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MicroRNA involvement in esophageal carcinogenesis

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Abstract

MicroRNAs (miRs) have recently emerged as a novel class of gene expression regulators. The number of studies documenting an altered miR expression pattern in cancer continues to expand rapidly. Critical information is continuously gained regarding how aberrantly expressed miRs contribute to carcinogenesis. Current studies provide evidence that analyses of miR expression patterns have potential clinical applications toward developing tumor biomarkers to identify the presence and dissemination of esophageal cancer, as well as to assess tumor chemo- or radiosensitivity. The incidence of esophageal cancer is on the rise, and this disease continues to portend a poor prognosis. The current review addresses ways in which altered miR expression contributes to esophageal carcinogenesis, along with how recent discoveries may be applied clinically.

Keywords

microRNA; esophageal cancer; esophageal adenocarcinoma; Barrett's esophagus; esophageal squamous cell cancer

Introduction

The discovery of RNA interference by Andrew Fire and Craig Mello in 1998[1] is a scientific landmark recognized by the 2006 Nobel Prize for Physiology. MicroRNAs (miRs) are an endogenous class of 17–25 nucleotide-long noncoding RNAs that play critical roles in gene expression regulation. The first study to identify a miR documented the involvement of lin4 in *Caenoharbditis elegans* cellular differentiation.[2] Current studies are rapidly expanding the number of identified miRs, while providing a better understanding of their roles in embryogenesis and human disease.[3–5]

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MicroRNA biogenesis and roles

MiRs are transcribed by RNA polymerase II into primary miRNA transcripts (pri-miRNAs) and further processed by the RNase II endonuclease Drosha and DGCRb into precursor miRs (pre-miRNAs). These 70 nucleotide-long structures are exported from the nucleus into the cytoplasm by exportin 5. In the cytoplasm, pre-miRNAs are processed by the enzyme Dicer to form 22 nucleotide-long imperfectly matched miRNA/miRNA duplexes that are loaded by the Ago protein and integrated into the RNA-induced signaling complex (RISC), where the passenger miRNA strand is degraded to yield a mature miRNA that will interact with the 3'UTR region of its cognate mRNAs.[3] Mature miRs bind mRNAs in a sequence-specific manner to inhibit gene expression by repressing translation and/or diminishing mRNA stability.[3] Numerous studies have focused on identifying individual mRNA targets of distinct miRs. However, a single miR may recognize and regulate multiple mRNAs, while the expression of a single gene may be regulated my multiple miRs. This fact suggests that miRs may act within networks to impact gene expression patterns. Therefore, trying to identify miRs individually responsible for a given disease may not be the best approach.[6]

MicroRNA involvement in esophageal carcinogenesis

Cancer has recently replaced cardiovascular disease as the leading cause of mortality in the US. Gastrointestinal tract tumors have among the top 10 incidences and cancer-related mortalities. The NIH estimates that 16,640 patients were newly diagnosed with esophageal cancer in 2010 and attributes 14,500 deaths to this disease (http://www.cancer.gov/cancertopics/types/esophageal/). Two types of esophageal cancer are described: 1) esophageal adenocarcinoma, which usually develops in the lower part of the esophagus and arises from Barrett's esophagus; and 2) esophageal squamous cell carcinoma, which originates in the squamous epithelium of the esophagus and is related to tobacco consumption.

Esophageal adenocarcinoma (EAC), considered a sequel of chronic gastroesophageal reflux, is preceded by the development of Barrett's esophagus (BE), a premalignant condition comprising intestinal metaplasia that develop as a result of gastro-esophageal reflux. Not all BE patients develop EAC; however, in a patient with BE, the risk of EAC is 30 times higher than in the general population.[7] In order to gain a better understanding of EAC pathogenesis, research focusing on this neoplasia has expanded to include the study of BE. This inclusive approach may yield better diagnostic tools as well as provide a basis for the development of novel therapeutic targets.

Current literature reveals miR expression profiles that differ between normal esophageal lining, BE, and EAC. Sequential upregulation of miRs–192, -194, -21 and –93 was reported by Feber et al. during progression of normal esophageal mucosa to BE and finally to EAC.[8] A study by Fassan et al. identified distinct patterns of miR expression that characterized each step of BE-to-EAC progression. These authors further refined their findings to develop a "progression signature" comprising upregulated levels of miR-215 and miR –192 and associated with decreased expression of miR-205, miR-203 and let-7c.[9] Yang et al. described several distinct miR sets that were expressed at different stages of EAC development from BE lesions: low-grade dysplasia (LGD) to high-grade dysplasia (HGD) progression was associated with increased expression of miR-200a*, miR-513, miR 125b, miR-101 and miR-197. The LGD to HGD transition was also characterized by reduced levels of miR-23b, miR-20b, miR-181b, miR-203, miR-193b and miR-636. Regarding the HGD to EAC transition, the same study documented 7 miRs that were downregulated (let-7b, let-7a. let-7c, miR-345, miR-494 and miR-193a).[10] Differential expression of miR-15b, -21, -203, -486-5p and –let 7a was also reported to mark the presence of HGD/

EAC in a BE lesion.[11] The upregulation of miR-196a along the normal - low grade dysplasia (LGD) – high grade dysplasia - EAC axis was shown to potentially contribute to EAC by targeting ANXA1, SPRR2C, S1009 and KRT5 and augmenting apoptosis resistance in EAC cells.[12, 13]

For already-developed esophageal tumors, Mathé et al. described up-regulation of miR-21, miR-223, miR-192 and miR-195 and reduced expression of miR203 in EAC.[14] With regard to disease progression, Feber's group further reported that miR-99b and miR-199a_3p and _5p levels were increased in patients with lymph node metastasis. These findings were suggested to reflect a microRNA signature that not only revealed extent of disease, but also predicted patient survival.[15] The miR 25 –93-106b polycistron is progressively upregulated during normal esophagus –BE- EAC progression and is associated with genomic amplification of the MCM7 locus at chromosome 7q22.1. MiRs-93 and –106 appeared to contribute to EAC carcinogenesis by targeting CDKN1A and impacting cell cycle progression. Mir-25 targeted BCL2L11 and Bim, reducing apoptosis.[16]

Clinically, miR-30e, miR-200a levels correlate with EAC patient survival, and miR-30e expression reflects a 2.5-old increase in the risk of disease recurrence after surgery.[17] The same study demonstrated an association between miR-16-2 expression and lymph node invasion and provided evidence for a correlation between miR-126 expression and poor differentiation status.[17] Reduced miR-375 expression in EAC was associated with shorter patient survival and, together with several inflammatory cytokines, was proposed in a molecular panel to assess disease prognosis.[14, 18] Hummel et al. showed that elevated miR-21 levels were correlated with lymph node positivity; these authors described an inverse correlation between miR-148 levels and EAC differentiation.[19] This study also demonstrated that miR-148 overexpression enhanced the effect of cisplatin and 5-FU in both EAC and ESCC chemo-sensitive cells, providing a basis for the potential use of miRs to either predict or improve patients' responses to chemotherapy.[20]

Genetics also appear to be involved in the contribution of miRs to esophageal adenocarcinoma pathogenesis. SNPs occurring in the sequences of pre-microRNA-423, -196a-2 and -631 are correlated with increased EAC risk in Caucasians.

Esophageal squamous cancer (ESCC) is related to alcohol and tobacco abuse. Enhanced miR21 expression and increased miR-205 levels were reported in both ESCC cell lines and tumor tissues.[14, 21–2324] MiR-10b levels were increased in ESCC samples compared to normal mucosae.[25] Overexpressed miR-21 is documented to facilitate ESCC growth by targeting PTEN and PDCD4.[21, 26] A study by Matsushima et al. found that enhanced miR-205 and miR-10a expression was a particular feature of ESCC cell lines, with the former miR contributing to epithelial-to-mesenchimal transition (EMT). However, when the authors of this study investigated miR-205 levels in ESCC tissues, they found no difference between tumor tissues and adjacent non-tumor mucosae (also suggesting no change in miR-205 expression when samples with different degrees of ESCC differentiation were compared).

Overexpression of miR-23a, miR-26a, miR-27b, miR-96, miR-128b and miR-129 has been detected in ESCC and correlates with prognosis, while overexpression of miR-129 is associated with poorer post-operative survival.[27] Feber et al demonstrated upregulation of miR-21, -93, -192 and –194 in ESCC tissues compared to normal esophageal mucosae.[8]

Hong et al. demonstrated that miR-296 contributes to ESCC growth by targeting cell CCND1 and p27, thus facilitating cell cycle progression.[28]

Certain miRs are underexpressed in ESCC, suggesting that they play a tumor-suppressive role. Decreased miR-375 expression was reported in ESCC tumor tissues compared to normal mucosae.[14] Feber et al. revealed that miRs -203 and –205 levels are reduced in ESCC, while miRs -27b, -125b and –100 are reduced in both EAC and ESCC.[8]

A potential mechanism underlying the tumor-suppressive role attributed to miR-203 relies on the posttranscriptional regulation exerted by this miR on the expression of the ΔNP63 oncogene, by contributing to the negative effect of miR-203 on ESCC cell proliferation. [29] MiR-210 has emerged as a tumor suppressor miR, as it is downregulated in ESCC. It targets FGFRL1 and exerts a negative effect on the cell cycle and proliferation.[30]

In addition to altered miR expression levels, changes in miR DNA sequence may also contribute to carcinogenesis. The C-T SNP in pre-miR-196a (rs11614913) and the G>C variant in pre-miR-146a increase ESCC risk in the Chinese Han population, the latter SNP being correlated with TNM staging.[31, 32]

Interestingly, overlapping mechanisms that regulate gene expression may converge to exert a permissive effect on tumorigenesis.[33] Li et al. demonstrated that promoter hypermethylation reduces miR-375 expression in ESCC, thereby augmenting 3-phopshoinositide-dependent protein kinase 1 (PDK1) expression.[34]

In addition to providing insights into ESCC pathogenesis, altered miR expression patterns offer the potential to reflect cancer dissemination to distant sites and to predict patient survival. Hamano et al. found that expression levels of miR-21 and miR-200c correlate with ESCC patient survival. Moreover, ESCC patients with enhanced miR-21 levels in noncancerous esophageal mucosae had a poorer prognosis.[14] These authors also demonstrated that increased miR-200c levels diminished the chemotherapeutic response by targeting PPP2R1B, an inhibitor of PKB-Akt.[35] Akagi et al. confirmed elevated miR-21 expression and further demonstrated its correlation with deeper mucosal invasion and the presence of lymph node metastasis in ESCC.[36] Mir-21 and miR-200c levels also correlate with ESCC patient survival.[35, 36]

There is a correlation between reduced let-7 expression in ESCC and tumor dissemination to lymph nodes. The antitumor effect of let-7 is mediated via post-transcriptional regulation of HMGA2 (high mobility group A2) protein.[37] Chen et al. showed that miR-92a overexpression contributes to ESCC lymph node dissemination by reducing CDH1 levels.[38]

MiR-143 and miR-145 manifest decreased levels in ESCC; their levels are inversely correlated with tumor invasion, while *in vitro* overexpression of these miRs impacts cell motility.[39, 40] After confirming reduced levels of miR-145,-133a and –133bin ESCC, Kano et al. demonstrated that miR-145, miR-133a and miR-133b converge to target Fascin 1 (FSCN), thereby reducing cell growth and invasion and providing a potential explanation for the correlations observed *in vivo* regarding tumor invasion. This same study showed that miR-145 expression is associated with ESCC recurrence and inversely correlated with patient survival.[41] Overexpression of miRs -103 and -107 is also inversely correlated with patient survival.[42] Increased miR-296 expression is not only associated with poorer patient prognosis, but is also with chemoresistance.[28]

Our group found that reduced levels of miR-593* in ESCC may contribute to carcinogenesis, as miR593* targets PLK1, which manifests increased expression in ESCC; moreover, miR-593* overexpression in ESCC cells reduces cell proliferation and results in G2M arrest.[43]

A molecular signature comprising of miR-10a, miR-22, miR-100, miR-148b, miR-223, miR-133a and miR-127-3p has shown potential to serve as a serum-based ESCC biomarker panel.[44]

Conclusions

The discovery of RNA interference and the continuous expansion of identified microRNAs offer fascinating insights into the complexity of gene expression regulation. Altered miR expression patterns exert a significant impact on the balance between tumor suppressors and oncogenes. The study of miR involvement in carcinogenesis is a rewarding field. In particular, studying altered miR expression patterns in esophageal cancers has offered great insights into the pathogenesis of this devastating disease. The detection of aberrantly expressed miRs also lay the groundwork for the future development of a whole new class of disease biomarkers and therapeutic targets.

Highlights

- Esophageal cancer is a devastating disease with a significant incidence and a dismal prognosis
- MicroRNAs (miRs) are important gene expression regulators
- Altered miR expression patterns have a significant impact on human disease, particularly in cancers
- Mir expression analysis provides insight into the mechanisms driving esophageal cancer formation and progression
- Aberrantly expressed miRs are potential biomarkers to detect the presence of an esophageal tumor, to assess the invasiveness of esophageal cancers, and to predict the patient’s prognosis and response to treatment

References

1. Fire A, Xu S, Montgomery MK, Kostas SA, Driver SE, Mello CC. Potent and specific genetic interference by double-stranded RNA in Caenorhabditis elegans. Nature. 1998; 391:806–811. [PubMed: 9486653]
2. Lee RC, Feinbaum RL, Ambros V. The C. elegans heterochronic gene lin-4 encodes small RNAs with antisense complementarity to lin-14. Cell. 1993; 75:843–854. [PubMed: 8252621]
3. Huntzinger E, Izaurralde E. Gene silencing by microRNAs: contributions of translational repression and mRNA decay. Nat Rev Genet. 12:99–110. [PubMed: 21245828]
4. Pauli A, Rinn JL, Schier AF. Non-coding RNAs as regulators of embryogenesis. Nat Rev Genet. 12:136–149. [PubMed: 21245830]
5. Asli NS, Pitulescu ME, Kessel M. MicroRNAs in organogenesis and disease. Curr Mol Med. 2008; 8:698–710. [PubMed: 19075669]
6. Peter ME. Targeting of mRNAs by multiple miRNAs: the next step. Oncogene. 29:2161–2164. [PubMed: 20190803]
7. van Soest EM, Dieleman JP, Siersema PD, Sturkenboom MC, Kuipers EJ. Increasing incidence of Barrett's oesophagus in the general population. Gut. 2005; 54:1062–1066. [PubMed: 15857935]
8. Feber A, Xi L, Luketich JD, Pennathur A, Landreneau RJ, Wu M, Swanson SJ, Godfrey TE, Litle VR. MicroRNA expression profiles of esophageal cancer. J Thorac Cardiovasc Surg. 2008; 135:255–260. discussion 260. [PubMed: 18242245]
9. Fassan M, Volinia S, Palatini J, Pizzi M, Baffa R, De Bernard M, Battaglia G, Parente P, Croce CM, Zaninotto G, Ancona E, Rugge M. MicroRNA expression profiling in human Barrett's carcinogenesis. Int J Cancer.

10. Yang H, Gu J, Wang KK, Zhang W, Xing J, Chen Z, Ajani JA, Wu X. MicroRNA expression signatures in Barrett's esophagus and esophageal adenocarcinoma. Clin Cancer Res. 2009; 15:5744–5752. [PubMed: 19737949]

11. Bansal A, Lee IH, Hong X, Anand V, Mathur SC, Gaddam S, Rastogi A, Wani SB, Gupta N, Visvanathan M, Sharma P, Christenson LK. Feasibility of MicroRNAs as Biomarkers for Barrett's Esophagus Progression: A Pilot Cross-Sectional, Phase 2 Biomarker Study. Am J Gastroenterol. 106:1055–1063. [PubMed: 21407181]

12. Luthra R, Singh RR, Luthra MG, Li YX, Hannah C, Romans AM, Barkoh BA, Chen SS, Ensor J, Maru DM, Broaddus RR, Rashid A, Albarracin CT. MicroRNA-196a targets annexin A1: a microRNA-mediated mechanism of annexin A1 downregulation in cancers. Oncogene. 2008; 27:6667–6678. [PubMed: 18663355]

13. Maru DM, Singh RR, Hannah C, Albarracin CT, Li YX, Abraham R, Romans AM, Yao H, Luthra MG, Anandasabapathy S, Swisher SG, Hofstetter WL, Rashid A, Luthra R. MicroRNA-196a is a potential marker of progression during Barrett's metaplasia-dysplasia-invasive adenocarcinoma sequence in esophagus. Am J Pathol. 2009; 174:1940–1948. [PubMed: 19342367]

14. Mathe EA, Nguyen GH, Bowman ED, Zhao Y, Budhu A, Schetter AJ, Braun R, Reimers M, Kumamoto K, Hughes D, Altorki NK, Casson AG, Liu CG, Wang XW, Yanaihara N, Hagiwara N, Dannenberg AJ, Miyashita M, Croce CM, Harris CC. MicroRNA expression in squamous cell carcinoma and adenocarcinoma of the esophagus: associations with survival. Clin Cancer Res. 2009; 15:6192–6200. [PubMed: 19789312]

15. Feber A, Xi L, Pennathur A, Gooding WE, Bandla S, Wu M, Luketich JD, Godfrey TE, Litle VR. MicroRNA Prognostic Signature for Nodal Metastases and Survival in Esophageal Adenocarcinoma. Ann Thorac Surg. 91:1523–1530. [PubMed: 21420070]

16. Kan T, Sato F, Ito T, Matsumura N, David S, Cheng Y, Agarwal R, Paun BC, Jin Z, Olaru AV, Selaru FM, Hamilton JP, Yang J, Abraham JM, Mori Y, Meltzer SJ. The miR-106b-25 polycistron, activated by genomic amplification, functions as an oncogene by suppressing p21 and Bim. Gastroenterology. 2009; 136:1689–1700. [PubMed: 19422085]

17. Hu Y, Correa AM, Hoque A, Guan B, Ye F, Huang J, Swisher SG, Wu TT, Ajani JA, Xu XC. Prognostic significance of differentially expressed miRNAs in esophageal cancer. Int J Cancer. 128:132–143. [PubMed: 20309880]

18. Nguyen GH, Schetter AJ, Chou DB, Bowman ED, Zhao R, Hawkes JE, Mathe EA, Kumamoto K, Zhao Y, Budhu A, Hagiwara N, Wang XW, Miyashita M, Casson AG, Harris CC. Inflammatory and microRNA gene expression as prognostic classifier of Barrett's-associated esophageal adenocarcinoma. Clin Cancer Res. 16:5824–5834. [PubMed: 20947516]

19. Hummel R, Hussey DJ, Michael MZ, Haier J, Bruewer M, Senninger N, Watson DI. MiRNAs and their association with locoregional staging and survival following surgery for esophageal carcinoma. Ann Surg Oncol. 18:253–260. [PubMed: 20628822]

20. Hummel R, Watson DI, Smith C, Kist J, Michael MZ, Haier J, Hussey DJ. Mir-148a improves response to chemotherapy in sensitive and resistant oesophageal adenocarcinoma and squamous cell carcinoma cells. J Gastrointest Surg. 15:429–438. [PubMed: 21246413]

21. Hiyoshi Y, Kamohara H, Karashima R, Sato N, Imamura Y, Nagai Y, Yoshida N, Toyama E, Hayashi N, Watanabe M, Baba H. MicroRNA-21 regulates the proliferation and invasion in esophageal squamous cell carcinoma. Clin Cancer Res. 2009; 15:1915–1922. [PubMed: 19276261]

22. Mori Y, Ishiguro H, Kuwabara Y, Kimura M, Mitsui A, Ogawa R, Katada T, Harata K, Tanaka T, Shiozaki M, Fujii Y. MicroRNA-21 induces cell proliferation and invasion in esophageal squamous cell carcinoma. Mol Med Report. 2009; 2:235–239. [PubMed: 21475818]

23. Kimura S, Naganuma S, Susuki D, Hirono Y, Yamaguchi A, Fujieda S, Sano K, Itoh H. Expression of microRNAs in squamous cell carcinoma of human head and neck and the esophagus: miR-205 and miR-21 are specific markers for HNSCC and ESCC. Oncol Rep. 23:1625–1633. [PubMed: 20428818]

24. Matsushima K, Isomoto H, Kohno S, Nakao K. MicroRNAs and esophageal squamous cell carcinoma. Digestion. 82:138–144. [PubMed: 20588024]

25. Tian Y, Luo A, Cai Y, Su Q, Ding F, Chen H, Liu Z. MicroRNA-10b promotes migration and invasion through KLF4 in human esophageal cancer cell lines. J Biol Chem. 285:7986–7994. [PubMed: 20075075]
26. Ma WJ, Lv GD, Tuersun A, Liu Q, Liu H, Zheng ST, Huang CG, Feng JG, Wang X, Lin RY, Sheyhidin I, Lu XM. Role of microRNA-21 and effect on PTEN in Kazakh's esophageal squamous cell carcinoma. Mol Biol Rep. 38:3253–3260. [PubMed: 21104017]
27. Ogawa R, Ishiguro H, Kuwabara Y, Kimura M, Mitsui A, Katada T, Harata K, Tanaka T, Fujii Y. Expression profiling of micro-RNAs in human esophageal squamous cell carcinoma using RT-PCR. Med Mol Morphol. 2009; 42:102–109. [PubMed: 19536617]
28. Hong L, Han Y, Zhang H, Li M, Gong T, Sun L, Wu K, Zhao Q, Fan D. The prognostic and chemotherapeutic value of miR-296 in esophageal squamous cell carcinoma. Ann Surg. 251:1056–1063. [PubMed: 20485139]
29. Yuan Y, Zeng ZY, Liu XH, Gong DJ, Tao J, Cheng HZ, Huang SD. MicroRNA-203 inhibits cell proliferation by repressing DeltaNp63 expression in human esophageal squamous cell carcinoma. BMC Cancer. 11:57. [PubMed: 21299870]
30. Tsuchiya S, Fujiwara T, Sato F, Shimada Y, Tanaka E, Sakai Y, Shimizu K, Tsujimoto G. MicroRNA-210 regulates cancer cell proliferation through targeting fibroblast growth factor receptor-like 1 (FGFRL1). J Biol Chem. 286:420–428. [PubMed: 21044961]
31. Wang K, Guo H, Hu H, Xiong G, Guan X, Li J, Xu X, Yang K, Bai Y. A functional variation in pre-microRNA-196a is associated with susceptibility of esophageal squamous cell carcinoma risk in Chinese Han. Biomarkers. 15:614–618. [PubMed: 20722507]
32. Guo H, Wang K, Xiong G, Hu H, Wang D, Xu X, Guan X, Yang K, Bai Y. A functional varient in microRNA-146a is associated with risk of esophageal squamous cell carcinoma in Chinese Han. Fam Cancer. 9:599–603. [PubMed: 20680470]
33. Sato F, Tsuchiya S, Meltzer SJ, Shimizu K. MicroRNAs and epigenetics. Febs J. 278:1598–1609. [PubMed: 21395977]
34. Li X, Lin R, Li J. Epigenetic Silencing of MicroRNA-375 Regulates PDK1 Expression in Esophageal Cancer. Dig Dis Sci.
35. Hamano R, Miyata H, Yamasaki M, Kurokawa Y, Hara J, Moon JH, Nakajima K, Takiguchi S, Fujiwara Y, Mori M, Doki Y. Overexpression of miR-200c induces chemoresistance in esophageal cancers mediated through activation of the Akt signaling pathway. Clin Cancer Res. 17:3029–3038. [PubMed: 21248297]
36. Akagi I, Miyashita M, Ishibashi O, Mishima T, Kikuchi K, Makino H, Nomura T, Hagiwara N, Uchida E, Takizawa T. Relationship between altered expression levels of MIR21, MIR143, MIR145, and MIR205 and clinicopathologic features of esophageal squamous cell carcinoma. Dis Esophagus.
37. Liu Q, Lv GD, Qin X, Gen YH, Zheng ST, Liu T, Lu XM. Role of microRNA let-7 and effect to HMGA2 in esophageal squamous cell carcinoma. Mol Biol Rep.
38. Chen ZL, Zhao XH, Wang JW, Li BZ, Wang Z, Sun J, Tan FW, Ding DP, Xu XH, Zhou F, Tan XG, Hang J, Shi SS, Feng XL, He J. microRNA-92a promotes lymph node metastasis of human esophageal squamous cell carcinoma via E-cadherin. J Biol Chem. 286:10725–10734. [PubMed: 21148309]
39. Wu BL, Xu LY, Du ZP, Liao LD, Zhang HF, Huang Q, Fang GQ, Li EM. MiRNA profile in esophageal squamous cell carcinoma: downregulation of miR-143 and miR-145. World J Gastroenterol. 17:79–88. [PubMed: 21218087]
40. Handy JM. Critical care transfers: the lack of information and systemic shortcomings continue. Anaesthesia. 66:337–340. [PubMed: 21453383]
41. Kano M, Seki N, Kikkawa N, Fujimura L, Hoshino I, Akutsu Y, Chiyomaru T, Enokida H, Nakagawa M, Matsubara H. miR-145, miR-133a and miR-133b: Tumor-suppressive miRNAs target FSCN1 in esophageal squamous cell carcinoma. Int J Cancer. 127:2804–2814. [PubMed: 21351259]
42. Guo Y, Chen Z, Zhang L, Zhou F, Shi S, Feng X, Li B, Meng X, Ma X, Luo M, Shao K, Li N, Qiu B, Mitchelson K, Cheng J, He J. Distinctive microRNA profiles relating to patient survival in esophageal squamous cell carcinoma. Cancer Res. 2008; 68:26–33. [PubMed: 18172293]

43. Ito T, Sato F, Kan T, Cheng Y, David S, Agarwal R, Paun BC, Jin Z, Olaru AV, Hamilton JP, Selaru FM, Yang J, Matsumura N, Shimizu K, Abraham JM, Shimada Y, Mori Y, Meltzer SJ. Polo-like kinase 1 regulates cell proliferation and is targeted by miR-593* in esophageal cancer. Int J Cancer.

44. Zhang C, Wang C, Chen X, Yang C, Li K, Wang J, Dai J, Hu Z, Zhou X, Chen L, Zhang Y, Li Y, Qiu H, Xing J, Liang Z, Ren B, Zen K, Zhang CY. Expression profile of microRNAs in serum: a fingerprint for esophageal squamous cell carcinoma. Clin Chem. 56:1871–1879. [PubMed: 20943850]