Cardio-miRNAs and onco-miRNAs: circulating miRNA-based diagnostics for non-cancerous and cancerous diseases

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INTRODUCTION
MicroRNAs (miRNAs) are short non-coding RNAs that primarily repress protein expression from target mRNAs with imperfect or perfect complementarity through mRNA degradation and translational inhibition or mRNA cleavage, respectively (Kasinski and Slack, 2011; van Rooij and Olson, 2012). For example, miR-15, miR-16, miR-20a, and miR-20b are anti-angiogenic miRNAs that repress VEGFA (VEGF) (Wang and Olson, 2009; Katoh, 2013b). miR-200 family members inhibit epithelial-to-mesenchymal transition (EMT) and self-renewal of stem cells through repression of ZEB1/2 and BMI1, respectively (Katoh and Katoh, 2008; Oishi et al., 2012; Feng et al., 2014). miRNAs regulate a variety of cellular processes, such as stemness, proliferation, senescence, apoptosis, inflammatory cytokine production, EMT, metastasis and drug resistance.

Cardiovascular diseases and cancers are the leading causes of morbidity and mortality in the world. MicroRNAs (miRNAs) are short non-coding RNAs that primarily repress target mRNAs. Here, miR-24, miR-125b, miR-195, and miR-214 were selected as representative cardio-miRs that are upregulated in human heart failure. To bridge the gap between miRNA studies in cardiology and oncology, the targets and functions of these miRNAs in cardiovascular diseases and cancers will be reviewed. ACVR1B, BCL2, BIM, eNOS, FGFR3, JPH2, MEN1, MYC, p16, and ST7L are miR-24 targets that have been experimentally validated in human cells. ARID3B, BAK1, BCL2, BMPR1B, ERBB2, FGFR2, IL6R, MUC1, SITR7, Smoothened, STAT3, TET2, and TP53 are representative miR-125b targets. ACVR2A, BCL2, CCND1, E2F3, GLUT3, MYB, RAF1, VEGF, WEE1, and WNT7A are representative miR-195 targets. BCL2L2, ß-catenin, BIM, CADM1, EZH2, FGFR1, NRAS, PTEN, TP53, and TWIST1 are representative miR-214 targets. miR-125b is a good cardio-miR that protects cardiomyocytes; miR-195 is a bad cardio-miR that elicits cardiomyopathy and heart failure; miR-24 and miR-214 are bi-functional cardio-miRs. By contrast, miR-24, miR-125b, miR-195, and miR-214 function as oncogenic or tumor suppressor miRNAs in a cancer (sub)type-dependent manner. Circulating miR-24 is elevated in diabetes, breast cancer and lung cancer. Circulating miR-195 is elevated in acute myocardial infarction, breast cancer, prostate cancer and colorectal adenoma. Circulating miR-125b and miR-214 are elevated in some cancers. Cardio-miRs and onco-miRs bear some similarities in functions and circulation profiles. miRNAs regulate WNT, FGF, Hedgehog and other signaling cascades that are involved in orchestration of embryogenesis and homeostasis as well as pathogenesis of human diseases. Because circulating miRNA profiles are modulated by genetic and environmental factors and are dysregulated by genetic and epigenetic alterations in somatic cells, circulating miRNA association studies (CMASs) within several thousands of cases each for common non-cancerous diseases and major cancers are necessary for miRNA-based diagnostics.

Keywords: Alzheimer’s disease, early diagnosis, gastric cancer, hypertension, pancreatic cancer, personalize medicine, rheumatoid arthritis, stem cells
on database screening. The targets and functions of these miRNAs in cardiovascular diseases and cancers are comprehensively reviewed, and then circulating miRNA-based diagnostics for non-cancerous and cancerous diseases are discussed with a focus on personal diversity related to genetic and environmental factors.

**REPRESENTATIVE CARDIO-miRs UPREGULATED IN HEART FAILURE**

Heart failure is a progressive decline in cardiac functions that occurs at the end stage of cardiovascular diseases, such as ischemic heart disease, hypertension and diabetes (Hill and Olson, 2008; Shah and Mann, 2011; Zhou et al., 2013b). Myocardial infarction is caused by coronary artery occlusion, which leads to the death of
cardiomyocytes in the infarcted region owing to insufficient oxygen supply. Ischemic stress occurs in surviving cardiomyocytes in the surrounding or peripheral area of an infarcted region, and then hypertrophic growth of myocardioctyes and interstitial fibrosis occur in the non-infarcted region of the heart. By contrast, persistent pressure overload causes cardiac wall thickening of the left ventricle and hypertrophic growth of cardiomyocytes. Cardiac hypertrophy leads to maladaptive remodeling of the left ventricle and eventually results in patient death owing to fatal arrhythmia and/or heart failure.

Forty-seven reports were recovered by initial screening of the literature in the PubMed and Web of Science (WoS) databases by using “heart failure,” “miRNA or miRNAs,” and “microarray.” Then, four reports on microarray analyses (van Rooij et al., 2006; Matkovich et al., 2009; Naga Prasad et al., 2009; Zhu et al., 2013) were selected by critical reading (Figure 1B). Based on the criterion “miRNA that is upregulated in at least two reports on microarray analyses,” miR-24, miR-125b, miR-195, and miR-214 were selected as candidate representative cardio-miRs that are upregulated in human heart failure (Figure 1C). Because data obtained by using microarray analyses are not always correct, upregulation of miR-24, miR-125b, miR-195, and miR-214 in human heart failure were then validated by using a deep sequencing report on miRNA profiles in human heart failure (Leptidis et al., 2013). Based on the exploration and validation processes, miR-24, miR-125b, miR-195, and miR-214 were designated the representative cardio-miRs upregulated in human heart failure (Figure 1B).

miR-24

**Human chromosomal loci of miR-24 genes**

miR-24 is derived from the miR-23b/miR-27b/miR-24-1 locus at human chromosome 9q22.32 and the miR-23a/miR-27a/miR-24-2 locus at human chromosome 19p13.13 (Figure 2).

**Targets of miR-24**

miRNA targets demonstrated in rodents are not always conserved in humans owing to species divergence (Le et al., 2009), while putative miRNA targets predicted by using bioinformatics tools, such as TargetScan (http://www.targetscan.org), PicTar (http://pictar.mdc-berlin.de) and miRanda (http://www.microrna.org), are not always true. In this review, miRNA targets validated in human cells are listed up (Table 1).

| ACVR1B (Activin receptor 1B) (Wang et al., 2008a), ARHGAP19 (Amelio et al., 2012), AURKB (Aurora kinase B) (Lal et al., 2009a), BCL2 (Srivastava et al., 2011), BCL2L11 (pro-apoptotic BIM) (Qian et al., 2011), CCNA2 (Cyclin A2) (Lal et al., 2009a), CDC2 (Lal et al., 2009a), CDK4 (Cyclin-dependent kinase 4) (Lal et al., 2009a), CDKN1B (p27 KIP1) (Giglio et al., 2013), CDKN2A (p16 INK4a) (Lal et al., 2008), DHFR (Dihydrofolate reductase) (Mishra et al., 2007), DIAPH1 (Diaphanos homolog 1) (Zhou et al., 2013a), DUSP16 (MKP7) (Zaidi et al., 2009), E2F2 (Lal et al., 2009a), eNOS (NOS3) (Meloni et al., 2013), FA1 (Fas-associated factor 1) (Qin et al., 2010), FEN1 (Lal et al., 2009a), FGFR3 (FGF receptor 3) (Rio-Machin et al., 2013), GATA2 (Fiedler et al., 2011), H2AFX (Histone H2AX) (Lal et al., 2009b), HNF4A (HNF4a) (Takagi et al., 2010), JPH2 (Junctophilin 2) (Xu et al., 2012b), LIMK2 (LIM-domain kinase 2) (Zhou et al., 2013a), MEN1 (Luzi et al., 2012), MYC (c-Myc) (Lal et al., 2009a), NET1 (NET1A or ARHGEF8) (Papadimitriou et al., 2012), PAK4 (Fiedler et al., 2011), PTPN9 (Protein tyrosine phosphatase, non-receptor type 9) (Du et al., 2013), PTPRF (Protein tyrosine phosphatase, receptor type F) (Du et al., 2013), RASA1 (Ras GAP) (Fiedler et al., 2011), SH3PXD2A (TSK5) (Amelio et al., 2012), SLC4A1 (Anion exchanger 1) (Wu et al., 2010), SPRY2 (Sprouty |
miR-24 inhibits the survival, migration, proliferation and tube formation of endothelial cells (angiogenesis) through repression of eNOS and actin cytoskeleton regulators, such as DIAPH1, LIMK2, and PAK4 (Fiedler et al., 2011; Meloni et al., 2013; Zhou et al., 2013a). miR-24 is upregulated in the chronic phase after myocardial infarction and promotes hypertrophic growth of cardiomyocytes in mouse model experiments and disturbs cardiac contraction through repression of JPH2 that is involved in the excitation-contraction coupling process of the heart (van Rooij et al., 2006; Xu et al., 2012b). Because miR-24 protects cardiomyocytes themselves and reduces cardiac fibrosis but inhibits angiogenesis and deteriorates heart failure, miR-24 is a multifunctional cardio-miR that plays good and bad roles in heart failure (Figure 3A).

Involvement of miR-24 in cardiovascular diseases

miR-24 is transcriptionally upregulated in acute myeloid leukemia (AML) with t(8;21) by the RUNX1-RUNXIT1 (AML1-ETO) fusion protein, which promotes proliferation and blocks differentiation of myeloid cells through repression of DUSP16 and subsequent activation of mitogen-activated protein kinase (MAPK) signaling (Zaidi et al., 2009). miR-24 is transcriptionally upregulated in breast cancer with lymph node metastasis in part by MYC (Li et al., 2013a), and overexpression of miR-24 in MCF-7 breast cancer cells promotes invasion and metastasis through repression of SPRY2 and subsequent MAPK activation (Li et al., 2013a), miR-24 is upregulated by the E6 and E7 oncoproteins of human papilloma virus type 16 (HPV16), which promotes proliferation through p27 repression (McKenna et al., 2012). Upregulation of miR-24 in glioblastoma promotes survival, proliferation and invasion through repression of tumor suppressor ST7L (Chen et al., 2013a). Upregulation of miR-24 in pancreatic endocrine tumors (Volinia et al., 2006) and parathyroid tumors (Luzi et al., 2012) can contribute to the progression of multiple endocrine neoplasia type 1 (MEN1) syndrome through repression of its causative gene product. miR-24 is also upregulated in colon cancer (Volinia et al., 2006), lung adenocarcinoma (Yanaihara et al., 2006), pancreatic ductal adenocarcinoma (Jamieson et al., 2012) and gastric cancer (Volinia et al., 2006; Bandres et al., 2009). Because pro-tumor miR-24 promotes survival, proliferation and invasion through repression of BIM, FAF1, p16, p27, SPRY2, and ST7L (Figure 3A), oncogenic miR-24 is upregulated in human cancers.

By contrast, miR-24 is downregulated in A549 and H1437 non-small-cell lung cancer cells owing to copy number loss of the miR-24-2 locus (Xie et al., 2013) (Table 2). miR-24 is also downregulated in prostate cancer (Volinia et al., 2006) and hepatocellular carcinoma (HCC) recurring after liver transplantation (Han et al., 2012). Because anti-tumor miR-24 promotes differentiation, growth arrest and apoptosis through repression of AURKB, BCL2, CCNA2, CDC2, CDK4, E2F2, MYC, and XIAP (Figure 3A), tumor suppressor miR-24 is downregulated in human cancers.

miR-24 functions as an oncogenic or tumor suppressor miRNA in a cancer (sub)type- or cell line-dependent manner (Figure 3A).

### Table 1 | Validated targets of miR-24, miR-125b, miR-195, and miR-214.

| miR-24  | miR-125b | miR-195 | miR-214 |
|---------|----------|---------|---------|
| ACVR1B  | ARID3B   | ACVR2A  | ASF1B   |
| ARHGAP19| BAK1     | ARL2    | BCL2L2  |
| AURKB   | BCL2     | BCL2L2  | BCL2    |
| BCL2    | BMIR1B   | BIRC5   | CADM1   |
| BIM     | CBFB     | CCND1   | CCL5    |
| CCNA2   | CDH5     | CCNE1   | CD276   |
| CDC2    | CDK4     | CDC4    | EZH2    |
| CDK4    | CDK2A2 (p14) | CDC42   | EZH2    |
| CDK11B (p27) | Dicer1 | CDK4 | FGF1R1 |
| CDK2A2 (p16) | E2F3   | CDK6   | GALNT7  |
| DHRFR   | EDN1     | E2F3    | HDGF    |
| DIAPH1  | EPO      | GLUT3   | ING4    |
| DUSP16  | EPOR     | IKKα    | ITGA3   |
| EZF2    | ERBB2    | MYB     | LTF     |
| eNOS (NOS3) | ERBB3 | RAF1    | LATS1   |
| FAF1    | ETS1     | TAB3    | MAP2K3  |
| FEN1    | FGF2R    | VAV2    | MAPK8   |
| FGF3    | IL6R     | VEGF    | NRAS    |
| GATA2   | IRF4     | WEE1    | PSMD10  |
| H2AFX   | JUN (c-Jun) | WNT7A | PTEN   |
| HNF4A   | LIN28A   | TAF2PC  |    |
| JPH2    | LIN28B   | TP53    |    |
| LIMK2   | MCL1     | TWIST1  |    |
| MEN1    | MMP13    | UBE2I   |    |
| MYC (c-Myc) | MUC1   | XBP1    |    |
| NET1    | NCOR2    |        |    |
| PAK4    | PGF      |        |    |
| PTPN9   | PRDM1    |        |    |
| PTRF    | SIRT7    |        |    |
| RASA1   | Smoothened |        |    |
| SH3PDX2A | ST18    |        |    |
| SLC4A1  | STARD13  |        |    |
| SPRY2   | STAT3    |        |    |
| ST7L    | TET2     |        |    |
| TRIB1   | TGF (TNF-α) |        |    |
| XIAP    | TNSFS4 |        |    |
| ZNF217  | TP53     |        |    |

*homolog 2* (Li et al., 2013a), ST7L (Chen et al., 2013a), TRIB3 (Tribbles pseudokinase 3) (Chan et al., 2010), XIAP (X-linked inhibitor of apoptosis) (Xie et al., 2013), and ZNF217 (Zinc finger protein 217) (Szczeryba et al., 2013) are all validated targets of miR-24 (Table 1).
miR-125b

**Human chromosomal loci of miR-125b genes**

miR-125b is derived from the miR-125b-1 and miR-125b-2 loci. miR-125b-1 is clustered with let-7a-2 and miR-100 at human chromosome 11q24.1 and miR-125b-2 is clustered with let-7c and miR-99a at human chromosome 21q21.1 (Figure 2).

**Targets of miR-125b**

ARID3B (Akhavantabasi et al., 2012), BAK1 (BCL2-antagonist/killer 1) (Shi et al., 2007), BCL2 (Zhao et al., 2012a), BCL2L2 (anti-apoptotic BCL-W) (Gong et al., 2013), BMPR1B (Setrom et al., 2009), CBFB (Core binding factor β) (Lin et al., 2011), CDH5 (VE-cadherin) (Muramatsu et al., 2013), CDKN2A (p14 ARF) (Amir et al., 2013), DICER1 (Klusmann et al., 2010), E2F3 (Huang et al., 2011a), EDN1 (Endothelin 1) (Li et al., 2010), EPO (Ferracin et al., 2013), EPOR (Ferracin et al., 2013), ERBB2 (Scott et al., 2007), ERBB3 (Scott et al., 2007), ETS1 (Zhang et al., 2011), FGFR2 (Xu et al., 2011), IL6R (Gong et al., 2013), IRF4 (Malumbres et al., 2009), JUN (c-Jun) (Kappelmann et al., 2013), LIN28A (Lin-28) (Wu and Belasco, 2012a), PTEN (BIM) (Bak et al., 2007), TFAP2C (TP53) (Bak et al., 2007).
miR-125b is a good cardio-miR that protects the heart from ischemia/reperfusion injury (Wang et al., 2014b). Ectopic miR-125b expression by using lentivirus reduces myocardial infarct size and preserves cardiac functions in a mouse experimental model of acute myocardial infarction (Wang et al., 2014b). miR-125b is a good cardio-miR that protects the heart from ischemia/reperfusion injury (Figure 3B).

Table 2 | Genetic and epigenetic alterations of miR-24, miR-125b, miR-195, and miR-214.

| miRNA gene | Chromosome locus | Disease | Genetic alteration | Epigenetic alteration | miRNA expression |
|------------|-----------------|---------|-------------------|----------------------|-----------------|
| miR-24-1   | 9q22.32         | Lung cancer | Deletion |                      | Down |
| miR-24-2   | 19p13.13        | AML and MDS | t(2;11)(p21;q24) |                       | Up  |
| miR-125b-1 | 11q24.1         | BCP-ALL | t(11;14)(q24;q32) |                      | Up  |
| miR-125b-2 | 21q21.1         | Breast cancer | Deletion | Epigenetic silencing | Down |
| miR-195    | 17p13.1         | DS-AMKL | 21 trisomy | Epigenetic silencing | Down |
| miR-214    | 1q24.3          | Liposarcoma | Gene amplification | Epigenetic silencing | Down |
|            |                 | Breast cancer | Deletion | Epigenetic silencing | Down |

AML, acute myeloid leukemia; MDS, myelodysplastic syndrome; BCP-ALL, B-cell precursor acute lymphoblastic leukemia; DS-AMKL, Down syndrome with acute megakaryocytic leukemia.

Involvement of miR-125b in human cancers

miR-125b is overexpressed in hematological malignancies owing to genetic alterations, such as chromosomal translocation and copy number gain (Table 2). miR-125b-1 at human chromosome 11q24.1 is upregulated as a result of chromosomal translocation in AML and myelodysplastic syndrome (MDS) with t(2;11)(p21;q24) (Bousquet et al., 2008; Thorsen et al., 2012) and B-cell precursor acute lymphoblastic leukemia (BCP-ALL) with t(11;14)(q24;q32) (Chapiro et al., 2010), miR-125b-2 at human chromosome 21q21.1 is upregulated as a result of copy number gain (21 trisomy) in Down syndrome with acute megakaryocytic leukemia (DS-AMKL) (Klusmann et al., 2010), which leads to the proliferation and self-renewal of hematopoietic progenitors of megakaryocytic and erythroid lineages in part through repression of DICER1 and ST18. miR-125b is also upregulated in childhood ALL with t(12;21)(p13.1;q22) (ETV6/RUNX1-ALL) (Gefen et al., 2010), pancreatic endocrine tumors (Volinia et al., 2006) and urothelial cancer at T2/T3 stages (Veerla et al., 2009). Upregulation of pro-tumor (oncogenic) miR-125b in human cancers promotes proliferation, survival and drug resistance of tumor cells through repression of BAK1, p14, ST18, and TP53 (Ozen et al., 2008) and colorectal cancer (Chen et al., 2009).

miR-125b is repressed in solid tumors as a result of deletion and epigenetic silencing (Table 2). miR-125b is downregulated in cervical cancer owing to a deletion of chromosome 11q24.1 that involves miR-125b-1 (Wilting et al., 2013) and in oral squamous cell carcinoma (OSCC) owing to deletions of chromosomes 11q or 21 involving miR-125b-1 or miR-125b-2, respectively (Henson et al., 2009). miR-125b is downregulated in breast cancer (Zhang et al., 2011) and HCC (Alpin et al., 2011) owing to epigenetic silencing induced by CpG hypermethylation of promoter region(s). miR-125b is also downregulated in prostate cancer (Poroka et al., 2007; Ozen et al., 2008) and colorectal cancer (Chen et al., 2009). Downregulation of anti-tumor (tumor suppressor) miR-125b in human cancers promotes survival, proliferation and invasion of tumor cells through de-repression of BCL2, BCL2L2,
miR-125b also functions as an oncogenic or tumor suppressor miRNA in a context-dependent manner (Figure 3B).

**miR-195**

**Human chromosomal locus of miR-195 gene**

miR-195 is derived from the miR-497/miR-195 locus at human chromosome 17p13.1 (Figure 2).

**Targets of miR-195**

miR-195 is upregulated in cardiac transgenic mice under control of the -MHC promoter (Aurora et al., 2012). miR-195 protects primary neonatal rat cardiomyocytes from apoptosis induced by ischemia-reperfusion injury and induces cell-cycle arrest in cardiac ventricles and induces cell-cycle arrest in cardiac ventricles (Porrello et al., 2011). Overexpression of miR-195 in primary neonatal rat cardiomyocytes by using adenoviral vector leads to hypertrophic growth and sarcomeric assembly, and overexpression of miR-195 in the heart of post-natal transgenic mice by using the α-MHC promoter gives rise to cardiac hypertrophy and dilated cardiomyopathy (van Rooij et al., 2006). During early post-natal development of mice, miR-195 is upregulated in cardiac ventricles and induces cell-cycle arrest in cardiomyocytes through repression of cell cycle regulators, such as Cdk2, Chek1, Birc5, Nusap1, and Spag5 (Porrello et al., 2011). Overexpression of miR-195 in the developing heart of transgenic mice by using the β-myosin heavy chain (MHC) promoter gives rise to perinatal cardiomyopathy in one line and ventricular hypoplasia and ventricular septal defects in another line (Porrello et al., 2011). Overexpression of miR-195 in primary neonatal rat cardiomyocytes by using adenoviral vector leads to hypertrophic growth and sarcomeric assembly, and overexpression of miR-195 in the heart of post-natal transgenic mice by using the α-MHC promoter gives rise to cardiac hypertrophy and dilated cardiomyopathy (van Rooij et al., 2006). In transgenic mice with the α-MHC mutation R403Q, miR-195 upregulation and subsequent repression of Cab39 in the heart leads to hypertrophic cardiomyopathy owing to inhibition of Lkb1/Stad/Cab39-dependent AMPK signaling (Chen et al., 2012). Together these facts indicate that miR-195 is a bad cardio-miR that elicits hypertrophic cardiomyopathy, dilated cardiomyopathy and heart failure (Figure 3C).

**Involvement of miR-195 in cancers**

miR-195 is upregulated in metastatic melanoma (Bhattacharya et al., 2013) and some cases of lung cancer (Volinia et al., 2006), colorectal cancer (Ding et al., 2013), prostate cancer (Volinia et al., 2006), gastric cancer (Bandres et al., 2009; Ding et al., 2013) and HCC (Ding et al., 2013). miR-195 can function as an oncogenic miRNA through repression of WEE1 kinase (Figure 3C).

By contrast, miR-195 is preferentially downregulated in breast cancer (Li et al., 2011), gastric cancer (Deng et al., 2013; Ding et al., 2013), colorectal cancer (Chen et al., 2009; Liu et al., 2010; Guo et al., 2013), HCC (Xu et al., 2009; Wang et al., 2013c), bladder cancer (Lin et al., 2012b; Itesako et al., 2014) and prostate cancer (Porkka et al., 2007). miR-195 is repressed in breast cancer (Li et al., 2011) and gastric cancer (Deng et al., 2013) owing to hypermethylation of CpG islands upstream of the miR-497/miR-195 locus. miR-195 is repressed in colorectal cancer owing to deletion of the miR-497/miR-195 locus (Guo et al., 2013), while miR-195 is repressed in colorectal adenoma mainly owing to epigenetic silencing and in part owing to deletion (Menigatti et al., 2013). miR-195 is downregulated in human cancers and precancerous lesions as a result of epigenetic silencing and deletion (Table 2). Because miR-195 is involved in repression of cell cycle accelerators (CCND1, CCNE1, CDK4, CDK6, and E2F3) and anti-apoptotic factors (BCL2, BCL2L2, and BIRC5) (Figure 3C), miR-195 functions as a tumor suppressor miRNA in various types of human cancers.

**miR-214**

**Human chromosomal locus of miR-214 gene**

miR-214 is derived from the miR-199a-2/miR-214 locus at human chromosome 1q24.3 (Figure 2).

**Targets of miR-214**

miR-214 is preferentially downregulated in breast cancer (Porkka et al., 2007), BCL2L2 (Wang et al., 2013a), β-catenin (CTNNB1) (Xia et al., 2012), BIM (Zhang et al., 2014), CADM1 (IGSF4A) (Momose et al., 2013), CCL5 (C-C motif ligand 5) (Mitra et al., 2012), CD276 (B7-H3) (Nygren et al., 2014), EZH2 (Derfoul et al., 2011), FGFR1 (Wang et al., 2013b), GALNT7 (N-acetylgalactosaminyltransferase 7) (Peng et al., 2012), HDGF (MGG1L2) (Shih et al., 2012b), ING4 (Zhang et al., 2010), ITGA3 (Integrin α3) (Penna et al., 2011), LTF (Lactoferrin) (Liao et al., 2010), LZTS1 (Xu and Wang, 2014), MAP2K3 (MEK3) (Yang et al., 2009), MAPK8 (JNK1) (Yang et al., 2009), NRAS (Huang et al., 2014a), PSMD10 (Misiewicz-Krzeminska et al., 2013), PTEN (Yang et al., 2008), TAP2C2 (AP2γ) (Penna et al., 2011), TP53 (Xu et al., 2012a), TWIST1 (Twist) (Li et al., 2012), UBE2I (UBC9) (Zhao et al., 2012b), and XBP1 (Duan et al., 2012) are all validated targets of miR-214 (Table 1).

**Involvement of miR-214 in cardiovascular diseases**

miR-214 is upregulated as a result of cardiac ischemia and heart failure. In a mouse model of ischemic cardiac injury induced by permanent ligation of the left anterior descending coronary artery, miR-214 prevents cardiomyocyte death owing to Ca2+ overload, subsequent cardiac insufficiency and cardiac fibrosis through repression of Slc8a1 (Ncx1, sodium/calcium exchanger), which is the primary Ca2+ outflow pump in cardiomyocytes (Aurora et al., 2012). miR-214 protects primary neonatal rat cardiomyocytes from apoptosis induced by ischemia-reperfusion injury and represses Bim, Camk2d (Calcmodulin kinase II delta) and Slc8a1 (Aurora et al., 2012). miR-214 also protects primary neonatal rat cardiomyocytes from apoptosis induced by H2O2 through PTEN repression (Lv et al., 2014). Overexpression of miR-214 in transgenic mice under control of the α-MHC promoter does not induce a deteriorating cardiac phenotype; however, adenovirus-mediated pri-miR-214 delivery
and lentivirus-mediated miR-214 delivery induce hypertrophic growth of primary neonatal rat cardiomyocytes in part through EzH2 repression (van Rooij et al., 2006; Yang et al., 2013). miR-214 is a bi-functional cardio-miR that plays good and bad roles (Figure 3D).

**Involvement of miR-214 in cancers**

Copy number gain of the 1q24.3 region around the miR-214 locus occurs in 35% of de-differentiated liposarcomas (Tap et al., 2011). miR-214 is upregulated in ovarian cancer (Yang et al., 2008; Xu et al., 2012a), gastric cancer (Volinia et al., 2006; Bandres et al., 2009), pancreatic cancer (Zhang et al., 2010; Jamieson et al., 2012), lung squamous cell carcinoma (Yanaihara et al., 2006), Sézary syndrome (Narducci et al., 2011), liposarcoma (Tap et al., 2011), osteosarcoma (Wang et al., 2014d) and nasopharyngeal cancer (Zhang et al., 2014). miR-214 upregulation in primary gastric cancer occurs as a result of its expression in mesenchymal stem cells (MSCs) rather than cancer cells (Wang et al., 2014a). Genetic alteration as well as tumor-stromal interaction are involved in miR-214 upregulation in human cancers.

Copy number loss of the miR-214 locus occurs in 24% of breast cancers (Derfoul et al., 2011). miR-214 is downregulated in cervical cancer (Peng et al., 2012; Wang et al., 2013a), HCC (Duan et al., 2012; Shih et al., 2012b), colorectal cancer (Chen et al., 2009), breast cancer (Derfoul et al., 2011), cholangiocarcinoma (Li et al., 2012), glioma (Zhao et al., 2012b), prostate cancer (Srivastava et al., 2013), and bladder cancer (Ratert et al., 2013).

Malignant phenotypes of cancer cells, such as proliferation, survival, drug resistance, invasion and metastasis, are induced by miR-214 upregulation through repression of BIM, CADM1, ING4, PTEN, TFAP2C, and TP53 and also by miR-214 downregulation through de-repression of BCL2L2, β-catenin, EZH2, FGFR1, GALNT7, HDGF, NRAS, TWIST1, UBE2I, and XB1 (Figure 3D). miR-214 performs oncogenic functions in some types/subtypes of human cancers and tumor-suppressor functions in other types/subtypes of human cancers.

**REGULATORY SIGNALING NETWORKS AND miRNA-BASED THERAPEUTICS**

Regulatory signaling networks are defined as mutual interactions or cross-talks of receptor tyrosine kinase (RTK), G protein-coupled receptor (GPCR) and other receptor signaling cascades (Katoh, 2013a), which are involved in orchestration of fetal development and post-natal homeostasis as well as pathogenesis of non-cancerous and cancerous diseases. WNT, FGF Hedgehog, Notch, TGF-β, BMP, Nodal, and Activin signaling cascades are major components of the regulatory signaling networks (Bailey et al., 2007; Katoh, 2007; Jayasena et al., 2008; Boulter et al., 2012; Nowell and Radtke, 2013; Coleman et al., 2014).

WNT signals are transduced through Frizzled receptors to the β-catenin-dependent (canonical) and β-catenin-independent (non-canonical) cascades (Cohen et al., 2007; Katoh and Katoh, 2007; Klaus and Birchmeier, 2008; Rao and Kühl, 2010). In the absence of canonical WNT signaling, β-catenin is phosphorylated by GSK-3β and is degraded in the proteasome system. By contrast, in the presence of canonical WNT signaling, β-catenin is released from the APC/AXIN degradation complex and activates transcription of canonical WNT target genes, such as CCND1, FGFR20, JAG1, and MYC (Figure 4A). β-catenin is a direct target of miR-200a (Saydam et al., 2009), miR-214 (Xia et al., 2012), miR-320a (Sun et al., 2012), and miR-1826 (Hirata et al., 2012). Downregulation of miR-200a, miR-214, miR-320a, and miR-1826 de-repress β-catenin and activate the canonical WNT signaling cascade in human cancers.

FGF signals are transduced to the RAS-ERK, PI3K-AKT, STAT3, and Ca²⁺-release signaling branches through FGFR1 (Figure 4B), FGFR2, FGFR3, and FGFR4 (Turner and Grose, 2010; Goetz and Mohammad, 2013; Katoh and Nakagama, 2014). FGFR1 is a direct target of miR-16 (Chamorro-Jorganes et al., 2011), miR-133b (Wen et al., 2013), miR-198 (Yang et al., 2014), miR-214 (Wang et al., 2013b), miR-382 (Mor et al., 2013), miR-424 (Chamorro-Jorganes et al., 2011), and miR-503 (Kim et al., 2013b). Upregulation of miR-382 in olfactory neuroepithelium of schizophrenia patients repress FGFRI (Mor et al., 2013). By contrast, downregulation of miR-133b and miR-214 in human cancers (Wen et al., 2013; Wang et al., 2013b) and that of miR-424 and miR-503 in pulmonary artery epithelial cells of patients with pulmonary arterial hypertension (Kim et al., 2013b) de-repress FGFRI and promote proliferation of tumor cells and endothelial cells, respectively, through FGF signaling activation.

Hedgehog signals are transduced from Patched receptors to Smoothened signal transducer, which activates GLI-dependent transcription of target genes, such as BCL2, FOXC2, JAG2, and MYCN (N-Myc) (Figure 4C). Hedgehog-Smoothened-GLI signaling cascade is involved in the regulation of cellular survival, proliferation, motility and stemness (Jiang and Hui, 2008; Katoh and Katoh, 2009; Lin and Matsui, 2012a). Smoothened is a direct target of miR-125b (Ferretti et al., 2008), miR-193b (Gonzalez-Gugel et al., 2013), miR-324-5p (Ferretti et al., 2008), miR-326 (Ferretti et al., 2008), and miR-338-3p (Huang et al., 2011b). Downregulation of miR-125b, miR-193b, miR-324-5p, miR-326, and miR-338-3p in human cancers de-repress Smoothened and promotes tumor proliferation and invasion through aberrant Hedgehog signaling activation.

miRNAs are therapeutic targets for non-cancerous diseases as well as cancers, because disease-related miRNAs dysregulate the regulatory signaling networks (Katoh and Katoh, 2008; Mo et al., 2013; Parpart and Wang, 2013; Katoh et al., 2013c). Reduction of elevated pro-disease miRNA and restoration of declined anti-disease miRNA are two major strategies of miRNA-based therapeutics. Locked-nucleic-acid-modified anti-miRNA oligonucleotides (LNA-anti-miRs) are utilized for the reduction of pro-disease miRNAs, while adenovirus and lentivirus vectors are utilized for the restoration of anti-disease miRNAs (Li et al., 2008; Kasinski and Slack, 2011; Shi et al., 2011; van Rooij and Olson, 2012). Reduction of FGFR1-targeting miRNAs for cancer therapy deteriorate diabetes and cardiac functions, because the FGFR1-P13K-AKT signaling cascade is involved in cancer promotion (Katoh et al., 2013c) as well as diabetes control (Suh et al., 2014). By contrast, restoration of miRNA targeting BAK1, BIM, or PTEN for cardiomyocyte protection promotes survival of tumor cells (Figure 3). miRNA-based therapy is at the risk of adverse effects owing to repression of verified targets in different
FIGURE 4 | WNT, FGF, and Hedgehog signaling cascades. (A) Canonical WNT signaling cascade and β-catenin. Canonical WNT signaling activation releases β-catenin from its degradation complex of APC and AXIN, which results in nuclear translocation of β-catenin and transcriptional activation of TCF/LEF-target genes, such as CCND1 (Cyclin D1), FGF20, JAG1, and MYC (c-Myc). β-catenin is a direct target of miR-200a, miR-214, miR-320a, and miR-1826. (B) FGF signaling cascades and FGFR1. FGF signals induce dimerization and auto-phosphorylation of a receptor tyrosine kinase FGFR1, which activates downstream RAS-ERK, PI3K-AKT, STAT3, and Ca²⁺-release signaling cascades. FGFR1 is a direct target of miR-16, miR-133b, miR-198, miR-214, miR-382, miR-424, and miR-503. (C) Hedgehog signaling cascade and Smoothened. Hedgehog signals are transduced from Patched receptor to Smoothened signal transducer, which activates transcription of GLI-target genes, such as BCL2, FOXC2, JAG2, and MYCN (N-Myc). Smoothened is a direct target of miR-125b, miR-193b, miR-324-5p, miR-326, and miR-338-3p.

disciplines. In addition, because multiple miRNAs repress the same target (Figure 4) and each miRNA represses multiple targets (Table 1), miRNA-based therapy is also at the risk of adverse effects owing to repression of unidentified targets in individual patients. There are many obstacles before clinical application of miRNA-based therapeutics.

CIRCULATING miR-24, miR-125b, miR-195, AND miR-214 miRNAs function within the cell where they were produced as well as in other cells that receive miRNAs secreted or released from the cell of their origin (Valadi et al., 2007; Skog et al., 2008). Extracellular miRNAs are detected in various types of body fluids, such as blood, tears, saliva, urine, vitreous humor, cerebro-spinal fluid, pleural fluid, peritoneal fluid, seminal fluid, breast milk, and amniotic fluid (Mitchell et al., 2008; Weber et al., 2010; Ragusa et al., 2013). Extracellular miRNAs are classified into miRNAs in the blood (circulating miRNAs) and those in other body fluids. Because circulating miRNAs within exosomes (Taylor and Gercel-Taylor, 2008), microvesicles (Hunter et al., 2008) and high-density lipoprotein (Vickers et al., 2011) or those conjugated with AGO2 protein (Arroyo et al., 2011) are stable, circulating miRNAs are going to be utilized as diagnostics and prognostic biomarkers (Table 3).

Circulating miR-24 is elevated in patients with breast cancer (Wu et al., 2012b; Sochor et al., 2014), lung cancer (Le et al., 2012), malignant peripheral nerve sheath tumor with the NF1 mutation (Weng et al., 2013), multiple system atrophy (Valelunga et al., 2014), osteoporotic fracture (Seeliger et al., 2014), Parkinson’s disease (Valelunga et al., 2014), preeclampsia in pregnancy (Wu et al., 2012a), rheumatoid arthritis (Murata et al., 2013) and type 1 diabetes (Nielsen et al., 2012). Wang et al. reported elevated miR-24 in type 2 diabetes patients (Wang et al.,...
Table 3 | Circulating miR-24, miR-125b, miR-195, and miR-214 in diseases.

| Circulating miRNA | Disease |
|-------------------|---------|
| miR-24 Up         | Breast cancer |
|                   | Lung cancer |
|                   | Malignant peripheral nerve sheath tumor with NF1 mutation |
|                   | Multiple system atrophy |
|                   | Osteoporotic fracture |
|                   | Parkinson's disease |
|                   | Preeclamptic pregnancy |
|                   | Rheumatoid arthritis |
|                   | Type 1 diabetes |
|                   | Type 2 diabetes |
| miR-24 Down       | Type 2 diabetes |
| miR-125b Up       | Breast cancer |
|                   | Non-alcoholic fatty liver disease |
|                   | Non-small-cell lung cancer |
|                   | Osteoporotic fracture |
| miR-125b Down     | Acute myocardial infarction |
|                   | Alzheimer's disease |
|                   | Atopic dermatitis |
|                   | Chronic kidney disease |
|                   | Melanoma |
|                   | Morbidly obese |
|                   | Psoriasis vulgaris |
| miR-195 Up        | Acute myocardial infarction |
|                   | Breast cancer |
|                   | Colorectal adenoma |
|                   | Prostate cancer |
| miR-195 Down      | Adrenocortical carcinoma |
|                   | Hepatocellular carcinoma |
|                   | Schizophrenia |
|                   | Type 2 Diabetes |
| miR-214 Up        | Breast cancer |
|                   | Malignant peripheral nerve sheath tumor |
| miR-214 Down      | Acute myocardial infarction |
|                   | Angina pectoris |

These facts clearly indicate that circulating miRNAs reported as cancer biomarkers are also dysregulated in non-cancerous diseases, and that miRNAs reported as biomarkers of non-cancerous diseases are also dysregulated in cancers (Table 3).

miRNA REGULATION BY GENETIC AND ENVIRONMENTAL FACTORS

Genetic factors are associated with individual traits and disease susceptibility (Lichtenstein et al., 2000; Zimmet et al., 2001; Milne et al., 2009). Single nucleotide polymorphisms (SNPs) and copy number variations (CNVs) are major germ-line variations. The SNP rs1434536 is located in the miR-125b-binding site within the 3′-untranslated region (UTR) of BMPR1B. The C and T alleles of the rs1434536 SNP are sensitive and resistant to BMPR1B repression by miR-125b, respectively (Sætrom et al., 2009). The homozygous T genotype of rs1434536 is associated with increased risk of breast cancer (Sætrom et al., 2009) and decreased risk of endometriosis (Chang et al., 2013). Copy number loss of the miR-195 locus occurs in autism patients (Vaishnavi et al., 2013). Copy number gain of the miR-125b-2 locus occurs in Down syndrome patients as a result of trisomy 21, which leads to elevated circulating miR-125b in pregnant women with a Down syndrome fetus (Kotlabova et al., 2013) and causes acute megakaryocytic leukemia in Down syndrome patients (Klusmann et al., 2010).

Genetic factors directly affect expression profiles and functions of miRNAs (Figure 5, upper left).

Environmental factors are also associated with disease susceptibility (Lichtenstein et al., 2000; Zimmet et al., 2001). Lifestyle (food/beverage intake, tobacco smoking, air toxin, irradiation, etc.) and chronic infection (papilloma virus, hepatitis virus, Helicobacter pylori, etc.) are environmental factors affecting individuals. Human miR-125b is downregulated in the bronchial epithelium of current smokers compared with never smokers (Schembri et al., 2009), and rat miR-125b is downregulated in the lungs of rats that were exposed to environmental smoke for 28 days (Izzotti et al., 2009). The expression profile of miRNAs in airway epithelial cells is altered by air toxins, such as diesel exhaust.

(2014c), whereas Zampetaki et al. reported reduced miR-24 in type 2 diabetes patients (Zampetaki et al., 2010).

Circulating miR-125b is elevated in patients with breast cancer (Wang et al., 2012a; Mar-Aguilar et al., 2013), non-alcoholic fatty liver disease (Pirola et al., 2014), non-small-cell lung cancer (Yuxia et al., 2012; Cui et al., 2013), osteoporotic fracture (Seeliger et al., 2014) and rheumatoid arthritis (Durox-Richard et al., 2014), whereas circulating miR-125b is reduced in patients with acute myocardial infarction (Huang et al., 2014b), Alzheimer's disease (Tan et al., 2014), atopic dermatitis (Koga et al., 2014), chronic kidney disease (Chen et al., 2013b), melanoma (Alegre et al., 2014), morbidly obese (Ortega et al., 2013), psoriasis vulgaris (Koga et al., 2014), and type 2 diabetes (Ortega et al., 2014).

Circulating miR-195 is elevated in patients with acute myocardial infarction (Long et al., 2012), breast cancer (Heneghan et al., 2010), colorectal adenoma (Kanaan et al., 2013), and prostate cancer (Mahn et al., 2011), whereas circulating miR-195 is reduced in adrenocortical carcinoma (Chabre et al., 2013), HCC (Qu et al., 2011), schizophrenia (Shi et al., 2012), and type 2 diabetes (Ortega et al., 2014).

Circulating miR-214 is elevated in patients with breast cancer (Schwarzenbach et al., 2012), malignant peripheral nerve sheath tumor (Weng et al., 2013) and ovarian cancer (Taylor and Gercel-Taylor, 2008), whereas circulating miR-214 is reduced in patients with acute myocardial infarction and angina pectoris (Lu et al., 2013).

These facts clearly indicate that circulating miRNAs reported as cancer biomarkers are also dysregulated in non-cancerous diseases, and that miRNAs reported as biomarkers of non-cancerous diseases are also dysregulated in cancers (Table 3).

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Genetic factors, such as single nucleotide polymorphism (SNP) and copy number variation (CNV), as well as environmental factors, including life style (food/beverage intake, tobacco smoking, air toxin, irradiation, etc.) and chronic infection (human papilloma virus, hepatitis virus, Helicobacter pylori, etc.) are involved in the regulation of expression profiles and functions of miRNAs (upper part). EZH2 and TET2 are epigenetic regulators that are involved in inactivation and activation of genes through repressive histone marking and CpG-island de-methylation, respectively. miRNA expression is downregulated by epigenetic silencing, while epigenetic regulators are repressed by multiple miRNAs. miRNAs and epigenetics are in the relationship of mutual regulation (lower part). Genetic and environmental factors regulate circulation miRNA profiles directly as well as indirectly through genetic and epigenetic alterations.

Epigenetics is chromatin-based genomic regulations that are involved in the modulation of expression landscapes of miRNAs and miRNAs during fetal development, post-natal homeostasis and pathogenesis of human diseases (Datta et al., 2008; Kulis and Esteller, 2010; Ordovás and Smith, 2010; Baylin and Jones, 2011; Dawson and Kouzarides, 2012). EZH2 and TET2 are representative epigenetic regulators that are repressed by miR-214 and miR-125b, respectively (Table 1). EZH2 is a human homolog of Drosophila Enhancer of zeste, which is a component of the Polycomb repressive complex 2 (PRC2) and PRC2-like complex (Sparmann and van Lohuizen, 2006). EZH2 is involved in epigenetic silencing of PRC target genes through trimethylation of histone H3 lysine 27 (H3K27me3) and CpG hypermethylation of promoters (Figure 5, lower part). Because EZH2 is a target of miR-25 (Esposito et al., 2012), miR-26a (Sander et al., 2008), miR-30d (Esposito et al., 2012), miR-101 (Varambally et al., 2008), and miR-214 (Derfoul et al., 2011), downregulation of miR-25, miR-26a, miR-30d, miR-101, and miR-214 in human cancers are associated with EZH2 upregulation and malignant phenotypes. TET2 is involved in promoter de-methylation through enzymatic conversion of 5-methylcytosine (5mC) to 5-hydroxymethyl-cytosine (5hmC) (Ito et al., 2010). Loss-of-function TET2 mutations occur in patients with myeloproliferative neoplasms, MDS and AML (Shih et al., 2012a), while upregulation of TET2-targeting miRNAs, such as miR-7, miR-29b, miR-29c, miR-101, and miR-125b, occur in AML patients with wild-type TET2 (Cheng et al., 2013). miRNAs targeting EZH2 and TET2 alter epigenetic regulations of disease-associated genes. By contrast, disease-associated miRNAs are epigenetically silenced owing to promoter CpG hypermethylation in human diseases (Table 2). Epigenetic alterations also play a key role for the regulation of miRNA profiles in somatic cells (Figure 5, lower part).

Genetic and environmental factors dynamically alter expression profiles of miRNAs in individuals and also indirectly alter miRNA profiles through genetic and epigenetic alterations in patients with non-cancerous diseases and cancers (Figure 5).

CIRCULATING miRNA-BASED DIAGNOSTICS

Circulating miR-195 is upregulated in colorectal adenoma (Kanaan et al., 2013); however, miR-195 in colorectal adenoma...
Dysregulation of circulating miRNAs occur in a variety of human disease. Circulating miRNA profiles in several thousands of cases each for non-cancerous common diseases (blue box) and major cancers (red box) should be investigated for the establishment of miRNA-based diagnostic platform.

Because circulating miRNA profiles are dynamically regulated by genetic and environmental factors (Figure 5), circulating miRNA profiles of cancer patients reflect co-existing non-cancerous diseases or individual whole-body conditions. Therefore, circulating miRNA association studies (CMASs) within several thousands of cases each for common non-cancerous diseases as well as major cancers (Figure 6) should be carried out to establish a reliable and robust platform of miRNA-based diagnostics.

CONCLUSION
Cardio-miRs and onco-miRs bear some similarities in functions and circulation profiles. miRNAs modulate the regulatory signaling networks that are involved in orchestration of embryogenesis and homeostasis as well as pathogenesis of human diseases. Circulating miRNA profiles within several thousands of cases each for non-cancerous and cancerous diseases are necessary for the establishment of miRNA-based diagnostics.

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