Hypoxia Induced Changes of Exosome Cargo and Subsequent Biological Effects

Hongxia Jiang [1,2], Hanqiu Zhao [1,2], Mengzhe Zhang [1,2], Yuanzhou He [1,2], Xiaochen Li [1,2], Yongjian Xu [1,2] and Xiansheng Liu [1,2]*

[1] Department of Pulmonary and Critical Care Medicine, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China, [2] Key Laboratory of Pulmonary Diseases, National Ministry of Health of The People's Republic of China, Wuhan, China

Exosomes are small extracellular vesicles that are secreted by almost all types of cells and exist in almost all extracellular spaces. As an important mediator of intercellular communication, exosomes encapsulate the miRNA, lncRNA, cirRNA, mRNA, cytokine, enzyme, lipid, and other components from the cytoplasm into its closed single membrane structure and transfer them to recipient units in an autocrine, paracrine, or endocrine manner. Hypoxia is a state of low oxygen tension and is involved in many pathological processes. Hypoxia influences the size, quantity, and expression of exosome cargos. Exosomes derived from hypoxic tumor cells transfer genetics, proteins, and lipids to the recipient units to exert pleiotropic effects. Different donor cells produce different cargo contents, target different recipient units and lead to different biological effects. Hypoxic exosomes derived from tumor cells uptaken by normoxic tumor cells lead to promoted proliferation, migration, and invasion; uptaken by extracellular space or liver lead to promoted metastasis; uptaken by endothelial cells lead to promoted angiogenesis; uptaken by immune cells lead to promoted macrophage polarization and changed tumor immune microenvironment. In addition to various types of tumors, hypoxic exosomes also participate in the development of diseases in the cardiovascular system, neuron system, respiratory system, hematology system, endocrine system, urinary system, reproduction system, and skeletomuscular system. Understanding the special characteristics of hypoxic exosomes provide new insight into elaborating the pathogenesis of hypoxia related disease. This review summarizes hypoxia induced cargo changes and the biological effects of hypoxic exosomes in tumors and non-malignant diseases in different systems.

Keywords: hypoxia, exosome, cargo, tumor, changes

INTRODUCTION

Hypoxia, a state of inadequate oxygen supply, is a common feature of many different diseases, like solid tumor (1), hypoxia induced pulmonary arterial hypertension (2), sleep-disordered breathing (3), hypoxic kidney injury (4), placental hypoxia (5) and so on. The main molecular mechanism to sense oxygen stress is Hypoxia Induced Factors (HIFs), which functions as a master regulator of oxygen homeostasis in all metazoan species (6). HIFs are dimeric proteins composed of an oxygen-sensitive - subunit (HIF-1α, HIF-2α, or HIF-3α) and a β-subunit (HIF-1β) (7). HIF-1α is ubiquitously expressed whereas HIF-2α and HIF-3α are selectively expressed in certain tissues (8). Under normoxia, HIF-α subunits are hydroxylated by prolyl hydroxylases (PHD1-3) and recognized and targeted for proteasomal degradation. The activity of PHD1-3 is oxygen dependent, so under hypoxia, the rate of HIF-α hydroxylation is suppressed (9), accumulated HIF-1α dimerizes with HIF-1β and binds to hypoxia-responsive elements(HREs) in promoters of target genes to promote a concerted transcriptional response (10).

Hundreds of genes are now known to respond directly or indirectly to hypoxia *via* HIFs (11). Human large-scale genomic sequencing projects have revealed that less than 2% of transcriptional output encodes for proteins, while the remaining genome encrypts different classes of non-coding RNAs, including miRNA, lncRNA, cirRNA, and so on (12, 13). Hypoxia upregulates or downregulates the expression of some key factors, including the non-coding RNAs, as well as mRNAs, proteins, and lipids in hypoxic cells and the hypoxic exosomes secreted by these cells. The upregulated or downregulated key factors were transferred to recipient cells or tissues through exosomes, leading to various biological effects involving angiogenesis, invasion, metastasis, and immune escape in tumor development (14), and other hypoxia involved disease mentioned above. Recently, myriads of research exploring hypoxia induced changes in exosomes loads and subsequent effects have emerged rapidly. This review tries to focus on the impact of hypoxia on exosomes secretion and cargo changes, and summarizing various biological results in various diseases.
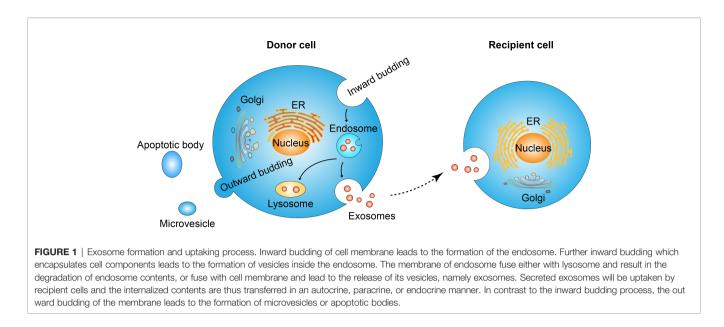
BIOGENESIS AND RECIPIENCE OF EXOSOMES

The exosome is one kind of extracellular vesicle. Extracellular vesicles are mainly classified into three types according to biogenesis. Namely, apoptotic bodies range from 500-2000 nm, microvesicles range from 200-2000 nm and exosomes range from 40-200 nm (15). The nomenclature of extracellular vesicles has not reached a broad agreement today (16–18), and in this review, we only discuss those studies clearly stated "exosome" in their elaboration. The formation of exosomes is the budding process of membrane organizations. Firstly, the inward budding of the cell membrane leads to the formation of the endosome (19). Endosome goes through different stages:

early endosome, recycling endosome, and end endosome (20), during the maturation from early endosome to end endosome, further inward budding inside an intracellular endosome occurs and leads to the formation of multivesicle body, characterized by the presence of intraluminal vesicles (21–23). During the process of endosome inward budding, cytosolic contents, transmembrane, and peripheral proteins are incorporated into the invaginating membrane (24). The membrane of the multivesicle body fuses either with lysosome leading to the degradation of vesicles contents (25) or fuses with cell membrane leading to the release of vesicles contents, namely exosomes (26, 27). In contrast to inward budding, the outward budding process leads to the formation of microvesicles or apoptotic bodies (15).

Extracellular vesicles were first found during the maturation of sheep reticulocytes in 1983 (28). In the beginning, people thought it was just a kind of cell debris for the disposal of cell waste (22, 29). Later, researchers found that exosomes encapsulate RNAs, DNA, proteins, and lipids, and play a significant role both in cell to cell and cell to its milieu communication by transferring its encapsulated contents, both locally and distally (30, 31) and these contents are not randomized distributed but a specific subset from endosomes, the plasm membrane and the cytosol (32), suggesting an endosomal sorting complex required for transport (ESCRT) during exosome formation. The ESCRT dependent and independent manner of sorting mechanism are described in detail by Guillaume van Niel (33). As for the uptake mechanisms of exosomes by recipient cells, at least five mechanisms are involved, including clathrin-dependent, micropinocytosis, lipid-raft, membrane fusion, and caveolin-dependent endocytosis (34). In another word, exosomes sort specific contents to load and uptaken by specific recipient cells to exert their function (**Figure 1**). In addition, exosomes are secreted by almost all kinds of cells (35, 36) in biological and pathological conditions. And exists in almost all body fluids like blood, urine, saliva, synovial fluid, bile, cerebrospinal fluid, bronchoalveolar fluid, nasal fluid, uterine fluid, amniotic fluid, breast milk, feces, seminal plasma (30). It has been reported that many factors, including hypoxia, the change in pH, temperature, oxidative stress, radiation, and shear stress can affect the secretion level and composition of exosomes (37). Here, we focus on the impact of hypoxia on the production and cargo changes of exosomes and subsequent biological effects, and we made a brief summary in **Table 1**.

HYPOXIC EXOSOMES PROMOTE THE DEVELOPMENT OF DIFFERENT TYPES OF TUMORS

Hypoxia is a common phenomenon in the solid tumor microenvironment. The release of exosomes and the contents of exosomes change dramatically under a short supply of oxygen, resulting in altered biological effects. Here, we make a summary of hypoxia induced changes in the cargos and subsequent

FIGURE 1 | Exosome formation and uptaking process. Inward budding of cell membrane leads to the formation of the endosome. Further inward budding which encapsulates cell components leads to the formation of vesicles inside the endosome. The membrane of endosome fuse either with lysosome and result in the degradation of endosome contents, or fuse with cell membrane and lead to the release of its vesicles, namely exosomes. Secreted exosomes will be uptaken by recipient cells and the internalized contents are thus transferred in an autocrine, paracrine, or endocrine manner. In contrast to the inward budding process, the out ward budding of the membrane leads to the formation of microvesicles or apoptotic bodies.

biological effects of tumor cell derived exosomes in various types of tumor, including glioma, ovarian cancer, breast cancer, prostate cancer, lung cancer, pancreatic cancer, colorectal cancer, liver cancer, oesophageal squamous cell carcinoma, and other types of cancer we retrieved (**Figure 2**).

In glioma, hypoxia promoted the secretion of glioma-derived exosomes and hypoxic exosomes which contain higher expression of miR-10a and miR-21 have a stronger ability than normoxic exosomes to induce myeloid-derived suppressor cells (MDSCs) expansion and potentiate their immunosuppressive functions (39). Hypoxic exosomes isolated from glioblastoma multiforme (GBM) cells have different miRNA and protein quantitative profiles and they were potent inducers of proliferation and angiogenesis *in vivo* and *in vitro*. Moreover, exosomes derived from the hypoxia condition show increased autocrine, promigratory activation of GBM cells (1, 38, 40). Several miRNAs were reported to be upregulated in hypoxic exosomes compared to normoxic exosomes and resulted in further deterioration of glioma. MiR-1246 and miR-10b-5p were enriched in exosomes that produced in the hypoxic microenvironment, and such exosomes were transferred to normoxic glioma cells, promoting their migration and invasion *in vitro* and *in vivo* (44). Plus, miR-1246 containing exosomes markedly induced M2 macrophage polarization, facilitating the formation of the immunosuppressive microenvironment, thus contributing to promoted glioma proliferation, migration, and invasion *in vitro* and *in vivo* (48). MiR-155-3p and interleukin 6 (IL-6) were highly expressed in hypoxic glioma-derived exosomes, and such exosomes also induced M2-like macrophage polarization and eventually promotes glioma progression (43). MiR-182-5p expression was significantly upregulated in glioblastoma secreted exosomes in hypoxic conditions. Exosomal miR-182-5p was uptaken by human umbilical vein endothelial cells, leading to KLF2 and KLF4 suppression and VEGFR accumulation, thus promoting tumor angiogenesis (47). miR-301a was also reported to be encapsulated in the hypoxic exosomes dervied from

glioblastoma cells, and was transferred to normoxic glioblastoma cells to promote radiation resistance by targeting the tumor suppressor gene TCEAL7 (50). In addition to miRNAs, some proteins were also reported to be increased in the hypoxic exosomes. Hypoxia upregulated the expression of lysyl oxidase homolog 2 and VEGF-F in the glioblastoma derived exosomes, the latter was able to enhance the blood-brain-barrier by interrupting the expression of claudin-5 and occludin (51, 190). Hypoxia also upregulated the monocarboxylate transporter 1(MCT1) and the cluster of differentiation 147 (CD147) in glioma cells and its secreted exosomes, transporting these pro-oncogenic molecules to recipient neighboring cells led to promoted tumor progression (49).

Besides contributing to glioma progression, miRNA containing exosomes also contributed to ischemic injury of peritumoral neurons. MiR-199a-3p was upregulated in a HIF-α dependent way in hypoxic culturing glioma cells derived exosomes. Exosomal miR-199a-3p mediated the oxygen-glucose deprivation (OGD)/reperfusion neuronal injury process by suppressing the mTOR signaling pathway (46). In patients with glioma, serum exosome miR-210 was significantly increased compared to healthy controls. The increased expression level reflected the hypoxic state of glioma patients by positively associated with HIF-α, and it also reflected the changes in malignant glioma loads (42). Apart from miRNA, lncRNA and protein were also encapsulated and transferred by exosomes in hypoxic microenvironment. It was reported that hypoxic glioma stem cells transferred lnc01060 containing exosomes to glioma cells, activating prooncogenic signaling and promoting disease progression. In addition, lnc01060 was upregulated in glioma patients and was significantly correlated with tumor grade and poor clinical prognosis (45). The protein content of secreted exosomes from GBM cells was able to induce differential gene expression in recipient glioma cells. Thus, intercellular communication was facilitated *via* exosomes secreted from hypoxic GBM cells. And prominent changes of

TABLE 1 | Summary of hypoxia induced changes of exosome cargos from different donor units to their corresponding target recipient units, and leading to different biological effects.

Related systems	Donor units	Hypoxia induced changes of exosome contents	Recipient units	Biological effects	Ref
Tumors	Glioma cells	Hypoxia-regulated mRNAs and proteins (matrix metalloproteinases, IL-8, PDGFs, caveolin 1, and lysyl oxidase) ↑	Endothelial cells, glioma cells	Promoted angiogenesis ex vivo and in vitro; increased autocrine, promigratory activation of GBM cells	(1)
	Glioblastoma cells (GBM)	Tissue factor ↑	Endothelial cells	Elicited an angiogenic phenotype	(38)
	Glioma tumor tissue	miR-10a ↑, miR-21 ↑	Myeloid-derived suppressor cells (MDSCs)	Induced MDSC expansion and activation	(39)
	CD133+ U87 glioblastoma cells	4 miRNAs ↑, 6 miRNAs ↓	Human brain microvascular endothelial cells (HBMEC) and U87 glioma cells	Increased cell viability	(40)
	Glioblastoma cells	Protein-lysine 6-oxidase (LOX) ↑, thrombospondin-1 (TSP1) ↑, vascular derived endothelial factor (VEGF) ↑ and a disintegrin and metalloproteinase with thrombospondin motifs 1 (ADAMTS1) ↑	Recipient glioma cells, endothelial progenitor cells (EPCs), neighboring normoxic tumor cells and possibly in surrounding stromal cells,	Induced differential gene expression in recipient glioma cells, increased various angiogenic, induced marked changes in the expression of genes	(41)
	Glioma tumor tissue	miR-210 ↑	Not mentioned	Served as a diagnostic, prognostic and hypoxic biomarker to reflect glioma status and hypoxic signatures.	(42)
	Glioma	Interleukin 6 (IL-6) ↑, miR-155-3p ↑	Macrophages, nude mice	Promoted glioma proliferation and migration in vitro and in vivo	(43)
	Hypoxic glioma	miR-1246 ↑, miR-10b-5p ↑	Normoxic glioma	Promoted migration and invasion	(44)
	Hypoxic Glioma Stem Cell	lnc01060 containing	Glioma	Promoted Progression	(45)
	Glioma	miRNA-199a-3p ↑	Peritumoral Neurons	Increased the ischemic injury of peritumoral neurons by inhibiting the mTOR pathway	(46)
	Glioblastoma cells	miR-182-5p ↑	Human umbilical vein endothelial cells	Promoted tumor angiogenesis, enhanced vascular permeability and tumor trans endothelial migration	(47)
	Glioma	miR-1246 ↑	M2 macrophage	Markedly induced M2 macrophage polarization, which subsequently promoted glioma proliferation, migration and invasion in vitro and in vivo	(48)
	Hypoxic glioma cells	MCT1 ↑, CD147 ↑	Neighboring cells	Promoted tumor progression	(49)
	Hypoxic glioblastoma cells	miR-301a	Normoxic glioma cells	Promote radiation resistance	(50)
	hypoxic glioblastoma cells	VEGF-A ↑	None	Enhanced the permeability of blood-brain-barrier	(51)
	Ovarian cancer cells	Potent oncogenic proteins-STAT3 and FAS	Immortalized fallopian tube secretory epithelial cells (FT)	Pro-tumorigenic in mouse fallopian tubes, cisplatin efflux via exosomes was significantly increased	(52)
	Ovarian cancer cells	miR-199a-5p ↓	Endothelial cells	Suppressing tumor metastasis	(53)
	Epithelial ovarian cancer (EOC)	miRNA-940 ↑	Macrophages	Stimulating TAM polarization	(54)
	Endometrial cancer KEL cells	miRNA-21 ↑	Monocyte cell line THP-1	Promoted monocyte THP-1 cell transformation to M2-like polarization macrophages	(55)
	Epithelial ovarian cancer cells	miR-21–3p ↑, miR-125 b-5p ↑, miR-181 d-5p ↑	Macrophages	Induced the polarization of M2 macrophages, which promoted EOC cell proliferation and migration in a feedback loop	(56)
	Breast cancer cell lines	Transforming growth factor-β, TGF-β	T cells	Suppressing T cell proliferation	(57)
	Breast cancer cells	MiR210 ↑	Surrounding tissue in the tumor microenvironment	Promoted their own survival and invasion	(58)
	Breast cancer cells	miR-210 ↑	Neighboring cells	Promoted angiogenesis	(59)
	Breast cancer cells	lncRNA SNHG1 ↑	HUVECs	promote the proliferation, migration and angiogenesis of HUVECs	(60)
	Breast cancer associated fibroblasts	GPR64 ↑	Breast cancer cells	Enhanced cancer cell invasive abilities	(61)
	Bone marrow-derived human mesenchymal stem cells	miR-let-7f ↑	4T1 cells	Attenuated proliferation and invasion	(62)

(Continued)

TABLE 1 | Continued

Related systems	Donor units	Hypoxia induced changes of exosome contents	Recipient units	Biological effects	Ref
	Natural killer (NK) cells: NK92 or NK92-hIL-15 cells	NK cells-specifically FasL ↑, perforin ↑, and granzyme B ↑	MCF-7 breast cancer and A2780 ovarian cancer cells	Significantly increased cytotoxicity, enhanced inhibition of cell proliferation	(63)
	Human prostate cancer cell line PC3 cells	MMP2 ↑, MMP9 ↑, extracellular matrix proteins (fibronectin and collagen) ↑	Nude mice	Promoted matrix metalloproteinases (MMPs) activity in several putative metastatic sites	(64)
	Bladder cancer cells	lncRNA-UCA1 ↑	Bladder cancer UMUC2 cells with low expression of lncRNA-UCA1	Promoted cell proliferation, migration and invasion. promote tumor growth and progression through epithelial-mesenchymal transition, *in vitro* and *in vivo*	(65)
	LNCaP and PC3 cells	MMP-2 ↑, MMP-9 ↑, cytokines and signaling molecules (TGF-β2, TNF1α, IL6, TSG101, Akt, ILK1, β-catenin) ↑	LNCaP and PC3 cells	Increased the invasiveness and motility of naïve LNCaP and PC3 cells, respectively. Promoted prostasphere formation by both LNCaP and PC3 cells, and enhanced α-SMA (a CAF biomarker) expression in prostate stromal cells	(66)
	Prostate cancer (PCa) cells	Lactic acid	None	Removed metabolic waste	(67)
	RCC cell lines	CA9	Human umbilical vein endothelial cells (HUVEC)	Promoted migration and tube formation, increased MMP2 expression, enhanced angiogenesis	(68)
	Hypoxic renal cell carcinoma cells	lncHILAR ↑	Normoxic renal cell carcinoma cells	Promoted RCC cell invasion and metastasis	(69)
	LNCaP cells	Top 11 miRNAs ↑, Top 9 miRNAs ↓	Not mentioned	Potential usefulness as a biomarker of hypoxia in PCa patients	(70)
	Hypoxic tumor-associated macrophages	miR-155-5p ↑	Clear cell renal cell carcinoma	Promoted renal cell carcinoma (RCC) progression	(71)
	Plasma	miR-92a-3p ↑, miR-709 ↑, miR-671-5p ↓, miR-882 ↓	Mouse TC1 and human adenocarcinoma cells lines	Significantly promoted TC1 malignant properties, enhanced proliferation and migration of human adenocarcinoma cells	(72)
	Lung cancer cells	miR-23a ↑	Endothelial cells	Enhanced angiogenesis, increased vascular permeability and cancer transendothelial migration	(73)
	Lung cancer cell lines	TGF-β and IL-10	HMEC-1	Promoting the migration of cancer cells	(74)
	Bone marrow-derived mesenchymal stem cells (BMSCs)	miR-193a-3p, miR-210-3p and miR-5100	Lung cancer cells	promoted cancer cell invasion and EMT	(75)
	Tumor tissue of lung adenocarcinoma (LUAD)	lncRNA-p21 ↑	Human umbilical vein endothelial cells (HUVECs)	Promoting tube formation and enhancing tumor cell adhesion to endothelial cells	(76)
	Hypoxic LUAD cells	miR-31-5p	Normoxic LUAD cells	Significantly enhanced the migration and invasion, contributing to tumor progression both *in vitro* and *in vivo*	(77)
	LUAD cell lines	circSETDB1	Normoxic LUAD cells.	Improved the migration, invasion, and proliferation	(78)
	A549 cells	miR101 ↓	THP-1 cells	Activated macrophages to induce inflammation in the tumor microenvironment	(79)
	A549 cells	HIF-1α/COX-2 ↑, miR-135b and miR-210 ↑	A549 cells	promoted the proliferation, migration, and angiogenesis of other A549 cells	(80)
	Hypoxic NSCLC cells	miR-21 ↑	Normoxic NSCLC cells	Facilitated normoxic cell resistance to cisplatin	(81)
	Cisplatin-resistant NSCLC cells	PKM2 ↑	NSCLC cells, cancer-associated fibroblasts (CAFs)	Elicted cisplatin resistance in sensitive NSCLC cells	(82)
	Non-Small-Cell Lung Cancer Cell	miR-582-3p ↑	Normoxic NSCLC cells	Promoted the proliferation, migration, and invasion of normoxic NSCLC cells	(83)
	A549 cells	Angiopoietin-like 4 (ANGPTL4)	A549 cells or human umbilical vein endothelial cells (HUVECs)	Promoted the proliferation, migration and invasion of A549 cells as well as the proliferation and angiogenesis of HUVECs.	(84)
	Pancreatic cancer cells	miR-301a-3p ↑	Activate macrophages to the M2 phenotype in a HIF-1α or HIF-2α-dependent manner	Facilitated the migration, invasion, and epithelial-mesenchymal transition of pancreatic cancer cells	(85)
	BSp73ASML cells	C4.4A- and α6β4-associated MMP14	Not mentioned	Promoted migration on LN111 and LN332	(86)

(Continued)

TABLE 1 | Continued

Related systems	Donor units	Hypoxia induced changes of exosome contents	Recipient units	Biological effects	Ref
	Hypoxic pancreatic cancer cells	circZNF91 ↑	Normoxic pancreatic cancer cells	Enhanced gemcitabine resistance	(87)
	Pancreatic stellate cells (PSCs)	miR-4465 ↑, miR-616-3p ↑	Pancreatic cancer cells	Promoting PC cell proliferation, migration, and invasion	(88)
	Pancreatic cancer (PC) cells	lncRNA UCA1 ↑	HUVECs	Promoted angiogenesis and tumor growth through the miR-96-5p/AMOTL2/ERK1/2 axis	(89)
	Pancreatic ductal adenocarcinoma (PDAC) cells	miR-30b-5p ↑	HUVEC	Promoted tube formation and angiogenesis	(90)
	Pancreatic stellate cells (PSCs)	lncRNA UCA1 ↑	Pancreatic cancer cells	Promoted Gemcitabine resistance and tumorigenesis by regulating the EZH2/SOCS3 axis	(91)
	Colorectal cancer (CRC) cells	Wnt4	Endothelial cells	Promoted angiogenesis through exosome-mediated Wnt/β-catenin signaling in endothelial cells	(92)
	Primary colorectal cancer (CRC)	miR-135a-5p ↑	liver	Initiated LATS2-YAP-MMP7 axis to promote the occurrences of CRC liver metastasis	(93)
	Hypoxic colorectal cancer cells	miR-210-3p ↑	Normoxic tumor cells	Elicited protumoral effects	(94)
	colorectal cancer	miR-361-3p ↑	colorectal cancer cells	Facilitated cell growth and suppressed cell apoptosis	(95)
	Hypoxic colorectal cancer cells	Circ-133 ↑	Normoxic colorectal cancer cells	Promoted cancer metastasis by acting on miR-133a/GEF-H1/RhoA axis	(96)
	Hypoxic colorectal cancer (CRC) cells	miR-410-3p ↑	Normoxic colorectal cancer (CRC) cells	Enhanced tumor progression	(97)
	Hypoxic colorectal cancer cells	Wnt4 ↑	Normoxic colorectal cancer cells	Promoted the migration and invasion abilities of normoxic CRC cells	(98)
	Hypoxic colorectal cancer cells	miR-1255b-5p ↓	Normoxic colorectal cancer cells	Enhanced epithelial-to-mesenchymal transition	(99)
	Colon cancer cells	Not mentioned	Colon cancer cells	Promoted self-growth	(100)
	Hypoxic colorectal cancer cell lines	miR-486-5p ↓, miR-181a-5p ↓, miR-30d-5p ↑	Not investigated	Retrieved as circulating markers of high-risk locally advanced rectal cancer	(101)
	Cancer-associated fibroblast	circEIF3K ↑	Human colorectal cancer cells HCT116 and SW620	Contributed to the proliferation, invasion and tube formation of recipient cells	(102)
	Granulocytic myeloid-derived suppressor cells	S100A9 ↑	Colorectal cancer cells	Promoted CRC cell stemness and growth	(103)
	Oesophageal squamous cell carcinoma cells	miR-340-5p ↑	Oesophageal squamous cell carcinoma cells	Alleviated radiation-induced apoptosis and accelerated DNA damage repair, leading to radioresistance	(104)
	ESCC Cells	hsa-circ-0048117↑	Macrophages	Promoted M2 polarization and M2 macrophages could enhance the ability of invasion and migration of tumor cells	(105)
	Nasopharyngeal carcinoma (NPC)	MMP-13	normoxic cells	Enhanced migration and invasiveness and induce microenvironment changes to promote NPC aggressiveness, enhancing the metastases of normoxic cells	(106)
	Adipocyte	miR-433-3p ↓	Nasopharyngeal carcinoma cells	Promoted proliferation, migration, and lipid accumulation	(107)
	Hypoxic hepatocellular carcinoma cells	miR-1273f ↑	Normoxic hepatocellular carcinoma cells	Enhanced the proliferation, migration, and invasiveness in addition to epithelial-to-mesenchymal transition (EMT)	(108)
	Hypoxic hepatocellular carcinoma	miR-155 ↑	HUVECs	Enhanced tube formation of HUVECs	(109)

(Continued)

TABLE 1 | Continued

Related systems	Donor units	Hypoxia induced changes of exosome contents	Recipient units	Biological effects	Ref
	HepG2 cells	miR23a ↑	HUVECs	Induced angiogenesis.	(110)
	Hypoxic hepatocellular carcinoma Huh7 cells	Not mentioned	Normoxic hepatocellular carcinoma Huh7 cells	Promoted cell proliferation, migration and invasion	(111)
	hepatocellular carcinoma (HCC) cells	lncRNA HMMR-AS1 ↑	Macrophages	Promoted the M2 macrophages polarization and accelerated the progression of HCC	(112)
	Oral squamous cell carcinoma (OSCC)	miR-21 ↑	Normoxic cells	Promoted prometastatic, increased the migration and invasion of OSCC cells	(113)
	OSCC cell lines: Cal-27 and SCC-9	miR-21 ↑	Gammadelta T cells	Enhanced the suppressive effect of myeloid-derived suppressor cells (MDSCs) on gammadelta T cells	(114)
	Esophageal squamous cell carcinoma (ESCC) cells	Not mentioned	HUVECs, nude mice	Promoted proliferation, migration, invasion and tube formation of HUVECs. Enhanced the tumor growth and lung metastasis in nude mice models	(115)
	Gastric cancer cells	miR-301a-3p ↑	Gastric cancer cells	Facilitated GC proliferation, invasion, migration, and epithelial-mesenchymal transition	(116)
	Papillary thyroid cancer (PTC)	miR-181a ↑	Human umbilical vein endothelial cells (HUVECs)	Promoted proliferation and capillary-like network formation	(117)
	A431 carcinoma cells	Proteins	Not mentioned	Enhanced angiogenic and metastatic potential, modulate their microenvironment and facilitate angiogenesis and metastasis.	(118)
	Melanoma cell lines	miR-494-5p ↑, miR-4497 ↑, miR-513a-5p ↑, miR-6087 ↑, miR-4454 ↑, miR-4299 ↑	Neighboring melanoma cells	Facilitated invasion and metastases.	(119)
	Melanoma cell lines: CRL-1424 and CRL-1675 cells	miRNAs were differently expressed in hypoxic exosomes	THP1 macrophages	Increased M1 markers (CXCL10 and IL6) in monocytes	(120)
	Mouse melanoma B16-F0 cells	CSF-1 ↑, CCL2 ↑, FTH ↑, FTL ↑, and TGF-beta ↑, miRNA let-7a ↑	Macrophages	Promoted M2-like polarization, enhanced oxidative phosphorylation of macrophages	(121)
	Endothelial cells	1,354 proteins (top changed): SEMG1 ↑, CO4A ↑, LOXL2 ↑, CO1A1 ↓, AN32E ↓, EPN1 ↓; 1,992 mRNAs(top changed): NDRG1 ↑, BNIP3 ↑, CIRBP ↓	Extracellular matrix	Cytoskeletal and extracellular matrix rearrangements	(122)
	Hypoxic Ewing's sarcoma (EWS) cells	miR-210 ↑	Ewing's sarcoma (EWS) cells	Promoted sphere formation, a stem-like phenotype	(123)
	Hypoxic multiple myeloma cells	miR-1305 ↑	Macrophages	Promoted tumor development	(124)
	Hypoxia-resistant multiple myeloma cells	miR-135b ↑	Endothelial cells	Suppressing the target factor-inhibiting hypoxia-inducible factor 1 (FIH-1), enhance endothelial tube formation	(125)
Cardiovascular system	Cardiomyoblast cells (H9c2)	miR-21-5p, miR-378-3p, miR-152-3p, and let-7i-5p	None	Mitigated hypoxia-induced H9c2 cells apoptosis	(126)
	Mouse bone marrow-derived MSCs	miR-210 ↑, neutral sphingomyelinase 2 (nSMase2) ↑	Infarcted heart	Significantly higher survival, smaller scar size and better cardiac functions recovery; increased vascular density, lower cardiomyocytes (CMs) apoptosis; reduced fibrosis and increased recruitment of cardiac progenitor cells in the infarcted heart	(127)
	Endothelial colony-forming cells (ECFCs)	miR-10b-5p ↓, neutral sphingomyelinase 2 (N-SMase2) ↓	Cardiac fibroblast	Anti-fibrotic effects of hypoxic exosomes were abolished	(128)
	Endothelial cells	6 miRNAs (including has-mir-383-3p) differently expressed	Endothelial cells	Promoted increased permeability and dysfunction of endothelial cells in vitro	(129)

(Continued)

TABLE 1 | Continued

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Hypoxia Induced Exosomal Change and Effects

Related systems	Donor units	Hypoxia induced changes of exosome contents	Recipient units	Biological effects	Ref
	Mesenchymal stem cells (MSCs)	lncRNA-UCA1 ↑	Rats with myocardial infarction	Played a cardioprotective role	(130)
	Cardiomyocytes	circHIPK3 ↑	Cardiac microvascular endothelial cells	Inhibiting miR-29a activity, leading to increased IGF-1 expression, exhibiting CMVECs protection	(131)
	Cardiomyocytes	circHIPK3 ↑	Cardiac endothelial cells, mice with myocardial infarction	Promoted cardiac endothelial cell migration, proliferation, and tube formation in vitro; effectively reduced the infarct area and promote angiogenesis in the border surrounding the infarcted area	(132)
	Cardiomyocytes	miR-30a ↑	Cardiomyocytes	Inhibited Autophagy	(133)
	Cardiomyocytes	lncRNA AK139128 ↑	Cardiac fibroblasts	Promoted apoptosis and inhibited proliferation, migration, and invasion	(134)
	Cardiomyocyte	TGF-beta ↑	RAW264.7 cells	Induced RAW264.7 cells into classically activated macrophages (M1) and M2 macrophages respectively	(135)
	AC16 cardiomyocytes	lncRNA HCG15	Cardiomyocytes	Induced cardiomyocyte apoptosis and the production of inflammatory cytokines	(136)
	Mesenchymal stem cells (MSCs)	HIFs is postulated	Human umbilical vein endothelial cells	Dose-dependent enhancement of in vitro proliferation, migration, and tube formation of endothelial cells	(137)
	Adipocyte	Enzymes related to de novo lipogenesis ↑, total amount of proteins increased by 3-4-fold ↑	3T3-L1 adipocytes, neighboring preadipocytes and adipocytes	Promoted lipid accumulation, affected lipogenic activity	(138)
	HIF-α-overexpressing donor MSCs (HIF-MSC)	Jagged1 ↑	Endothelial cells	Promoted angiogenic	(139)
	Bone marrow mesenchymal stem cells (BMSCs)	High mobility group box 1 protein (HMGB1) ↑	Human umbilical vein endothelial cells (HUVECs)	Enhancing angiogenesis	(140)
	Bone marrow-derived mesenchymal stem cells (MSCs)	Not mentioned	Infarcted hearts	Improved cardiac function, reduced infarct size and enhanced angiogenesis	(141)
	Human adipose-derived MSCs (hAD-MSCs)	VEGF↑	Human umbilical vein endothelial cells (HUVECs)	Improved angiogenesis	(142)
	Human cardiosphere-derived cells (CDCs)	miR-126 ↑, miR-130a ↑, miR-210 ↑	Human umbilical vein endothelial cells (HUVECs)	Enhancing angiogenesis	(143)
	Cardiac progenitor cells (CPCs)	miR-292↑, miR-210↑, miR-103↑, miR-17↑, miR-20a↑, miR-15b↑, miR-199a↑	Endothelial cells	Enhanced tube formation of endothelial cells and decreased profibrotic gene expression in TGF-β-stimulated fibroblasts	(144)
	Bovine aortic endothelial cells	(IGFBP3, EDN1, CA9, MMP9, VEGFA) ↑, (NAMPT, PLAU, ODC1, EGR1) ↓	Bovine aortic endothelial cells	Increased tube formation	(145)
	Cardiac endothelial cells	HIF ↑, miR-126 ↑, miR-210 ↑	Cardiac progenitor cells (CPCs)	Increased survival of transplanted CPCs in the ischemic heart	(146)
	Cardiac fibroblasts (CFs)	1616 proteins	Cardiomyocyte	Increased myocyte viability under hypoxia	(147)
	Adipose mesenchymal stem cells	Not mentioned	Human umbilical vein endothelial cells (HUVECs)	Promoted neovascularization and graft survival	(148)
	Bone marrow mesenchymal stem cells (BMSCs)	miR-98-5p ↑	Rats with myocardial ischemia-reperfusion injury (MI/RI)	Promoted cardiac function and suppressed myocardial enzyme levels, oxidative stress, inflammation response, macrophage infiltration and infarct size	(149)
	Bone marrow mesenchymal stem cells (BMSCs)	microRNA-24 ↑	H9c2 cells, rats with acute myocardial infarction	decreased the apoptosis rate of H9c2 cells, reduced infarct size and improved cardiac function in acute myocardial infarction rats.	(150)

(Continued)

TABLE 1 | Continued

Related systems	Donor units	Hypoxia induced changes of exosome contents	Recipient units	Biological effects	Ref
	Mesenchymal stem cells (MSCs)	miR-210 ↑	Cardiomyocytes, rats with myocardial infarction	Enhanced cardiomyocyte survival, reduced infarct size and improved heart function	(151)
	Human adipose-derived mesenchymal stem cells	lncRNA-MALAT1 ↑	Cardiomyocytes	Protected cardiomyocytes from Dox-induced cardiac damage	(152)
	Adipose mesenchymal stem cells	VEGF ↑, EGF ↑, FGF ↑, VEGF-R2 ↑, VEGF-R3 ↑, MCP-2 ↑, MCP-4 ↑	Human umbilical vein endothelial cells (HUVECs), a nude mouse model of subcutaneous fat grafting	promoted proliferation, migration and tube-formation capability of HUVECs, improved neovascularization around the graft in the nude mouse	(153)
	Bone marrow mesenchymal stem cells (BM-MSCs)	miR-125b-5p ↑	Mice with permanent condition of myocardial infarction (MI)	Exerted a marked cardioprotective function post-MI	(154)
	M1-type macrophage	miR-222	Bone marrow mesenchymal stem cells (BMSCs)	Promoted BMSCs apoptosis	(155)
	Human cardiosphere-derived cells (CDCs)	Not mentioned	Human embryonic stem cell-derived cardiomyocytes	Increase the survival of cardiomyocytes by inhibiting apoptosis	(156)
	C2C12 cells (myotubes)	miR-21 ↑	Mouse tubular epithelial cells (mTECs)	Protected renal tubules from sepsis-induced kidney injury	(157)
Neuron system	Astrocytes	Prion protein ↑	Neurons	Improved survival of neurons	(158)
	Bone marrow mesenchymal stromal cells	NLRP3 ↓, ASC ↓, Caspase-1 ↓, GSDMD-N ↓, cleaved IL-1β↓, IL-18 ↓	Mouse neuroblastoma N2a cells, rat primary cortical neurons	Exhibited significant neuroprotective effects against NLRP3 inflammasome-mediated pyroptosis	(159)
	Mesenchymal stromal cells (MSCs)	miR-21 ↑	APP/PS1 mice	Improved the learning and memory capabilities of APP/PS1 mice,	(160)
	SH-SY5YAPP (695) cells	Aβ40 ↑, Aβ42 ↑	Transgenic APP/PS1 mice	Enhancing the interaction between CD147 and Hook1	(161)
	Microglia	miR-424-5p ↑	Brain microvascular endothelial cells (BMEC)	Aggravated oxygen glucose deprivation (OGD) induced BMEC viability and integrity damage as well as the loss of vascular formation	(162)
	Adipose-Derived Mesenchymal Stem Cells	miR-499a-5p	Neuronal cells, Rats with Spinal Cord Injury	Reduced neuronal apoptosis, reduced cavities formation in the injured area and improved the functional recovery of the hindlimbs of rats	(163)
	Neural progenitor cells	miR-210 ↑	Neural progenitor cells	Increased or inhibited cell viability according to the amount of miR-210	(164)
	SH-SY5Y and HEK293 cells	amyloid-beta (Abeta) ↑	None	Aggravated Alzheimer's disease (AD)	(165)
	Astrocytes	miR-92b-3p ↑	Neurons	Attenuated oxygen and glucose deprivation-induced neuron death and apoptosis	(166)
Respiratory system	Mesenchymal stromal cell (MSC)	Not mentioned	Mice which exposed to hypoxia after injection	Exerted a pleiotropic protective effect on the lung and inhibit PH through suppression of hyperproliferative pathways, including STAT-3 mediated signaling induced by hypoxia	(167)
	Primary PASMC	miR-143 ↑	Pulmonary artery endothelial cells	Enhanced angiogenesis and cell migration	(168)
	Pulmonary artery endothelial cells (PAEC)	Not mentioned	Pulmonary artery smooth muscle cells (PASMC)	Promoted proliferation and induced apoptosis resistance in PASMC, contributing to the pathogenesis of pulmonary hypertension	(169)

(Continued)

TABLE 1 | Continued
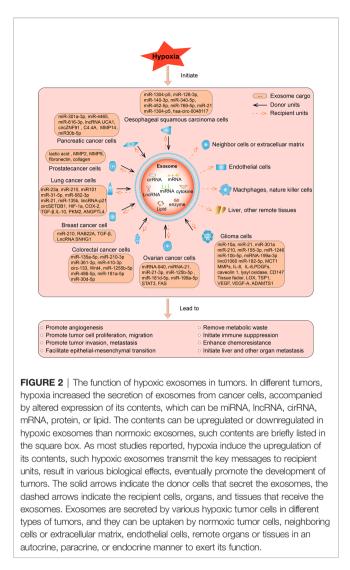
Related systems	Donor units	Hypoxia induced changes of exosome contents	Recipient units	Biological effects	Ref
Hematology system	TF-1 cells	miR-486 ↑	TF-1 cells, cord blood CD34+ cells	Induced the erythroid differentiation of TF-1 cells and CD34+ cells	(170)
	K562 cells	A subset of miRNAs (including miR-210) ↑	HUVECs	Significantly enhanced tube formation by HUVECs compared with exosomes produced in normoxic conditions	(171)
	Mesenchymal stem cells	Jagged-1 (Notch ligand) ↑,	Umbilical cord blood hematopoietic stem cells	Enhanced proliferation, increased the self-renewal capacity, quiescence, and clonogenic potential of recipient cells	(172)
Endocrine system	Plasma	Not mentioned	Human naive adipocytes	Promoted the presence of insulin resistance	(3)
	Adipose stem cells	miR-21-3p ↑, miR-126-5p ↑, miR-31-5p ↑, miR-99b ↓, miR-146-a ↓	Diabetic mice	Promoted diabetic wound healing and inhibit inflammation through PI3K/AKT signaling pathway	(173)
	Pericytes	circEhmt1 ↑	Endotheliocytes	Protected endotheliocytes from high glucose induced injury	(174)
	Umbilical cord-derived mesenchymal stem cells	miR-125b ↑	Endothelial cells	Increases endothelial cell proliferation, migration, and inhibited apoptosis, accelerated wound healing	(175)
Urinary system	Injured epithelial cells	TGF-β1 mRNA containing	Fibroblast	Promoted proliferation, alpha-smooth muscle actin expression, F-actin expression, and type I collagen production in fibroblasts.	(4)
	Renal tubular epithelial cells	miR-20a-5p ↑	Renal tubular epithelial cells, mouse model of ischemia-reperfusion-induced acute kidney injury (IRI-AKI)	Inhibition of TECs mitochondrial injury and apoptosis, protected against acute tubular injury	(176)
	Primary renal tubular epithelial cells	miR-21 ↑	Bone marrow-derived dendritic cells (BMDCs)	Promoted the maturation of dendritic cells	(177)
	Renal tubular epithelium cells (NRK-52E)	miR-150-5p ↑	Kidney fibroblasts (NRK-49F), rats with unilateral ischemia reperfusion injury	Activated kidney fibroblasts (NRK-49F), aggravated renal fibrosis	(178)
	Endothelial cell	Lysyl oxidase family member lysyl oxidase-like 2 (LOXL2) ↑	Extracellular matrix (ECM)	Mediated extracellular matrix crosslink and remodelling	(179)
Reproductive system	Placental mesenchymal stem cells (pMSC)	390 proteins	Placental microvascular endothelial cells (hPMEC)	Increased hPMEC migration by 1.6 folds, increased hPMEC tube formation by 7.2 folds; contributed to placental vascular adaptation to low oxygen tension	(180)
	Bovine endometrial stromal cells	128 proteins	Not mentioned	Played a crucial role in maternal-fetal crosstalk and could also affect placental development	(181)
	Cytotrophoblast (CT)	Oxygen-dependent changes of protein	HTR-8/SVneo (EVT)	Promoted EVT invasion and proliferation	(5)
Skeletomuscular system	Mesenchymal stem cell	miR-216a-5p ↑	BV2 microglia in vitro; mice with spinal cord injury in vivo	Promoted functional behavioral recovery by shifting microglial polarization from M1 to M2 phenotype	(182)
	Mesenchymal stem cells	miR-126 ↑	HUVEC	Promoted angiogenesis, proliferation and migration	(183)
	tenocytes and adjacent adipose-derived mesenchymal stem cells (ADMSCs)	Tenocytes derived exosomes:THSB1, NSEP1, ITIH4 and TN-C. ADMSCs derived exosomes: MMP2, COL6A, CTSD and TN-C	Not mentioned	Involved in multiple signaling pathways of ECM repair and regeneration	(184)
	Polymorphonuclearmyeloid-derived suppressor cells	miR-29a-3p ↑, miR-93-5p ↑	CD4(+) T cell, collagen-induced arthritis (CIA) mouse	Inhibited the proliferation of CD4(+) T, alleviated the arthropathy of CIA mice more effectively	(185)
	Mesenchymal Stem Cells	Not mentioned	Human umbilical vein endothelial cells (HUVECs), rat with steroid-induced osteonecrosis of the femoral head	Promoted angiogenesis and prevented bone loss	(186)

(Continued)

TABLE 1 | Continued

Related systems	Donor units	Hypoxia induced changes of exosome contents	Recipient units	Biological effects	Ref
	Synovial fibroblasts (SFs)	miR-424 ↑	T cells	Significantly induced T cells differentiation, which Th17 cells increased and Treg cells decreased	(187)
	Pericytes	Not mentioned	Endothelial cells	Faster wound healing, greater endothelial cord formation in cell culture assays, and greater vascular density in spinal cord tissue	(188)
	Adipose tissue-derived mesenchymal stem/stromal cells (ADSCs)	lncGm37494 ↑	Microglia BV2 cells, mice with spinal cord injury (SCI)	Shifted microglia from M1 to M2 polarization, repaired spinal cord injury	(189)

FIGURE 2 | The function of hypoxic exosomes in tumors. In different tumors, hypoxia increased the secretion of exosomes from cancer cells, accompanied by altered expression of its contents, which can be miRNA, lncRNA, cirRNA, mRNA, protein, or lipid. The contents can be upregulated or downregulated in hypoxic exosomes than normoxic exosomes, such contents are briefly listed in the square box. As most studies reported, hypoxia induce the upregulation of its contents, such hypoxic exosomes transmit the key messages to recipient units, result in various biological effects, eventually promote the development of tumors. The solid arrows indicate the donor cells that secret the exosomes, the dashed arrows indicate the recipient cells, organs, and tissues that receive the exosomes. Exosomes are secreted by various hypoxic tumor cells in different types of tumors, and they can be uptaken by normoxic tumor cells, neighboring cells or extracellular matrix, endothelial cells, remote organs or tissues in an autocrine, paracrine, or endocrine manner to exert its function.

genes expression were induced in neighboring normoxic tumor cells and possibly in surrounding stromal cells, many of which are involved in cancer progression and treatment resistance mechanisms (41).

In ovarian cancer, hypoxia also promoted the release of exosomes from cancer cells, and miRNA containing exosomes played a vital role in facilitating tumor progression. MiRNA-940 was upregulated in hypoxic exosomes derived from epithelial ovarian cancer (EOC) (54). EOC cell-derived exosomes delivered miRNAs to induce M2 macrophage polarization, which promoted EOC cell proliferation and migration (56). A similar situation occured in endometrial cancer, the expression of miRNA-21 was increased in exosomes derived from endometrial cancer KLE cells cultured in hypoxia. Exosomal transfer of miRNA-21 to monocyte THP-1 cell promoted its transformation to M2-like polarization macrophages, forming the immune microenvironment in cancer progression (55). In some cases, miRNA was downregulated to facilitate tumor progression. MiR-199a-5p was reported to be downregulated in cancer tissue. Hypoxic culturing further decreased the miR-199a-5p level in both ovarian cancer cells and

their secreted exosomes. The downregulation of miR-199a-5p promoted tumor metastasis through targeting HIF-2α to regulate Wnt/β-catenin path-way (53). Besides miRNAs, protein containing exosomes were also involved in ovarian cancer development. It was found that exosomes from hypoxic culturing ovarian cancer cell lines carried more potent oncogenic proteins-STAT3 and FAS, and significantly increased cell migration, invasion, and chemo-resistance *in vitro* and promoted tumor progression, metastasis *in vivo*. In addition, cisplatin efflux *via* exosomes was significantly increased in ovarian cancer cells under hypoxic conditions, contributing to chemo-resistance (52).

In breast cancer, activation of hypoxic signaling also resulted in a significant increase in exosome release. Exposing three different breast cancer cell lines to moderate (1% O_2) and severe (0.1% O_2) hypoxia led to a significant increase in the number of exosomes and an increase of miR-210 in exosomes (58). MiR-210 was involved in the expression of vascular remodeling related genes, such as Ephrin A3 and PTP1B, which function to promote angiogenesis (59). In addition to miR-210, lncRNA SNHG1, which was enriched in the hypoxic breast cancer cells secreted exosomes, also promoted the angiogenesis, as well as the proliferation and migration of HUVECs (60). And some research indicated that hypoxic exosomes were preferentially taken up by hypoxic cancer cells (191). The autophagy-associated GPR64 was reported to be upregulated in the hypoxic exosomes derived from the breast cancer associated fibroblast, it stimulated the NF-KB pathway to enhance the invasiveness in recipient breast cancer cells (61). microRNA let-7f was reported to be upregulated both in bone marrow-derived human mesenchymal stem cells (hMSCs) and its secreted exosomes under hypoxic culture, and miR-let-7f attenuated the proliferation and invasion in recipient 4T1 cells (62). In addition to autocrine, hypoxic exosomes also function in a paracrine manner in tumor development. It is reported that under hypoxia, breast cancer cells encapsulate TGF-β into exosomes, such exosomes were able to be taken up by T cells and mediated the suppression of T cell proliferation. Such immunosuppression microenvironment contributes to tumor progression (57). In contrast to cancer cell derived exosomes, natural killer (NK) cells, which play an important role in the tumor immune microenvironment, can also produce exosomes in the tumor microenvironment. Hypoxia enhanced the release of exosomes and increased the expression of three functional proteins of NK cells-specifically FasL, perforin, and granzyme B in hypoxic exosomes. And such hypoxic exosomes exhibited significantly increased cytotoxicity, enhanced inhibition of cell proliferation on breast and pancreatic cancer cells than normoxic exosomes (63).

In prostate cancer, cancer cells secreted more exosomes in a hypoxic microenvironment as a survival mechanism to remove metabolic waste like lactic acid (67). Hypoxia changed not only the secretion amount but also the average size of exosomes secreted by prostate cancer cells. Hypoxic exosomes had a smaller average size and a higher level of exosome biomarkers compared to normoxic exosomes. Co-culturing of hypoxic exosomes with normoxic prostate cancer cells increased the

stemness, motility, and invasiveness, promoted prostasphere formation, and enhanced α-SMA expression. Compared to normoxia, hypoxic exosomes showed higher metalloproteinases activity and a higher number of proteins, primarily associated with the remodeling of the epithelial adherens junction pathway (66, 70). Hypoxic exosomes were also involved in cancer metastasis progress. Exosomes derived from hypoxic culturing prostate cancer cells enhanced the level of MMP2, MMP9, and extracellular matrix proteins (fibronectin and collagen) at selective pre-metastatic niches sites, contributing to cancer metastasis (64). Hypoxic exosomes also prompted the development of bladder tumors and renal cell carcinoma (RCC). In bladder tumors, hypoxic exosomes derived from tumor cells showed higher expression levels of lncRNA-UCA1 which could promote tumor growth and progression through epithelial-mesenchymal transition, *in vitro* and *in vivo* (65). In RCC, hypoxia and treatment with CoCl2, a hypoxia mimic agent, increased the CA9 level in exosomes in all RCC cell lines. CA9 exosomes released from hypoxic RCC were postulated to enhance angiogenesis in the microenvironment, thereby contributing to cancer progression (68). MiR-155-5p was found to be upregulated in RCC specimens and hypoxia promoted its selective enrichment in exosomes secreted by hypoxic tumor-associated macrophages (TAM). The exosomes transferred miR-155-5p to RCC and promoted the tumor progression partially through activating IGF1R/PI3K/AKT cascades (71). lncHILAR was also reported to be secreted by hypoxic cancer cells and transferred to normoxic cancer cells through exosomes to activate the miR-613/206/1-1-3p/Jagged-1/Notch/CXCR4 axis, thereby promoting cell invasion and metastasis (69).

In lung cancer, cancer cells produced more exosomes under hypoxic conditions than normoxic conditions. MiRNA, cirRNA, lncRNA, and protein were both reported to be encapsulated in cancer cell derived exosomes and contributed to tumor progression. MiR-23a was significantly upregulated in hypoxic exosomes, resulting in enhanced angiogenesis through regulation of endothelial cells (73). Besides immunosuppressive function, TGF-β, as well as IL-10 which were increased in hypoxic lung cancer cell derived exosomes, also played a positive role in regulating cancer cell migration (74). MiR-31-5p and miR-582-3p were largely internalized within hypoxic exosomes. Exosomal transfer of miRNAs from hypoxic cancer cells to normoxic cancer cells significantly enhanced the proliferation, migration, and invasion of receptive normoxic lung cancer cells *in vitro*, and promoted lung adenocarcinoma metastasis (77, 83). Similarly, hypoxia induced the upregulation of angiopoietin-like 4 (ANGPTL4), HIF-1α/COX-2 and miR-135b and miR-210 in the exosome cargo of A549 cells, exosome transfer of these factors to other A549 cells led to the enhanced proliferation, migration, angiogenesis, and tumor progression (80, 84). In hypoxic tumor microenvironment, bone marrow-derived mesenchymal stem cells (BMSCs) secreted exosomes that contained miR-193a-3p, miR-210-3p and miR-5100, these exosomes were taken up by neighboring epithelial lung cancer cells, led to STAT3 signaling activation and increased expression

of mesenchymal related molecules (75). In addition to metastasis and tumor progression, chemoresistance is also involved. Hypoxia upregulated the miR-21 expression in non-small cell lung cancer (NSCLC) cells and cell-derived exosomes, while exosomal miR-21 contributed to cisplatin resistance by downregulating phosphatase and tensin homolog (PTEN) in its recipient normoxic NSCLC cells (81). In some cases, hypoxia decreased the expression of some key genes. It was reported that hypoxic stress suppressed the expression of miR101 in A549 cell secreted exosomes, the exosomes with suppressed expression of miR101 were transferred to THP-1 cells and upregulating the expression of IL-1 and IL-6, contributing to the promoted inflammation of macrophages in the tumor microenvironment (79). Besides miRNA and protein, cirRNA and lncRNA also play a role in tumor progression. circSETDB1 was found to be significantly upregulated in hypoxia-induced exosomes from lung adenocarcinoma (LUAD) cell lines in comparison to normoxic exosomes. And such exosomes improved the migration, invasion, and proliferation capacity of normoxic LUAD cells (78). LncRNA-p21 was reported to be upregulated by hypoxia in non-small cell lung cancer tumor tissue and a higher level of lncRNA-p21 encapsulated exosomes in blood indicates a shorter time to relapse and shorter overall survival. In addition, lncRNA-p21 enriched exosomes promoted tube formation of endothelial cells and enhanced tumor cell adhesion to endothelial cells (76). Besides continuous hypoxia, intermittent hypoxia also has a stronger prosurvival effect than normoxia. Circulating exosomes released under intermittent hypoxia conditions significantly promoted lung carcinoma cells' malignant properties (72). Hypoxic exosomes also play a role in the chemoresistance of lung cancer therapy. In NSCLC, normoxic and hypoxic exosomes derived from cisplatin-resistant cancer cells were analyzed. As a result, the expression of PKM2 was elevated in hypoxic exosomes. PKM2 promoted glycolysis and finally may neutralize reactive oxygen species (ROS) induced by cisplatin, eventually promoting cisplatin resistance in sensitive NSCLC (82).

In the digestive system malignant disease, including pancreatic cancer, colorectal cancer (CRC), hepatocellular cancer, oesophageal squamous cell carcinoma (OSCC), and other relatively less frequently diagnosed malignant disease like oral squamous cell carcinoma, nasopharyngeal carcinoma, and gastric cancer, hypoxia also exerted a great impact on exosomes and thus contributed to tumor development.

In pancreatic cancer, hypoxic pancreatic cancer cells secreted exosomes that contained miRNA, lncRNA, cirRNA or protein to promote tumor progression. Hypoxia was reported to upregulate a series of miRAN including hsa-miR-29b-3p and hsa-miR-216a-5p,hsa-miR-148a-3p and islet cell damage marker hsa-miR-375 in the exosomes derived from human islets (192). MiR-301a-3p-rich exosomes were induced in the hypoxic microenvironment from pancreatic cancer cells, such exosomes then polarized macrophages to promote malignant behaviors of pancreatic cancer cells (85). miR-30b-5p enriched hypoxic exosomes that derived from pancreatic ductal adenocarcinoma (PDAC) cells, was transferred to HUVEC, leading to enhanced

tube formation and angiogenesis (90). LncRNA UCA1 was also reported to be highly expressed in exosomes derived from hypoxic pancreatic cancer cells. Exosomal transfer of lncRNA UCA1 promoted cell migration and tube formation of human umbilical vein endothelial cells (HUVECs), contributing to angiogenesis and tumor growth (89). Interestingly, lncRNA UCA1 was also enriched in exosomes derived from pancreatic stellate cells (PSCs), and such exosome was able to promote the Gemcitabine resistance of pancreatic cancer cells through SOCS3/EZH2 Axis (91). CircZNF91 was encapsulated and transmitted to normoxic pancreatic cancer cells through hypoxic exosomes, eventually enhancing the stability of HIF-1α and leading to glycolysis and chemoresistance of normoxic pancreatic cancer cells (87). C4.4A, a molecular which was upregulated in several tumor types, was upregulated in the pancreatic cancer cells and its secreted exosomes, promoting wound healing and tumor metastasis (86). Pancreatic stellate cells (PSCs), the important components of the tumor microenvironment in pancreatic cancer (PC), also contributed to its development and metastasis through exosome delivery. In tumor hypoxic microenvironment, miR-4465 and miR-616-3p were encapsulated in PSCs secreted exosomes and transmitted to pancreatic cancer cells, promoting PC cell proliferation, migration, and invasion, contributing to PC progression and metastasis (88).

In colorectal cancer (CRC), the hypoxic microenvironment boosted exosome release. Hypoxia promoted colon cancer cells to release more exosomes and thereby promoting self-proliferation in a time-and dose-dependent manner through shortening mitosis duration and upregulating phosphorylated STAT3 (100). Many proteins, miRNAs, cirRNAs were indicated to be upregulated in hypoxic conditions and internalized into exosomes and transferred from hypoxic CRC cancer cells to normoxic cancer cells to promote tumor deterioration. Wnt4, S100A9, MiR-210-3p, miR-361-3p, miR-410-3p, circ-133 were reported to be remarkably elevated in hypoxic CRC exosomes, and can be transferred to normoxic CRC cells, leading to facilitated cell growth and suppressed cell apoptosis, eliciting a protumoral effect, promoting cancer metastasis and enhancing tumor progression. In addition, some miRNA or cirRNA were also enriched in the plasma exosomes of CRC patients and positively associated with a poor prognosis of colorectal cancer (94–98, 103). Some hypoxic colorectal cancer derived exosomes, like exosomes enriched with miR-135a-5p, were phagocytosed by Kupffer cells and transferred from blood circulation into the liver, initiating the large tumor suppressor kinase 2-yes-associated protein-matrix metalloproteinase 7 axis to promote liver metastasis (93). It is worth noting that CRC cells not only secreted exosomes to promote tumor development, but also uptaken exosomes in some case. For example, hypoxic exosomes that was enrich with circEIF3K and derived from cancer-associated fibroblasts (CAF), could be uptaken by colorectal cancer cells (CRC) HCT116 and SW620, and contributed the proliferation, invasion, and tube formation. Knocking down circEIF3K in CAF could mitigate hypoxia induced CRC progression (102). Hypoxic exosomes derived

from colorectal cancer cells also enhanced angiogenesis in tumor progression by promoting the proliferation and migration of endothelial cells. Suppression of exosome secretion inhibited these effects (92). In some cases, hypoxia suppressed specific gene expression to adapt to oxygen stress. It was reported that hypoxia downregulated the exosomal miR-1255b-5p that was secreted by colorectal cancer cells and eventually enhanced the epithelial-to-mesenchymal transition as a response to hypoxia (99). Hypoxia also downregulated miR-486-5p and miR-181a-5p while upregulated miR-30d-5p in the cancer cell derived exosomes, both of which were associated with organ-invasiveness and lymph node metastases (101).

In liver cancer, hypoxia promoted tumor self-growth through exosome transfer. Hypoxic exosomes derived from hypoxic hepatocellular carcinoma cancer cells promoted cell proliferation, migration and invasion of normoxic cancer cells through a paracrine manner (111). miR-1273f was reported to be upregulated by hypoxia in the exosomes derived from hepatocellular carcinoma cells, and it was transferred to normoxic cancer cells to promote their proliferation, migration, and invasiveness by targeting LHX6 and subsequently activating Wnt/beta-catenin signaling pathway (108). LncRNA HMMR-AS1 was also increased in the hypoxic exosomes from hepatocellular carcinoma cells, and could be transferred to promote the M2 macrophages polarization and promote the progression of HCC (112). In addition to hepatocellular carcinoma cells, hypoxic tumor exosomes can also be uptaken by HUVECs. It was reported that hypoxia upregulated the miR-155 and miR23a in the hepatocellular carcinoma secreted exosomes. Such exosomes remarkably enhanced tube formation of HUVECs, indicating its facilitating role in promoting angiogenesis in hepatocellular carcinoma (109, 110).

Hypoxia induced significant upregulation of a series of miRNAs in exosomes isolated from oesophageal squamous cell carcinoma (OSCC) cell lines, among which miR-340-5p was reported to be transferred to normoxic OSCC cells through hypoxic exosomes. Such hypoxic exosomes alleviated radiation-induced apoptosis and accelerated DNA damage repair, leading to radioresistance (104). Besides miRNA, hsa-circ-0048117 rich exosomes were also generated in the hypoxic microenvironment in OSCC. Exosomal hsa-circ-0048117 could be transmitted to macrophages to promote M2 polarization and M2 macrophages could enhance the ability of invasion and migration of tumor cells (105). It was reported that hypoxic exosomes derived from esophageal squamous cell carcinoma cells had stronger effects than normoxic exosomes both *in vitro* and *in vivo*. Hypoxic exosomes which contains altered gene information had better effects in promoting proliferation, migration, invasion and tube formation of HUVECs than normoxic exosomes. And hypoxic exosomes also significantly promoted the tumor growth and lung metastasis in nude mice (115). Hypoxic tumor derived exosomes were also reported to influence tumor immune microenvironment. It was reported that the OSCC cell lines: Cal-27 and SCC-9 secreted hypoxic exosomes which contain miR-21 and such exosomes were

transferred to myeloid-derived suppressor cells (MDSCs), promoting its suprressive effect on gammadelta T cells, eventually affecting the anti-and pro-tumoral equilibrium (114).

In oral squamous cell carcinoma cells, a hypoxic microenvironment promoted the enrichment of miR-21 in its secreted exosomes. These exosomes were delivered to normoxic cells and promoted metastatic behaviors (113). In nasopharyngeal carcinoma, hypoxic adipocyte-derived exosomes transferred low expression of miR-433-3p into cancer cells, promoting proliferation, migration, and lipid accumulation in cancer cells (107). In many cases, HIF was involved in the pathological process of tumor malignant behaviors. Hypoxic cancer cell derived exosomes can enhance the metastases in a HIF-1α dependent manner. HIF-1α stimulated MMPs expression to affect cell migration and invasion (106). In gastric cancer, hypoxia promoted miR-301a-3p expression in a HIF-α dependent manner and exosomes released from cancer cells were also increased in the hypoxic tumor microenvironment. The miR-301a-3p enriched exosomes were transmitted among gastric cancer cells, eventually leading to cancer cell proliferation, invasion, migration, and epithelial-mesenchymal transition (116).

In many cell types, hypoxia induced the change of RNA and proteins components in cells and such changes were also reflected in hypoxic exosomes (122). In papillary thyroid cancer, hypoxia promoted both the expression of miR-181a in cancer cells and the secretion of miR-181a enriched exosomes from cancer cells. Human umbilical vein endothelial cells (HUVECs) which uptake such exosomes exhibited enhanced proliferation and capillary-like network formation, contributing to tumor angiogenesis (117). In skin carcinoma A431 cells, hypoxia induced the expression of proteins involved in angiogenesis, focal adhesion, extracellular matrix-receptor interaction, and immune cell recruitment. These proteins were encapsulated into exosomes and facilitated angiogenesis and metastasis in the microenvironment (118). In melanoma cells, hypoxia induced the upregulation of 15 miRNAs and downregulation of 3 miRNAs in exosomes derived from cancer cells through miRNA profile analysis (119). Co-culturing of hypoxic exosomes derived from melanoma cells which contained alternated miRNA profiles with THP1 macrophages led to increased M1 markers (CXCL10 and IL6) in macrophages (120). Hypoxia also upregulated the immunomodulatory proteins and chemokines including CSF-1, CCL2, FTH, FTL, and TGFbeta in exosomes from mouse melanoma B16-F0 cells, and such exosomes promoted M2-like polarization of macrophages. And the upregulated miRNA let-7a in hypoxic exosomes enhanced oxidative phosphorylation in macrophages (121). In Ewing's sarcoma (EWS), hypoxic cancer cells secreted miR-210 enriched exosomes to normoxic cancer cells, leading to promoted sphere formation by targeting the proapoptotic protein CASP8AP2 (123). In multiple myeloma, hypoxia upregulated the expression of miR-1305 in cancer cell secreted exosomes, thus the cellular miR-1305 decreased and its target genes increased, eventually promoting the oncogenic activity of multiple myeloma cells. On the other hand, macrophages

uptaken the miR-1305 containing exosomes and exhibited tumor-promoting, M2-macrophage phenotypes (124). miR-135b was also reported to be increased by hypoxia in the exosomes derived from multiple myeloma cells. Such exosomes enhanced endothelial tube formation under hypoxia (125). To conclude, hypoxia increase the release of exosomes from malignant cells and the content of exosomes changed under low oxygen tension, which induce recipient cells to alter gene expression and eventually promote tumor progression.

HYPOXIC EXOSOMES IN CARDIOLOGY

Cardioprotective Effect of Hypoxic Exosomes

Under hypoxia, a series of miRNA were encapsulated into the exosomes and transferred to recipient cells to exhibit cardioprotective effects. A series of cardioprotective miRNAs, including miR-21-5p, miR-378-3p, miR-152-3p, and let-7i-5p were identified in hypoxic exosomes derived from cardiomyocyte H9c2 cells. These anti-apoptotic miRNAs mitigate hypoxia-induced H9c2 cells apoptosis (126). In contrast to these miRNAs, lncRNA HCG15 in the exosomes derived from hypoxic cardiomyocytes led to increased apoptosis, reduced proliferation, and release of inflammatory factors (136). Hypoxia also promoted the accumulation of TGF-beta in exosomes from cardiomyocyte H9c2 cells, and such exosomes could be taken up by RAW264.7 cells and induce the polarization of macrophages and reduce the apoptosis of cardiomyocytes (135). There were large amounts of studies that investigated exosomes derived from mesenchymal stem cells, such exosomes exhibited protective effects in cardiac injury and many miRNAs were reported to be encapsulated in exosome cargo. Especially, exosomes derived from hypoxia pretreated bone marrow-derived mesenchymal stem cells (BMSCs) were able to improve the cardiac function, reduce the infarct size and enhance the angiogenesis of the infarcted hearts (141). miR-98-5p was upregulated by hypoxia in exosomes derived from BMSCs and injection of such exosomes to rats with myocardial ischemia-reperfusion injury improved the cardiac function by targeting TRL4 and activating PI3K/AKT signaling pathway (149). miR-24 in exosomes derived from BMSCs was also upregulated by hypoxia, and such exosomes decreased the apoptosis rate of H9c2 cells, reduced infarct sized and improved cardiac function in acute myocardial infarction rats (150). miR-210 in exosomes derived from mesenchymal stem cells was increased under hypoxic culture, administration of such exosomes enhanced cardiomyocyte survival to hypoxia *in vitro*, reduced infarct size and improved heart function *in vivo* (151). Injecting such hypoxic exosomes into the infarcted heart of C57BL/6 mouse resulted in significantly higher survival, smaller scar size, and better cardiac functions recovery. Hypoxic exosomes conferred increased vascular density, lower cardiomyocytes apoptosis, reduced fibrosis, and increased recruitment of cardiac progenitor cells in the infarcted heart relative to exosomes isolated from the same cell line cultured under normoxia

(127). miR-125b-5p in the exosomes from mesenchymal stem cells was also upregulated by hypoxia, adminstration of such exosomes to mice with myocardial infarction suppressed the expression of the proapoptotic genes p53 and BAK1 in cardiomyocytes and exerted a marked cardioprotective function post-infarction (154). Hypoxic exosomes derived from human cardiosphere-derived cells also exhibited protective effects in cardiomyocytes by inhibiting apoptosis (156).

Although most miRNAs were upregulated in hypoxic exosomes, some miRNAs were enriched in normoxic exosomes rather than hypoxic exosomes. miR-10b-5p was reported to be downregulated in hypoxic exosomes derived from endothelial colony forming cells compared to normoxic exosomes. Due to a reduction of miR-10b-5p, which targets the fibrotic genes Smurf1 and HDAC4, the anti-fibrotic effects of exosomes were abolished (128). Besides continuous hypoxia, intermittent hypoxia also alters endothelial cell derived exosome cargo, including has-mir-383-3p, and such exosomes promote increased permeability and dysfunction of endothelial cells, contributing to cardiovascular dysfunction (129). Apart from miRNAs, lncRNA and cirRNA are also important non-coding RNAs that are induced and transferred through hypoxic exosomes. LncRNA-UCA1 is elevated both in myocardial infarction patients and exosomes derived from hypoxic culturing mesenchymal stem cells (hMSCs). Intramyocardial injection of lncRNA-UCA1 containing exosomes to rats with myocardial infarction demonstrated that hypoxic exosomes had a better cardioprotection effect than normoxic exosomes (130). lncRNA-MALAT1 was increased by hypoxia in exosomes from human adipose-derived mesenchymal stem cells, such exosomes functioned as competing endogenous RNAs (ceRNAs) binding to miR-92a-3p to protect cardiomyocyte from doxorubicin (Dox) induced cardiac damage (152). CirRNA is also involved in cardioprotective effects. circHIPK3 expression was found to be significantly upregulated in hypoxic exosomes compared to normoxic exosomes. Such circHIPK3 encapsulated exosomes were transferred from cardiomyocytes to cardiac microvascular endothelial cells (CMVECs). Leading to promoted endothelial cell migration, proliferation, and tube formation *in vitro*, and can effectively reduce the infarct area and promote angiogenesis in the border surrounding the infarcted area in myocardial infarction mice (132). Hypoxia also upregulated a series of proteins, like vascular endothelial growth factor (VEGF), epidermal growth factor (EGF), fibroblast growth factor (FGF) and their receptors (VEGF-R2, VEGF-R3), and monocyte chemoattractant protein 2 (MCP-2), monocyte chemoattractant protein 4 (MCP-4) in the exosomes derived from adipose mesenchymal stem cells, administration of such hypoxic exosomes promoted proliferation, migration, and tube-formation capability of HUVECs, and also improved neovascularization around the graft in the nude mice model of fat grafting (153).

In addition to protective effects, the hypoxia augmented miRNA in exosomes can also be harmful in some cases. MiR-30a was highly enriched in exosomes either from the culture medium of cardiomyocytes after hypoxic stimulation *in vitro* or the serum of acute myocardial infarction (AMI) patients *in vivo*.

The miR-30a enriched exosomes were regulated by HIF-α and were efficiently transferred between cardiomyocytes in an autocrine manner after hypoxia. But miR-30a inhibits the expression of core autophagy regulators, which are beneficial in ischemic heart disease. Inhibition of such exosomes release or inhibition of miR-30a was considered a promising treatment strategy in AMI (133). miR-222 was also reported to be transferred under hypoxic culture from M1-type macrophages to bone marrow mesenchymal stem cells, and co-culturing with such exosomes led to decreased cell viability, migration and increased apoptosis in the recipient cells, such effects were partly abolished by the exosome secretion inhibitor GM4869. Similarly, lncRNA AK139128 was also increased in hypoxia and played a negative role. Cardiomyocyte derived exosomal which contained lncRNA AK139128 promoted apoptosis and inhibited proliferation, migration, and invasion in cardiac fibroblasts. Such exosomes could also exacerbate myocardial infarction in the rat model (134).

Hypoxic Exosomes Promote Angiogenesis in Cardiology

Upon hypoxia, exosomes and microvesicles released by bone marrow mesenchymal stem cells (MSCs) were easily taken up by human umbilical vein endothelial cells (HUVECs), which led to promoted angiogenesis and improved cardiac function in infarction attack (137). The total amount of proteins secreted from exosomes increased by 3-4 folds under hypoxic conditions (138). Overexpressing HIF-1α in MSCs led to an increased angiogenic capacity mediated by its secreted exosomes (139). High mobility group box 1 protein (HMGB1) was induced by hypoxia in MSCs derived exosomes. Exosomal HMGB1 transferred to HUVECs activated JNK signaling and induced HIF-1α dependent VEGF expression, eventually led to enhanced angiogenesis (140). Compared with normoxia, hypoxic exosomes were more easily to be taken up by HUVECs and their angiogenesis stimulatory activity was also significantly enhanced. The expression of vascular endothelial growth factor (VEGF) and activation of the protein kinase A (PKA) signaling pathway in HUVECs was significantly increased by hypoxia-exposed exosomes (142). Besides, HUVECs also uptaken exosomes derived from hypoxic culturing human cardiosphere derived cells and exhibited enhanced tube formation. Pro-angiogenic exosomal miRNAs including miR-126, miR-130a, and miR-210 showed a substantial increase in the hypoxic exosomes compared to normoxic exosomes (143).
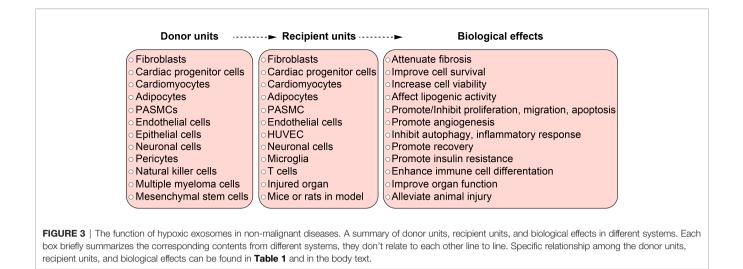
Besides bone marrow meschmenal stem cells, cardiac progenitor cells (CPCs), and other stem cell types were also attractive candidates for the treatment of myocardial infarction, however, the role of exosomes in the treatment remains unclear. Recent research shows that upon hypoxia, exosomes secreted by cardiac progenitor cells enhanced tube formation of endothelial cells and decreased profibrotic gene expression in TGF-β-stimulated fibroblasts. Microarray analysis identified 11 miRNAs that were upregulated in hypoxic exosomes compared with normoxic exosomes. Hypoxic exosomes improved cardiac function and reduced fibrosis (144). In research involving

different degrees of hypoxia, human CPCs were cultured under normoxia (21% O_2), physoxia (5% O_2), and hypoxia (1% O_2) conditions. As a result, the release of exosomes under physoxia increased 1.6 folds and significantly increased tube formation compared to normoxia and hypoxia (145). Interestingly, exosomes secreted by endothelial cells cultured under hypoxia can be taken up by CPCs, giving them increased tolerance when subjected to *in vitro* hypoxic stress. These exosomes overexpress HIF1 and have higher contents of miR-126 and miR-210 which activated prosurvival kinases and induced a glycolytic switch in recipient cells (146). These studies revealed close crosstalk between cardiac progenitor cells and endothelial cells *via* exosomes. For stem cell derived exosomes, the stemness of the cell is crucial for the treatment effect. In research evaluating the effect of donor's age and hypoxia to exosomes, cardiac progenitor cells secreted exosomes from older children were reparative only when subjected to hypoxic conditions (193).

HYPOXIC EXOSOMES IN NON-MALIGNANT DISEASE FROM DIFFERENT SYSTEMS

Besides cardiovascular system, hypoxic exosomes also play a comprehensive role in diseases from other systems. A wide range of donor units and recipient units are involved, and various biological effects are induced (**Figure 3**).

Neuron System

In the neuron system, different hypoxic exosomal content has been reported and they play a neuron protective role from different perspectives. Amyloid-β (Aβ), which is related to the pathogenesis of Alzheimer's disease, was accumulated during a hypoxic environment. Hypoxia increased the level of Aβ40 and Aβ42 in human neuroblastoma SH-SY5Y cells derived exosomes and such exosomes promote amyloids propagation (161). Hypoxia also increased Amyloid-beta (Aβ) both in the extracellular and exosomes of HEK293, which aggravated Alzheimer's disease (AD) (165). Prion protein in astrocytes is a sensor for oxidative stress and mediates beneficial cellular responses. Under hypoxic and ischemic conditions, the release of exosomes carrying enriched prion protein and other molecules led to improved survival of neurons (158). The expression of NLRP3, ASC, Caspase-1, GSDMD-N, cleaved IL-1β and IL-18 were decreased in neuron cells after taking up bone marrow mesenchymal stromal cells-derived exosomes. Hypoxic exosomes had more significant effects to decrease these molecules, and exhibited a more pronounced neuroprotective effect against oxygen-glucose deprivation injury (159). MiR-21 was also reported to be increased by hypoxia in exosomes derived from mesenchymal stromal cells and mediated the improvement of neurologic conditions. And hypoxic exosomes were demonstrated to have better effects than normoxic exosomes to ameliorate cognitive decline in APP/PS1 mice by rescuing synaptic dysfunction and regulating inflammatory responses (160). miR-92b-3p was reported to be upregulated in exosomes

FIGURE 3 | The function of hypoxic exosomes in non-malignant diseases. A summary of donor units, recipient units, and biological effects in different systems. Each box briefly summarizes the corresponding contents from different systems, they don't relate to each other line to line. Specific relationship among the donor units, recipient units, and biological effects can be found in **Table 1** and in the body text.

derived from oxygen-glucose deprivated (OGD) astrocytes, such exosomes could be uptaken by neurons and attenuated OGD-induced neuron death and apoptosis (166). miR-499a-5p that was encapsulated into exosomes from hypoxic adipose tissue-derived stromal cells (ADSCs) reduced neuronal apoptosis after oxygen-glucose deprivation and reperfusion (OGD/R) *in vitro*, and relieved the damage of rats with spinal cord injury (SCI) *in vivo* (163).

Apart from the protective role, hypoxic exosomal content can be harmful as well. MiR-424-5p was upregulated in the exosomes derived from oxygen-glucose deprivation activated microglia. Such exosomes induced significant cell damage and permeability of microvascular endothelial cells. This interpreted how microglia secreted exosomes participate in neurovascular unit injury under the ischemic and hypoxic state (162). miR-210 was upregulated by hypoxia in exosomes from neural stem/progenitor cells, but high levels of miR-210 inhibited the cell viability of recipient neural stem/progenitor cells (164).

Respiratory System

Hypoxia is a broad accepted factor to induce vascular remodeling and the development of pulmonary hypertension. Hypoxic exosomes from different donor cells play a different role in this process. Hypoxia and inflammation could induce pulmonary artery endothelial cells (PAECs) to release exosomes. These exosomes were involved in overproliferation and apoptosis resistance in pulmonary arterial smooth muscle cells (PASMCs), by which they may contribute to the pathogenesis of pulmonary hypertension (169). In contrast, hypoxia can also induce PASMCs to release exosomes and the exosomes were transferred to PAECs in a paracrine manner, affecting the migration and apoptosis of PAECs, then promoting the development of pulmonary arterial hypertension (168). Exosomes transferred between PAECs and PASMCs promoted the development of pulmonary hypertension while exosomes derived from mesenchymal stromal cells prevented the development of pulmonary hypertension. Hypoxic mesenchymal stromal cells derived exosomes exerted a pleiotropic protective effect on the lung and inhibit hypoxic pulmonary

hypertension through suppression of hyperproliferative pathways, including STAT-3 mediated signaling induced by hypoxia (2).

Hematology System

Hypoxia enhanced the package of miRNA and protein in exosomes derived from hematology system and such exosomes could be taken up by endothelial cells and leading to enhanced tube formation, or they could be taken up by other hematology cells and promoting further differentiation. Compared to normoxia, hypoxia significantly upregulated a subset of miRNAs, including miR-210, in exosomes derived from human leukemia cells. Coculturing such exosomes with HUVECs remarkably enhanced tube formation by HUVECs compared with exosomes produced in normoxic conditions (171). MiR-486 was also upregulated by hypoxia both in intracellular space and in the secreted exosomes of erythroleukemia TF-1 cells. Exosomal miR-486 played critical roles in regulating the hypoxia-induced erythroid differentiation of hematopoietic cells (170). Hypoxia also upregulated the the Jagged-1 (Notch ligand) in the exosomes from mesenchymal stem cells, and co-culture such exosomes with hematopoietic stem cells (HSCs) enhanced the proliferation, increased the self-renewal capacity, quiescence, and clonogenic potential of HSCs (172).

Endocrine System

Hypoxic exosomes play a bilateral role in diabetic disease. On one hand, hypoxic exosomes led to insulin resistance in some cases. Exosomes isolated from sleep fragmentation and intermittent hypoxia exposed mice induced attenuated p-AKT/total AKT responses to exogenous insulin, leading to insulin resistance in adipocytes (3). On the other hand, hypoxic exosomes internalized miRNA or lncRNA to exert a protective role in diabetic disease. Compared to normoxia, miR-21-3p, miR-126-5p, miR-31-5p were significantly upregulated while miR-99b and miR-146-a were significantly downregulated in hypoxic exosomes derived from adipose stem cells. Hypoxic exosomes exhibited significantly better effects in promoting wound healing than normoxic exosomes when they were

injected into diabetic mice (173). miR-125b was also upregulated by hypoxia in the exosomes from umbilical cord-derived mesenchymal stem cells (ucMSCs), such exosomes can be taken up by endothelial cells and promoted cell proliferation, migration, inhibited apoptosis, and accelerated wound healing by targeting and suppressing the tumor protein p53 inducible nuclear protein 1 (TP53INP1) (175). In addition, it was reported that hypoxia upregulated circEhmt1 both in pericytes and its secreted exosomes. CircEhmt1 that were encapsulated into exosomes were transmitted to endotheliocytes, protecting endotheliocytes against high glucose induced injury (174). In another word, hypoxic exosomes mediated impaired insulin sensitivity in the intermittent hypoxia process.

Urinary System

In the urinary system, hypoxia did not change the average size of exosomes secreted by rat renal proximal tubular cells, but significantly increased exosome production in a time-dependent manner. HIF-1 induction also promoted exosome secretion, pharmacological and genetic suppression of HIF-1 abrogated the increase of exosome secretion under hypoxia (194). Many miRNAs were reported to be encapsulated in the exosomes from tubular epithelial cells and exhibited renal protective effects both *in vivo* and *in vitro*. Hypoxia induced the enrichment of miR-20a-5p in exosomes from renal tubular epithelial cells. Such exosomes were protective in acute tubular injury by promoting tubular epithelial cells proliferation and improving mitochondrial functions (176). Hypoxia increased the miR-21 both in tubular epithelial cells and in the exosomes of bone marrow-derived dendritic cells. And it was postulated that the upregulated miR-21 of tubular epithelial cells promoted dentritic cell maturation (177). Hypoxia upregulated the miR-150-5p in the exosomes from rat renal tubular epithelium cells (NRK-52E), such exosomes could activate rat kidney fibroblasts (NRK-49F), and injection of such exosomes alleviated renal fibrosis in rats with unilateral ischemia reperfusion injury (178). Hypoxia also upregulated the miR-21 in the exosomes from myotubes C2C12 cells, and such exosomes protected renal tubes from sepsis-induced kidney injury (157). In addition to tubular epithelial cells, exosomes from epithelial cells were also more active under hypoxia. Hypoxia promoted epithelial cells to produce an increased number of exosomes containing TGF-β1 mRNA, to activate fibroblasts, contributing to fibrosis that involved in the pathology of hypoxia induced kidney injury (4). Hypoxia upregulated the lysyl oxidase family member lysyl oxidase-like 2 (LOXL2) in the exosomes from endothelial cells, and such exosomes mediated extracellular matrix crosslink and remodelling (179).

Reproductive System

Different degree of hypoxia has different impacts on exosome contents. Compared to the controls (8% O_2), exosomes released from placental mesenchymal stem cells increased by 3.3 folds in 1% O_2 and 6.7 folds in 3% O_2 respectively. Such changes may contribute to placental vascular adaptation to low oxygen tension under both physiological and pathological conditions (180). Similarly, in endometrial stromal cells, the secretion of exosomes

cultured at 1% O_2 was increased by about 3.6 folds compared with 8% O_2. Mass spectrometry analysis identified 128 proteins unique to exosomes produced at 1% O_2 compared with only 46 proteins unique to those produced at 8% O_2. Differential production of proteins was associated with different specific biological processes (181). It was reported that hypoxic cytotrophoblast derived exosomes promoted extravillous trophoblasts' invasion and proliferation (5). Implying the mechanism of hypoxic placenta contributing to the pathophysiology of preeclampsia. Besides proteins encapsulated in hypoxic exosomes, hypoxic exosomal miRNA may also contribute to the pathogenesis of preeclampsia. The level of circulating exosomal total-miRNA and the hypoxia sensitive hsa-miR-210 was elevated in preeclampsia and it was higher in the severe form. Hsa-miR-210 was secreted *via* exosomes, which may play a role in the pathomechanism of the disease (195).

Skeletomuscular System

In the skeletomuscular system, hypoxic exosomes play an important role to promote angiogenesis and injury recovery in different joint damage. In the spinal cord injury model, hypoxia resulted in an enrichment of miR-216a-5p in the exosomes from mesenchymal stem cells (MSCs). Hypoxic exosomes promoted functional behavioral recovery by shifting microglial polarization from M1 to M2 phenotype *in vivo* and *in vitro* (182). LncGm37494 was also reported to be upregulated by hypoxia in the exosomes from adipose tissue-derived mesenchymal stem/stromal cells, and such hypoxic exosomes were more effective than normoxic exosomes in repairing spinal cord injury (189). In spinal cord angiogenesis, preconditioning pericyte with hypoxia mimic and coculture it with endothelial cells resulted in faster wound healing, greater endothelial cord formation, and greater vascular density in the spinal cord tissue. Exosome secretion and the physical presence of stimulated pericytes were necessary for the promotion of angiogenic outcomes (188). In a research of bone fracture healing, hypoxia enhanced the production of exosomal miR-126 through the activation of HIF-1α. Such exosomes were transferred to HUVECs and promoted angiogenesis, proliferation, and migration *in vitro*. *In vivo* experiments demonstrated that hypoxic exosome administration promoted bone fracture healing through exosomal miR-126 transfer (183). In rotator cuff tendon injuries (RCTI), the hypoxic environment triggered tenocytes and adjacent adipose-derived mesenchymal stem cells (ADMSCs) to release exosomes to the extracellular matrix (ECM). Tenocytes secreted exosomes encapsulated THSB1, NSEP1, ITIH4, and TN-C. ADMSCs secreted exosomes encapsulated MMP2, COL6A, CTSD, and TN-C. These proteins were involved in multiple signaling pathways of ECM repair and regeneration, protecting the tendon matrix from injury (184). In the arthropathy of collagen-induced arthritis (CIA), hypoxia upregulated the expression of miR-29a-3p and miR-93-5p in exosomes derived from polymorphonuclear myeloid-derived suppressor cells. Compared to normoxic exosomes, hypoxic exosomes could inhibit the proliferation of CD4(+) T cells more effectively. And the administration of hypoxic exosomes alleviated mice with CIA more effectively (185). In steroid-induced

osteonecrosis of the femoral head (ONFH) model, hypoxic exosomes derived from bone marrow mesenchymal stem cells (BMMSCs) exhibited better therapeutic effects in promoting angiogenesis and preventing bone loss (186). In rheumatoid arthritis, hypoxia induced the upregulation of miR-424 in exosomes derived from synovial fibroblasts. Exosomal miR-424 could significantly induce T cells differentiation and contribute to the aggravation of rheumatoid arthritis (187).

CONCLUSION

In many hypoxia related diseases, miRNAs have been reported most to be internalized into exosomes under hypoxia. The master regulator of oxygen homeostasis and a hypoxia sensitive transcription factor HIF, has been reported to have crosstalk with miRNA by many studies. HIF-1α/HIF-1β dimmer can bind to the promoters of target miRNAs and regulate extensive cellular processes, including proliferation, metastasis, apoptosis, and drug resistance, etc. Also, tumor-related miRNAs can modulate the activity of HIF-1α, and play a positive or negative role in tumor development (196). Whether HIF regulated miRNAs are more easily to be encapsulated into exosomes and if there is crosstalk between HIF and other lncRNAs, cirRNAs, proteins, and Lipids that internalized into hypoxic exosomes still awaits further investigation.

As mentioned above, in various types of tumors and other diseases, hypoxia not only increases the quantities of exosome release but also alters the contents of exosomes. Since exosomes are a crucial mediator of genetic, protein, and lipid information carrier and transmitter, manipulating the release, degradation, cargo sorting, and receiving of exosomes becomes a promising strategy to interfere with disease development. In tumor development, hypoxic tumor cells secret more exosomes, such hypoxic exosomes disseminate the malignant information to recipient cells, tissue, and organs, contributing to tumor progression. Reducing exosomes release, promoting lysosome degradation, inhibiting key factors encapsulating, or disrupting exosomes uptaking could be a possible way to prevent the invasion and metastasis of tumors. In fact, through high-throughput screening, a series of inhibitors and activators of exosomes biogenesis have been identified in prostate cancer cells (197). And the mechanisms of how inhibitors function have been well reviewed (198, 199). But targeting exosome donor cells exploration, a broader range of cell line study and the *in vivo* effects investigation is warranted. Vice versa, when exosomes are beneficial, for example, exosomes derived from mesenchymal stem cells play a cardioprotective role and promote angiogenesis in acute myocardial infarction, and prevent the development of pulmonary hypertension. Under such circumstances, facilitating the secretion and function of exosomes is profitable for improving health conditions. In fact, there are already attempt to applying exosomes in cancer therapy. Reprocessing exosomes that target immune cells to induce an immune response against the tumor, as well as other infectious diseases has been investigated by researchers (200). Such strategies were also explored in several tumor types, including colorectal cancer,

metastatic melanoma, and non-small cell lung cancer (201). More research is needed to extend such kind of engineer for disease control.

In addition, although the release of exosomes is increased under hypoxia, there is also baseline release of exosomes under a physiological state. In another word, almost all cell types within the body produce exosomes and the mixed exosomes exist in almost all intercellular space and body fluids. The increased amount of exosome secretion and some specific encapsulated markers make exosomes a potential biomarker for detecting tumors. The closed and naturally biocompatible membrane structure, stable circulation in the blood, and ability to cross the blood-brain-barrier make exosomes ideal candidates to deliver drugs or genes to target spots (202, 203). But how to classify the exosomes, distinguish their parent cells, identify their target cells remains less elucidated. More research is needed to investigate the specific molecular markers of exosomes to categorize them. Elucidating the specific mechanism of exosomes network and function has great potential for deep understanding and accurate interferer with disease progression.

To conclude, hypoxia increased the release of exosomes in tumor development and other diseases. Donor cells grown in hypoxic microenvironment release exosomes that encapsulate miRNA, lncRNA, circRNA, mRNA, cytokines, and enzymes and transfer them to recipient cells, tissue or, organs in an autocrine, paracrine, or endocrine manner. Such exosomal transfer eventually leads to promoted angiogenesis, tumor progression and metastasis, epithelial meschemenal transition, metabolic waste disposal, immune suppression, and chemoresistance in tumor development. In non-malignant disease, hypoxic exosomes can lead to attenuated fibrosis, altered cell proliferation/migration/apoptosis, autography and inflammation inhibition, immune cell differentiation, insulin resistance, injury recovery, and organ function improvement. Understanding the biogenesis, sorting, and receiving of exosomes provide new perspectives to interfere with the disease.

AUTHOR CONTRIBUTIONS

HJ, writing—original draft. HZ and MZ, writing—discussing about the ideas in the draft. YH and XCL, writing—review and editing. YX and XSL, resources, funding acquisition, project administration, and writing—review and editing. All authors contributed to the article and approved the submitted version.

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GLOSSARY

HIFs	Hypoxia Induced Factors
PHD	prolyl hydroxylases
HREs	hypoxia-responsive elements
ESCRT	endosomal sorting complex required for transport
MDSCs	myeloid-derived suppressor cells
GBM	glioblastoma multiforme
IL-6	interleukin 6
RORA	RAR-related orphan receptor alpha
PTEN	phosphatase and tensin homolog
MCT1	monocarboxylate transporter 1
CD147	cluster of differentiation 147
OGD	oxygen-glucose deprivation
EOC	epithelial ovarian cancer
hMSCs	human mesenchymal stem cells
NK	natural killer
RCC	renal cell carcinoma
TAM	tumor-associated macrophages
ANGPTL4	angiopoietin-like 4
BMSCs	bone marrow-derived mesenchymal stem cells
PTEN	phosphatase and tensin homolog
LUAD	lung adenocarcinoma
NSCLC	non-small cell lung cancer
ROS	reactive oxygen species
CRC	colorectal cancer
OSCC	oesophageal squamous cell carcinoma
HUVECs	human umbilical vein endothelial cells
PSCs	Pancreatic stellate cells
PC	pancreatic cancer
OSCC	oesophageal squamous cell carcinoma
MDSCs	myeloid-derived suppressor cells
HUVECs	Human umbilical vein endothelial cells

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EWS	Ewing's sarcoma
BMSCs	bone marrow mesenchymal stem cells
ceRNAs	competing endogenous RNAs
Dox	doxorubicin
CMVECs	cardiac microvascular endothelial cells
VEGF	vascular endothelial growth factor
EGF	epidermal growth factor
FGF	fibroblast growth factor
MCP	monocyte chemoattractant protein
AMI	acute myocardial infarction
MSCs	mesenchymal stem cells
HUVECs	human umbilical vein endothelial cells
HMGB1	High mobility group box 1 protein
PKA	protein kinase A
CPCs	cardiac progenitor cells
Aβ	Amyloid-β
AD	Alzheimer's disease
PAECs	pulmonary artery endothelial cells
PASMCs	pulmonary arterial smooth muscle cells
HSCs	hematopoietic stem cells
ucMSCs	umbilical cord-derived mesenchymal stem cells
TP53INP1	tumor protein p53 inducible nuclear protein 1
LOXL2	lysyl oxidase-like 2
MSCs	mesenchymal stem cells
RCTI	rotator cuff tendon injuries
ADMSCs	adjacent adipose-derived mesenchymal stem cells
ECM	extracellular matrix
CIA	collagen-induced arthritis
ONFH	osteonecrosis of the femoral head
BMMSCs	bone marrow mesenchymal stem cells
PDAC	pancreatic ductal adenocarcinoma
PSCs	pancreatic stellate cells
ADSCs	adipose tissue-derived stromal cells
OGD/R	oxygen-glucose deprivation and reperfusion
SCI	spinal cord injury