digestive Disease, LKS Institute of Health Sciences, The Chinese University of Hong Kong, Hong Kong 999077, China*

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Abstract

Keloids are defined as benign dermal scars invading adjacent healthy tissue, characterized by aberrant fibroblast dynamics and overproduction of extracellular matrix. However, the aetiology and molecular mechanism of keloid production remain poorly understood. Recent discoveries have shed new light on the involvement of a class of non-coding RNAs known as microRNAs (miRNA), in keloid formation. A number of miRNAs have differential expression in keloid tissues and keloid-derived fibroblasts. These miRNAs have been characterized as novel regulators of cellular processes pertinent to wound healing, including extracellular matrix deposition and fibroblast proliferation. Delineating the functional significance of miRNA deregulation may help us better understand pathogenesis of keloids, and promote development of miRNA-directed therapeutics against this condition.

Introduction

Keloids are clinically defined as being benign dermal scars invading adjacent healthy tissue, due to abnormal wound healing (1–3). Other clinical manifestations of keloids include itching, aching and cosmetic disfigurement. Overproduction of extracellular matrix (ECM), such as collagen, fibronectin and elastin, occurs in keloid fibrosis (4,5). Disruption of cellular dynamics characterized by increased fibroblast proliferation and reduced fibroblast apoptosis has also been implicated in their formation (6,7). However, aetiology and molecular mechanisms of keloid deposition remain poorly understood. In addition, their management is a major clinical challenge for dermatologists and plastic surgeons (8–10). Although many conservative treatments have been adopted, their therapeutic efficacies are often inconsistent (11–13). Thus, alternative treatment methods are needed, and these require better understanding of pathophysiological processes of keloid formation (14,15).

microRNAs (miRNAs) are a group of short non-coding RNAs involved in post-transcriptional regulation of gene expression (16–20). They play important roles in many biological and pathological processes, including ECM production and aberrant cell proliferation (18,21–27). Importantly, accumulating evidence shows that miRNAs are deregulated in many inflammatory and malignant skin diseases (28–30). Recent studies also have reported abnormal miRNA expression in keloids (31–33), and these studies indicate that miRNAs may play significant roles in their development (31–33). Investigating keloid miRNA deregulation and functions may thus help in understanding their molecular mechanisms. In this review, we summarize current evidence concerning deregulation and functional roles of miRNAs in keloid formation and also discuss the implications of miRNAs as potential therapeutic tools for their clinical management.

Altered miRNA expression profiles

Genome-wide expression analysis has been widely used for evaluation of differential gene and miRNA expression between diseased tissues and normal controls (34–36). In miRNA research, microarray profiling followed by validation with quantitative reverse transcription-PCR (qRT-PCR) is a common approach for identifying deregulated miRNAs in clinical specimens (37–39). Accumu-

Correspondence: Z. Li, Department of Orthopaedic Surgery, Peking Union Medical College Hospital, Chinese Academy of Medical Science and Peking Union Medical College, Beijing 100730, China. Tel.: +86 010 69152812; Fax: +86 010 69152812;
E-mail: kleeo@163.com
Xin Yu and Zheng Li contributed equally to this work.

lating studies show that many miRNAs are deregulated in keloids, using this miRNA profiling approach (40). Here, we summarize data on miRNA expression profiling in keloids.

Liu *et al.* profiled miRNA expression in 12 pairs of keloid tissue and corresponding normal skin using miRNA microarrays and qRT-PCR (31), in which a total of 32 differentially expressed miRNAs were identified. Of these, 23 miRNAs (e.g. miR-21, miR-4269, miR-382) were up-regulated while nine miRNAs (e.g. miR-203, miR-205, miR-200b/c) were down-regulated compared to normal skin tissues. Furthermore, bioinformatic analysis predicted that these differentially expressed miRNAs might participate in signalling pathways related to wound healing, such as mitogen-activated protein kinase (MAPK), focal adhesion and biosynthesis of collagen protein. MAPK and focal adhesion have been shown to be involved in collagen synthesis and fibroblast mechanotransduction during scar formation (41,42), suggesting that deregulated miRNAs might contribute to pathogenesis of keloids.

In a further study, Li *et al.* compared miRNA expression in fibroblasts isolated from keloid and normal dermis using miRNA microarrays (33). They demonstrated that miRNA expression profiles in keloid fibroblasts were different from those derived from normal skin, with six miRNAs (miR-152, miR-23b-3p, miR-31-5p, miR-320c, miR-30a-5p, hsv1-miR-H7) up-regulated and three (miR-4328, miR-145-5p, miR-143-3p) down-regulated. Furthermore, these differentially expressed miRNAs were predicted to participate in signalling pathways relevant to scar formation. These data suggest that altered miRNA expression may contribute to keloid development by deregulating fibroblast functions.

Specific deregulated miRNAs with functional implications

miR-7

Expression of miR-7 is low in keloid tissues compared to normal skin, as revealed by PCR array analysis. Interestingly, inhibiting miR-7 in normal dermal fibroblasts increased expression of type I α2 collagen *in vitro*, suggesting reduced miR-7 expression might contribute to pathogenesis of keloids by collagen overproduction (43). It is noteworthy that miR-7 has been reported to function as a tumour suppressor in breast cancer (44) but exerts oncogenic effects in lung cancer, hepatocellular carcinoma (HCC) and gastric cancer (45–48), indicating that this miRNA might function in an organ- or tissue-specific manner.

miR-21

miR-21 is up-regulated and acts oncogenically in many types of cancer (49–52), and it has been documented as targeting many cancer-related genes, such as *PTEN*, *TPM1* and *PDCD* (50,53). In the skin, miR-21 is up-regulated after injury and is closely related to major events during wound healing; it also plays a significant role in wound contraction (54). There is also evidence that miR-21 promotes keratinocyte migration and re-epithelialization during wound healing by targeting TIMP3 and TIAM1 (55). miR-21 expression is high in keloid tissues in comparison to adjacent normal skin tissues; in addition, protein expression of PTEN is inversely correlated to miR-21 and is also high during fibroblast proliferation in normal skin. Thus, miR-21 may assume a significant role in regulation of keloid fibroblast proliferation (56).

miR-196a

miRNA-196a has been reported to be down-regulated in sera and involved skin, of patients with localized scleroderma (57). Kashiyama *et al.* compared miRNA expression between keloid-derived fibroblasts and normal fibroblasts using miRNA expression microarrays (32). They demonstrated that 27 miRNAs were differentially expressed in keloid-derived fibroblasts compared to their normal counterparts. Of these differentially expressed miRNAs, miR-196a exhibited highest fold-change down-regulation in keloid-derived fibroblasts. Furthermore, miR-196a inhibits expression of secreted type I/III collagens. Importantly, direct binding of miR-196a to COL1A1 and COL3A1 has been demonstrated in reporter assays (32). These data suggest that down-regulation of miR-196a may underlie increased collagen deposition in keloids.

miR-199a-5p

miR-199a-5p is deregulated in various diseases, including organ fibrosis and malignancies (58–62). For example, Shen *et al.* found that expression of miR-199a-5p was low in HCC where its down-regulation promoted metastasis by inhibiting DDR1 (63). In addition, miR-199a-5p inhibited proliferation, migration and invasion of testicular cancer cells (64). Nevertheless, miR-199a is up-regulated in gastric cancers compared to normal gastric tissues (65). Using miRNA microarrays, 17 miRNAs were found to be differentially expressed in keloid tissues compared to normal skin (40). Of these, miR-199a-5p down-regulation in keloids was confirmed by qRT-PCR and its restored expression inhibited fibroblast proliferation with length-

ened S and G_2/M phases (40), suggesting its down-regulation in keloids might promote abnormal fibroblast proliferation by influencing the cell cycle.

miR-200b

miR-200b belongs to the miR-200 family, which is deregulated in many types of cancer (66–69). miR-200b has been associated with aberrant proliferation of fibroblasts (67,70) and deregulated in various fibrogenic diseases, including biliary atresia and liver fibrotic progression (71,72). Previous data have reported that up-regulation of miR-200b repressed proliferation and induced apoptosis of hypertrophic scar fibroblasts, whereas its down-regulation had the opposite effect (70). miR-200b is down-regulated in hypertrophic scar tissues and human hypertrophic scar fibroblasts, suggesting a correlation between miR-200b expression and hypertrophic scarring. In addition, miR-200b represses hypertrophic scarring by targeting type I/III collagen I, fibronectin, transforming growth factor-β1 and α smooth muscle actin (70). Thus, miR-200b may be a potential therapeutic miRNA for management of hypertrophic scarring.

Conclusion

miRNAs play significant roles in formation and progression of keloids by regulating many processes, including transforming growth factor-β signalling, ECM deposition and fibroblast proliferation. As few treatment options are effective against keloids, miRNA modulation might be a novel therapeutic approach. Some down-regulated miRNAs in keloids may play significant anti-fibrotic roles and thus could potentially be used as therapeutic agents. In contrast, miRNA inhibitors could target up-regulated miRNAs. Nevertheless, further translational studies are needed for establishing therapeutic values of these miRNA-based agents.

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References

1 Zhang Z, Nie F, Chen X, Qin Z, Kang C, Chen B *et al.* (2015) Upregulated periostin promotes angiogenesis in keloids through activation of the ERK 1/2 and focal adhesion kinase pathways, as well as the upregulated expression of VEGF and angiopoietin1. *Mol. Med. Rep.* **11**, 857–864.
2 Careta MF, Fortes AC, Messina MC, Maruta CW (2013) Combined treatment of earlobe keloids with shaving, cryosurgery, and intralesional steroid injection: a 1-year follow-up. *Dermatol. Surg.* **39**, 734–738.
3 Love PB, Kundu RV (2013) Keloids: an update on medical and surgical treatments. *J. Drugs Dermatol.* **12**, 403–409.
4 Suarez E, Syed F, Alonso-Rasgado T, Mandal P, Bayat A (2013) Up-regulation of tension-related proteins in keloids: knockdown of Hsp27, alpha2beta1-integrin, and PAI-2 shows convincing reduction of extracellular matrix production. *Plast. Reconstr. Surg.* **131**, 158e–173e.
5 Cho JW, Il KJ, Lee KS (2013) Downregulation of type I collagen expression in silibinin-treated human skin fibroblasts by blocking the activation of Smad2/3-dependent signaling pathways: potential therapeutic use in the chemoprevention of keloids. *Int. J. Mol. Med.* **31**, 1148–1152.
6 Huang C, Murphy GF, Akaishi S, Ogawa R (2013) Keloids and hypertrophic scars: update and future directions. *Plast. Reconstr. Surg. Glob. Open* **1**, e25.
7 Huang C, Ogawa R (2013) Pharmacological treatment for keloids. *Expert Opin. Pharmacother.* **14**, 2087–2100.
8 Mamalis AD, Lev-Tov H, Nguyen DH, Jagdeo JR (2014) Laser and light-based treatment of Keloids–a review. *J. Eur. Acad. Dermatol. Venereol.* **28**, 689–699.
9 Manca G, Pandolfi P, Gregorelli C, Cadossi M, de Terlizzi F (2013) Treatment of keloids and hypertrophic scars with bleomycin and electroporation. *Plast. Reconstr. Surg.* **132**, 621e–630e.
10 Hwang SH, Hwang K (2013) Outcomes of surgical excision with pressure therapy using magnets and identification of risk factors for recurrent keloids. *Plast. Reconstr. Surg.* **132**, 666e–667e.
11 Pikula M, Zebrowska ME, Poblocka-Olech L, Krauze-Baranowska M, Sznitowska M, Trzonkowski P (2014) Effect of enoxaparin and onion extract on human skin fibroblast cell line - therapeutic implications for the treatment of keloids. *Pharm. Biol.* **52**, 262–267.
12 Kazal LA Jr (2013) Another treatment option for keloids. *J. Fam. Pract.* **62**, 464.
13 Litrowski N, Boullie MC, Dehesdin D, De Barros A, Joly P (2014) Treatment of earlobe keloids by surgical excision and cryosurgery. *J. Eur. Acad. Dermatol. Venereol.* **28**, 1324–1331.
14 Ud-Din S, Bayat A (2014) New insights on keloids, hypertrophic scars, and striae. *Dermatol. Clin.* **32**, 193–209.
15 Zheng Z, Zhu L, Zhang X, Li L, Moon S, Roh MR *et al.* (2015) RUNX3 expression is associated with sensitivity to pheophorbide a-based photodynamic therapy in keloids. *Lasers Med. Sci.* **30**, 67–75.
16 Li Z, Yu X, Shen J, Wu WK, Chan MT (2015) MicroRNA expression and its clinical implications in Ewing's sarcoma. *Cell Prolif.* **48**, 1–6.
17 Li Z, Yu X, Shen J, Jiang Y (2015) MicroRNA dysregulation in uveal melanoma: a new player enters the game. *Oncotarget* **6**, 4562–4568.
18 Yu X, Li Z, Liu J (2015) MiRNAs in primary cutaneous lymphomas. *Cell Prolif.* **48**, 271–277.
19 Li Z, Yu X, Shen J, Chan MT, Wu WK (2015) MicroRNA in intervertebral disc degeneration. *Cell Prolif.* **48**, 278–283.
20 Tang J, Shen L, Yang Q, Zhang C (2014) Overexpression of metadherin mediates metastasis of osteosarcoma by regulating epithelial-mesenchymal transition. *Cell Prolif.* **47**, 427–434.
21 Yu X, Li Z (2014) MicroRNAs regulate vascular smooth muscle cell functions in atherosclerosis (review). *Int. J. Mol. Med.* **34**, 923–933.
22 Li Z, Yu X, Wang Y, Shen J, Wu WK, Liang J *et al.* (2014) By downregulating TIAM1 expression, microRNA-329 suppresses gastric cancer invasion and growth. *Oncotarget* **6**, 17559–17569.
23 Zhou H, Guo W, Zhao Y, Wang Y, Zha R, Ding J *et al.* (2014) MicroRNA-135a acts as a putative tumor suppressor by directly

targeting very low density lipoprotein receptor in human gallbladder cancer. *Cancer Sci.* **105**, 956–965.
24 Yu X, Li Z, Shen J, Wu WK, Liang J, Weng X *et al.* (2013) MicroRNA-10b promotes nucleus pulposus cell proliferation through RhoC-Akt pathway by targeting HOXD10 in intervetebral disc degeneration. *PLoS ONE* **8**, e83080.
25 Li Z, Lei H, Luo M, Wang Y, Dong L, Ma Y *et al.* (2015) DNA methylation downregulated mir-10b acts as a tumor suppressor in gastric cancer. *Gastric Cancer* **18**, 43–54.
26 Yang Z, Han Y, Cheng K, Zhang G, Wang X (2014) miR-99a directly targets the mTOR signalling pathway in breast cancer side population cells. *Cell Prolif.* **47**, 587–595.
27 Yu X, Zhang X, Bi T, Ding Y, Zhao J, Wang C *et al.* (2013) MiRNA expression signature for potentially predicting the prognosis of ovarian serous carcinoma. *Tumour Biol.* **34**, 3501–3508.
28 Lovendorf MB, Skov L (2015) miRNAs in inflammatory skin diseases and their clinical implications. *Expert Rev. Clin. Immunol.* **11**, 467–477.
29 Li D, Li X, Wang A, Meisgen F, Pivarcsi A, Sonkoly E *et al.* (2015) MicroRNA-31 promotes skin wound healing by enhancing keratinocyte proliferation and migration. *J. Invest. Dermatol.* **135**, 1676–1685.
30 Rebane A, Runnel T, Aab A, Maslovskaja J, Ruckert B, Zimmermann M *et al.* (2014) MicroRNA-146a alleviates chronic skin inflammation in atopic dermatitis through suppression of innate immune responses in keratinocytes. *J. Allergy Clin. Immunol.* **134**(836–847), e811.
31 Liu Y, Yang D, Xiao Z, Zhang M (2012) miRNA expression profiles in keloid tissue and corresponding normal skin tissue. *Aesthetic Plast. Surg.* **36**, 193–201.
32 Kashiyama K, Mitsutake N, Matsuse M, Ogi T, Saenko VA, Ujifuku K *et al.* (2012) miR-196a downregulation increases the expression of type I and III collagens in keloid fibroblasts. *J. Invest. Dermatol.* **132**, 1597–1604.
33 Li C, Bai Y, Liu H, Zuo X, Yao H, Xu Y *et al.* (2013) Comparative study of microRNA profiling in keloid fibroblast and annotation of differential expressed microRNAs. *Acta Biochim. Biophys. Sin. (Shanghai)* **45**, 692–699.
34 Dong R, Liu X, Zhang Q, Jiang Z, Li Y, Wei Y *et al.* (2014) miR-145 inhibits tumor growth and metastasis by targeting metadherin in high-grade serous ovarian carcinoma. *Oncotarget* **5**, 10816–10829.
35 Bae HJ, Noh JH, Kim JK, Eun JW, Jung KH, Kim MG *et al.* (2014) MicroRNA-29c functions as a tumor suppressor by direct targeting oncogenic SIRT1 in hepatocellular carcinoma. *Oncogene* **33**, 2557–2567.
36 Schirmer U, Doberstein K, Rupp AK, Bretz NP, Wuttig D, Kiefel H *et al.* (2014) Role of miR-34a as a suppressor of L1CAM in endometrial carcinoma. *Oncotarget* **5**, 462–472.
37 Zeng X, Xiang J, Wu M, Xiong W, Tang H, Deng M *et al.* (2012) Circulating miR-17, miR-20a, miR-29c, and miR-223 combined as non-invasive biomarkers in nasopharyngeal carcinoma. *PLoS ONE* **7**, e46367.
38 Osanto S, Qin Y, Buermans HP, Berkers J, Lerut E, Goeman JJ *et al.* (2012) Genome-wide microRNA expression analysis of clear cell renal cell carcinoma by next generation deep sequencing. *PLoS ONE* **7**, e38298.
39 Song MY, Pan KF, Su HJ, Zhang L, Ma JL, Li JY *et al.* (2012) Identification of serum microRNAs as novel non-invasive biomarkers for early detection of gastric cancer. *PLoS ONE* **7**, e33608.
40 Wu ZY, Lu L, Liang J, Guo XR, Zhang PH, Luo SJ (2014) Keloid microRNA expression analysis and the influence of miR-199a-5p on the proliferation of keloid fibroblasts. *Genet. Mol. Res.* **13**, 2727–2738.
41 Sato M, Shegogue D, Gore EA, Smith EA, McDermott PJ, Trojanowska M (2002) Role of p38 MAPK in transforming growth factor beta stimulation of collagen production by scleroderma and healthy dermal fibroblasts. *J. Invest. Dermatol.* **118**, 704–711.
42 Rustad KC, Wong VW, Gurtner GC (2013) The role of focal adhesion complexes in fibroblast mechanotransduction during scar formation. *Differentiation* **86**, 87–91.
43 Etoh M, Jinnin M, Makino K, Yamane K, Nakayama W, Aoi J *et al.* (2013) microRNA-7 down-regulation mediates excessive collagen expression in localized scleroderma. *Arch. Dermatol. Res.* **305**, 9–15.
44 Zhang H, Cai K, Wang J, Wang X, Cheng K, Shi F *et al.* (2014) MiR-7, inhibited indirectly by lincRNA HOTAIR, directly inhibits SETDB1 and reverses the EMT of breast cancer stem cells by downregulating the STAT3 pathway. *Stem Cells* **32**, 2858–2868.
45 Liu H, Huang J, Peng J, Wu X, Zhang Y, Zhu W *et al.* (2015) Upregulation of the inwardly rectifying potassium channel Kir2.1 (KCNJ2) modulates multidrug resistance of small-cell lung cancer under the regulation of miR-7 and the Ras/MAPK pathway. *Mol. Cancer.* **14**, 59.
46 Li J, Zheng Y, Sun G, Xiong S (2014) Restoration of miR-7 expression suppresses the growth of Lewis lung cancer cells by modulating epidermal growth factor receptor signaling. *Oncol. Rep.* **32**, 2511–2516.
47 Xie J, Chen M, Zhou J, Mo MS, Zhu LH, Liu YP *et al.* (2014) miR-7 inhibits the invasion and metastasis of gastric cancer cells by suppressing epidermal growth factor receptor expression. *Oncol. Rep.* **31**, 1715–1722.
48 Ma C, Qi Y, Shao L, Liu M, Li X, Tang H (2013) Downregulation of miR-7 upregulates Cullin 5 (CUL5) to facilitate G1/S transition in human hepatocellular carcinoma cells. *IUBMB Life* **65**, 1026–1034.
49 Selaru FM, Olaru AV, Kan T, David S, Cheng Y, Mori Y *et al.* (2009) MicroRNA-21 is overexpressed in human cholangiocarcinoma and regulates programmed cell death 4 and tissue inhibitor of metalloproteinase 3. *Hepatology* **49**, 1595–1601.
50 Wang LJ, He CC, Sui X, Cai MJ, Zhou CY, Ma JL *et al.* (2015) MiR-21 promotes intrahepatic cholangiocarcinoma proliferation and growth in vitro and in vivo by targeting PTPN14 and PTEN. *Oncotarget* **6**, 5932–5946.
51 Liu M, Wu H, Liu T, Li Y, Wang F, Wan H *et al.* (2009) Regulation of the cell cycle gene, BTG2, by miR-21 in human laryngeal carcinoma. *Cell Res.* **19**, 828–837.
52 Yu X, Wu Y, Liu Y, Deng H, Shen Z, Xiao B *et al.* (2014) miR-21, miR-106b and miR-375 as novel potential biomarkers for laryngeal squamous cell carcinoma. *Curr. Pharm. Biotechnol.* **15**, 503–508.
53 Lv L, Huang F, Mao H, Li M, Li X, Yang M *et al.* (2013) MicroRNA-21 is overexpressed in renal cell carcinoma. *Int. J. Biol. Markers* **28**, 201–207.
54 Wang T, Feng Y, Sun H, Zhang L, Hao L, Shi C *et al.* (2012) miR-21 regulates skin wound healing by targeting multiple aspects of the healing process. *Am. J. Pathol.* **181**, 1911–1920.
55 Yang X, Wang J, Guo SL, Fan KJ, Li J, Wang YL *et al.* (2011) miR-21 promotes keratinocyte migration and re-epithelialization during wound healing. *Int. J. Biol. Sci.* **7**, 685–690.
56 Liu Y, Wang X, Yang D, Xiao Z, Chen X (2014) MicroRNA-21 affects proliferation and apoptosis by regulating expression of PTEN in human keloid fibroblasts. *Plast. Reconstr. Surg.* **134**, 561e–573e.
57 Honda N, Jinnin M, Kajihara I, Makino T, Makino K, Masuguchi S *et al.* (2012) TGF-beta-mediated downregulation of microRNA-196a contributes to the constitutive upregulated type I collagen

expression in scleroderma dermal fibroblasts. *J. Immunol.* **188**, 3323–3331.
58 Yi H, Liang B, Jia J, Liang N, Xu H, Ju G *et al.* (2013) Differential roles of miR-199a-5p in radiation-induced autophagy in breast cancer cells. *FEBS Lett.* **587**, 436–443.
59 Su SF, Chang YW, Andreu-Vieyra C, Fang JY, Yang Z, Han B *et al.* (2013) miR-30d, miR-181a and miR-199a-5p cooperatively suppress the endoplasmic reticulum chaperone and signaling regulator GRP78 in cancer. *Oncogene* **32**, 4694–4701.
60 Monastyrskaya K, Sanchez-Freire V, Hashemi Gheinani A, Klumpp DJ, Babiychuk EB, Draeger A *et al.* (2013) miR-199a-5p regulates urothelial permeability and may play a role in bladder pain syndrome. *Am. J. Pathol.* **182**, 431–448.
61 Zhang S, Liu L, Wang R, Tuo H, Guo Y, Yi L *et al.* (2013) MiR-199a-5p promotes migration and tube formation of human cytomegalovirus-infected endothelial cells through downregulation of SIRT1 and eNOS. *Arch. Virol.* **158**, 2443–2452.
62 Zhang PX, Cheng J, Zou S, D'Souza AD, Koff JL, Lu J *et al.* (2015) Pharmacological modulation of the AKT/microRNA-199a-5p/CAV1 pathway ameliorates cystic fibrosis lung hyper-inflammation. *Nat. Commun.* **6**, 6221.
63 Shen Q, Cicinnati VR, Zhang X, Iacob S, Weber F, Sotiropoulos GC *et al.* (2010) Role of microRNA-199a-5p and discoidin domain receptor 1 in human hepatocellular carcinoma invasion. *Mol. Cancer.* **9**, 227.
64 Chen BF, Gu S, Suen YK, Li L, Chan WY (2014) microRNA-199a-3p, DNMT3A, and aberrant DNA methylation in testicular cancer. *Epigenetics* **9**, 119–128.
65 He XJ, Ma YY, Yu S, Jiang XT, Lu YD, Tao L *et al.* (2014) Up-regulated miR-199a-5p in gastric cancer functions as an oncogene and targets klotho. *BMC Cancer* **14**, 218.
66 Sun L, Yao Y, Liu B, Lin Z, Lin L, Yang M *et al.* (2012) MiR-200b and miR-15b regulate chemotherapy-induced epithelial-mesenchymal transition in human tongue cancer cells by targeting BMI1. *Oncogene* **31**, 432–445.
67 Kurashige J, Mima K, Sawada G, Takahashi Y, Eguchi H, Sugimachi K *et al.* (2015) Epigenetic modulation and repression of miR-200b by cancer-associated fibroblasts contribute to cancer invasion and peritoneal dissemination in gastric cancer. *Carcinogenesis* **36**, 133–141.
68 Peng F, Jiang J, Yu Y, Tian R, Guo X, Li X *et al.* (2013) Direct targeting of SUZ12/ROCK2 by miR-200b/c inhibits cholangiocarcinoma tumourigenesis and metastasis. *Br. J. Cancer* **109**, 3092–3104.
69 Kohler CU, Bryk O, Meier S, Lang K, Rozynek P, Brüning T *et al.* (2013) Analyses in human urothelial cells identify methylation of miR-152, miR-200b and miR-10a genes as candidate bladder cancer biomarkers. *Biochem. Biophys. Res. Commun.* **438**, 48–53.
70 Li P, He QY, Luo CQ (2014) Overexpression of miR-200b inhibits the cell proliferation and promotes apoptosis of human hypertrophic scar fibroblasts in vitro. *J. Dermatol.* **41**, 903–911.
71 Lee JW, Park YA, Choi JJ, Lee YY, Kim CJ, Choi C *et al.* (2011) The expression of the miRNA-200 family in endometrial endometrioid carcinoma. *Gynecol. Oncol.* **120**, 56–62.
72 Xiao Y, Wang J, Chen Y, Zhou K, Wen J, Wang Y *et al.* (2014) Up-regulation of miR-200b in biliary atresia patients accelerates proliferation and migration of hepatic stallate cells by activating PI3K/Akt signaling. *Cell. Signal.* **26**, 925–932.