**Oncogenic Effects of Exosomes in** **γ-herpesvirus Associated Neoplasms**

**Abstract**

Kaposi's sarcoma-associated herpesvirus (KSHV) and Epstein Barr Virus (EBV) are both herpesvirus that remarkably associate with human malignancies. Given exosomes can shuttle a lot of herpesvirus related biomolecules from host cells to recipient cells. Therefore, exosomes pathway is utilized by herpesvirus to achieve extensive infections and even oncogenesis. In this review, we outlined the oncogenic biomolecules in exosomes derived from KSHV or EBV infected cells. Moreover, the exosomal biomolecules lead to oncogenesis mainly via three ways, including regulating downstream signals, leading to immune dysfunction and transforming cells.

Key words: Exosome, KSHV, EBV, Neoplasms, Signal Transduction, Immunomodulation, Cell transformation

1. **Introduction**

Exosome was first discovered by Johnstone RM et al. [1] in the research of sheep reticulocyte maturation. It exists in microenvironment and even distant intercellular spaces, manipulating tumor microenvironment by transferring lipids, proteins, nucleic acids and etc. into recipient cells. Exosome is a kind of extracellular vesicles (EVs), but its biogenesis and secretion are different from of other types of vesicles. Exosomes are endocytic origin, also known as exosome pathway. The inward budding of cellular plasma membrane leads to the formation of early endosomes. Early endosomes further bud inwardly leading to the formation of late endosomes or termed as MVBs (multivesicular bodies), which endosomal membrane invaginates to generate ILVs (intraluminal vesicles) in the lumen of the organelles [2]. Cellular contents are constantly loaded into the vesicles during the inward budding. Alternatively, MVB may fuse with lysosome leading to the degradation of vesicular contents [3, 4] or may fuse with the cell membrane to release into extracellular environment as exosomes[5, 6]. Cargos incorporate into exosomes mainly through endosomal sorting complex required for transport (ESCRT) processes and ESCRT-independent processes. ESCRT consists of four main complexes (ESCRT-0, I, II, and III) which are responsible for delivering ubiquitinated proteins for lysosomal deregulation and protein recycling [7, 8]. Besides, with the help of sphingomyelinase [9], tetraspanin proteins [10] etc. ESCRT-independent processes are also possibly to produce ILVs and MVB.

Global statistics revealed that about 15.4% of human tumors can be attributed to infection, of which viruses are predominant. Herpesviruses are medium-sized double-strand DNA viruses and divided into four subfamilies including α, β, γ and unclassified herpesvirus. Specially, γ subfamilies are the most significant oncogenic herpesviruses for both EBV and KSHV are classified as group 1 carcinogenic agents by Agency for Research on Cancer (IARC) [11]. However, the mechanisms of viruses leading to neoplasms need to be further investigate. Recently, a lot studies have demonstrated that γ-herpesvirus affect host cell exosomal pathway to release virus-modified components into the exosomes. After integrating with recipient cells, virus modified exosomes exert oncogenic biofunctions via regulation of signals, phenotypic transformation and immune modulation. In this review, we summarized the oncogenic effects on EBV and KSHV associated exosomes in anticipation of providing a new inside to oncogenic virus and the targets for clinical diagnosis and treatments.

1. **E****xosomes and KSHV-related Neoplasms**

KSHV was first defined as a new human herpesvirus by Chang Y et al. [12] via representational difference analysis on Kaposi's sarcoma tissue. Latency and lytic replication are two phases of KSHV infection [13]. According to previous studies, Kaposi's sarcoma (KS), primary effusion lymphoma (PEL), multicentric Castleman's disease (MCD) are closely related to KSHV infection [14]. Compared with KS, PEL showed stronger correlation with KSHV and EBV co-infection in most case [15]. KSHV inducing malignancy by promoting proliferation, angiogenesis and immune evasion [14]. Notably, KSHV associated exosomes further manipulate microenvironments and promote malignance in extensive cells.

**2.1 Proteins in KSHV-related exosomes**

Exosomes derived from KSHV infected cells promote malignance by influencing the communication between normal cells and KSHV infected cells. Though Chugh PE et al. [16] had detected neither virions nor KSHV-encode proteins in exosomes by utilizing electron microscopy (EM) and mass spectrometry, other proteins released by KSHV infected cells have been demonstrated existing in exosomes. Jeon H et al. [17] utilized proteomic analysis to demonstrate that KSHV infection can alter the distributions of proteins in extracellular vesicles. They analyzed 318 proteins in human umbilical vein endothelial cells (HUVECs) derived exosomes with liquid chromatography tandem mass spectrometry (LC-MS/MS) and found that 239 proteins are increased more than 2 folds following KSHV infection, 82 proteins of which are specific to KSHV associated exosomes. The study suggested that exosomal proteins would be changed after KSHV infection and participate in pathogenesis of KSHV-related diseases. Likewise, Meckes DG et al. [18] analyzed 871 proteins in exosomes derived from different B cell lines by mass spectrometry technique. Compared with the exosomes released by KSHV- cells, 22 proteins are unique to the exosomes derived from KSHV infected B cells. What’s more, proteins involve in metabolism, translation, migration and chromatin modeling are abundant in KSHV infected B cells derived exosomes.

**IFI16（interferon-inducible protein 16）**

Singh VV et al. [19] reported that gamma interferon-inducible protein 16 (IFI16) and cleaved IL-1β released from BCBL-1 cells during KSHV latency through exosome pathways. Both in vitro and in vivo experiments exhibited perinuclear cytoplasmic colocalization of IFI16 and adaptor molecule apoptosis-associated speck-like protein containing a caspase activation and recruitment domain (ASC), which induces IFI16-mediated inflammasome in KSHV pathogenesis.

**Cleaved IL-1β**

Mature IL-1β is an apoptosis factor in several cell types, including glandular epithelial cells, neural precursor cells, cardiomyocyte and so on [20-22]. Exosomal IL-1β is distinct from mature IL-1, for it is functionally inactive, as it cannot engage the surface IL-1 receptor. Hence, exosomal IL-1β is utilized by KSHV to subvert constitutive secretion of proapoptotic mature IL-1β, which facilitates KSHV latency [19].

**Enzymes**

Several enzymes associated with glycolysis are obviously up-regulated in PEL derived exosomes, including hexokinase, pyruvate kinase and lactose dehydrogenase [18]. These enzymes might induce glycolysis of recipient cells and resulting in Warburg effect. Aerobic glycolysis is more suitable for tumor growth for it not only satisfies the needs of rapid growth of tumor cells, also results in acidification of tumor microenvironment. On the ground of acid-mediated invasion hypothesis, H+ ions alter the tumor stroma interface leading to enhanced invasiveness [23].

**2.2 micro RNAs(miRNAs) in KSHV-related exosomes**

MiRNAs were detected in exosomes both isolated from KS clinical samples and mouse models [16]. Hoshina S et al. [24] compared miRNAs in exosomes from KSHV-uninfected cells and KSHV-infected cells via sequencing analysis. They found that 48% miRNAs from KSHV-related exosomes are encoded by KSHV. Moreover, Chugh PE et al. [16] shed a light on two distinct clusters of exosomal miRNAs in KSHV pathogenesis. The studies mentioned above suggested that exosomal miRNAs play a crucial role in the progress of KSHV-associated malignancies.

KSHV encodes 25 mature miRNAs that originated from 12 pre-miRNAs. Each mature miRNA contains a looped, double-stranded pre-miRNA. These 12 pre-miRNAs are distributed throughout KSHV genome. MiR-K12-1 to miR-K12-9 and miR-K12-11 are encoded by K12 intron, while miR-K12-10a and miR-K12-10b are located within the K12 open reading frame (ORF). MiR-K12-12 is transcribed by the 3’UTR of K12 [25]. All of 12 KSHV-encode miRNAs are existing in exosomes. However, exosomal KSHV-encode miRNAs are various from different cell types derived exosomes. For instance, all of the 12 KSHV encoded miRNAs are present in primary LEC infected with BAC16-derived WT KSHV (KLEC) derived exosomes, while only miR-K12-10 and miR-K12-12 are detected in miRNA cluster-deleted KSHV (ΔmiR-KLEC) which have similar KSHV genome copy number as KLEC and expression levels of other latent genes[26]. The binding of miRNAs to the mRNAs regulates the expression of related genes by post-transcription processing, which participates in the interaction with cell signals, cell metabolism, cell cycles, cell proliferation and immune escape.

**Interaction with signals**

Chugh PE et al. [16] demonstrated that KSHV-associated exosomes contain high levels of miRNAs that involved in cell malignant transformation. Gene Ontology pathway analysis (GO pathway analysis) revealed that exosomal miRNAs target multiple signal pathways associated with the central of pathogenesis of KSHV-related tumors including: 1. Signal pathways that regulate cell proliferation, such as PI3K/Akt signals pathway, MAPK signals pathway and Wnt signals pathway. Especially, the PI3K/Akt show the highest correlation to upregulated miRNAs. 2. TGF-beta is silenced by miRNAs, which contributes to KSHV latency; 3. Focal adhesion and adherens junctions are associated with cytoskeletal remodeling and cell adhesion. Pathways regulated by KSHV-associated exosomal miRNAs involve in cell proliferation, chronic inflammation, cell carcinogenesis, and cell metastasis, which take together to promote KSHV infection and KS tumorigenesis. The author emphasized miR-17-92 cluster miRNAs for KS malignancy, which targets various pathways and exerts multiple biofunctions, including angiogenesis, TLR, MAPK, STAT, TGF-beta and NF-kB signaling[16]. Besides, Yogev O et al. [26] reported that transfer of miRNAs by exosomes increases the migration ability of uninfected endothelial cells leading to angiogenesis via stabilization of HIF1α.

**Regulations of metabolism**

KSHV miRNAs regulate the metabolism in both host cells and neighboring uninfected cells. MiRNAs modulate the key cellular genes involved in mitochondrial activity and regulation of glucose metabolism to induce aerobic glycolysis in infected cells. Importantly, KSHV-infected endothelial cells transfer viral-encoded miRNAs to neighboring cells via exosomes and result in a metabolic transformation toward aerobic glycolysis in surrounding uninfected cells [26]. This phenomenon is also termed as “reverse Warburg effect” which means that aerobic glycolysis in tumor stromal cells stimulates tumor growth and metastasis through providing energy-rich metabolites to tumor cells [27].

On the ground of increasing evidences suggested that viruses and exosomes share the similar host biogenesis pathways [17], we suggested that other miRNAs associated with immune regulations, cell survival and KSHV latency might involve in KSHV-associated exosomal pathways. For instance:

1/ Immune escape, KSHV-encoded miRNAs inhibit the innate immune response. MiR-K12-9 regulates interleukin-1 receptor-associated kinase 1 (IRAK1) and miR-K12-5 regulates myeloid differentiation primary response 88 (MYD88) [28]. Both IRAK1 and MYD88 mediate TLR/IL-1R signaling and decrease the levels of IL-6 and IL-8 in IL-1α stimulation of endothelial cells, by which they weaken inflammation to inhibit immune responses. What’s more, KSHV encoded miR-K12-7 silences the expression of major histocompatibility complex class-I related chain B (MICB) resulting in reduction of killing effect in NK cells and promoting immune evasion by blocking the NKG2D (the MICB ligand) interaction [29].

2/ miRNAs also promote cell proliferation and induce anti-apoptosis to achieve cell survival. In both PEL-derived B-cell lines and KSHV-negative Burkitt's lymphoma cell line BL40, miR-k1 targets the cellular cyclin-dependent kinase inhibitor p21 to depress p21 expression. Downregulation of p21 leads to attenuate cell cycle arrest, which promotes abnormal proliferation [30]. Besides, in endothelial cells, MiR-K12-10 resists to TWEAK-induced apoptosis by down-regulating tumor necrosis factor-like weak inducer of apoptosis receptor (TWEAKR), which is beneficial to cell survival and correlates with KS lesions [31].

3/ miRNAs regulate the KSHV life cycle by targeting viral replication function-related genes or cellular genes that regulate KSHV replication. MiR-K9 and miR-K7 target to immediate-early gene ORF50, inhibiting the expression of the replication and transcription activator (RTA) encoded within KSHV gene [32-34]. In addition, miR-k11 contributes to KSHV latency via down regulation of MYB which associated with RTA expression. The indirect inhibition of RTA expression, KSHV replication and transcription together contribute to KSHV latency [35].

* 1. **KSHV associated exosomes and complement system**

Extracellular vesicles derived from KSHV-infected HUVECs activate the complement system through endogenous C3 complement proteins and properdin, leading to deposition of terminal complement complex C5b-9. However, exact factor responsible for activation is still unclear. It does not prevent KSHV infection despite the active complement system [17]. KS is a highly inflammatory tumor [36]. The activated complement system promotes cell survival through activating NF-κB pathway, and KSHV switch to latency by downregulating lytic replication in response to NF-κB pathway. Hence, exosomes derived from KSHV infected cells contribute to inflammatory and endurance of latent infection [17].

1. **Exosomes and EBV-related Neoplasms**

Epstein–Barr virus, also known as human herpesvirus 4, is an enveloped double-stranded linear DNA virus. Similar with KSHV, EBV also contains lytic infection and latent infection. According to the statistics published by Centers for Disease Control and Prevention (CDC), EBV infection occurs in 95 per cents of general population. However, EBV is usually latent in host cells and cause asymptomatic infection. Exosomes derived from EBV infected cells contain a lot of cargos, including EBV encode proteins, signal proteins, nucleic acids, etc. Tumor environment is changed after exosomes integrating into recipient cells. EBV associated exosomes are closely correlated with lymphoma, nasopharyngeal carcinoma, gastric carcinoma.

**3.1 EBV encode proteins in EBV-associated tumor-derived exosomes**

**LMP1 (Epstein-Barr virus (EBV)-encoded latent membrane protein 1)**

LMP1 is one of the major oncogenes of EBV. Up to date, a lot of reaches have been demonstrated that LMP1 secreted into exosomes. Exosomal LMP1 was detected in both EBV infected cell mediums and serum derived from C15 NPC xenograft mouse. Exosomal localization of LMP1 depends on CD63 and the C-terminal farnesylation of UCH-L[37, 38]. LMP1 is located on the membrane of the exosomes, which alter the contents and functions of exosomes. The LMP1 containing exosomes are uptake by various cell types, including epithelia cells, endothelial cells and fibroblast [39]. LMP1+ exosomes exert three biofunctions after the integration with recipient cells:

**1/ immune modulation:** Middeldorp, J. M. [40] suggested that exosomes derived from EBV infected lymphoblastoid cells (LCLs) contain high levels of MHC-II molecules, which induce homogeneous antigen-specific T cells response. Generally speaking, Antigen Presentation Cell (APC) derived exosomes could active T cells. However, previous studies had demonstrated that LMP1 or its fragments have direct immune suppressive effect to T cells and NK cells. Thus, this effect is both MHC class I and MHC class II independent [41]. Notably, T cells could also be suppressed by LMP1+ exosomes. Experimental results has suggested that LMP1+ exosomes elicit immunosuppressive effects [40]. Moreover, Danny F. Dukers et al. [41] for the first time to indicate that EBV+ B cell lines (LCL) secrete LMP1+ exosomes and mediate immune suppression on tumor-infiltrating lymphocytes.

**2/ active downstream signals:** exosomal LMP1 interacts with a lot of key signals, including PI3-K, Akt and ERK. Utilizing LMP1+ exosomes to co-culture with HUVECs and Rat-1 cells showed that the levels of Akt and ERK are upregulated[39]. Besides, in the research of gastric cancer cell line AGS, Sato Y et al. [42] pointed out that exosomes derived from LMP1+ cells induce IL-8 expression in the LMP1-nagative recipient cells, leading to phosphorylation of EGFR, and enhance proliferation of the LMP1-nagative cells. LMP1 activation of signals is the basis of cell transformation and excessive multiplication.

Moreover, a study of proteomics to exosomes utilized Ingenuity Pathway Analysis (IPA) software to predict more exosomal signals and found out that LMP1+ exosomes could interact with extensive signals, including P53, Janus Kinase/signal transducers and activators of transcription (JAK/STAT), NF-κB, interferon regulatory factor 7 (IRF-7), MAPK [18]. However, the exosomal signals mentioned above lack experimental verification.

**3/ transform recipient cells:** Asuka Nanbo et al. [43] isolated three types exosomes derived from EBV-uninfected , EBV-infected B cells of type I and EBV-infected B cells of type III latency, then internalized the three exosomes into EBV-negative epithelial cells. Results revealed that the exosomes derived from type III latency cells upregulate proliferation and the expression levels of intercellular adhesion molecule 1 (ICAM-1) in the recipient cells more significantly than those derived from EBV-negative and type I latency cells. They further confirmed that LMP1 upregulate ICAM-1 expression in epithelia cells significantly. What’s more, LMP1 cooperates with HIFα on regulations of the expression of E-cadherin and N-cadherin, by which exosomes conduct phenotype transformation that associate with epithelial–mesenchymal transition (EMT) [44]. The transformation of recipient cells correlates with tumor proliferation and metastasis.

**LMP2 (Epstein-Barr virus (EBV)-encoded latent membrane protein 2)**

LMP2 includes LMP2A and LMP2B. Up to now, only LMP2A has been demonstrated to exist in EBV-associated exosomes. The secretion of LMP2A into exosomes is regulated by cholesterol. Masato Ikeda et al. [45] showed that the depletion of cholesterol from plasma membrane increase the levels of exosomal LMP2A. LMP2 and LMP1 share the similar characteristics in vivo, as they all contain cytosolic amino- and carboxyl-terminal domains and six or twelve transmembrane domains [45]. Biological functions of LMP2A have been further investigated in the host-cells, including its interaction with MAPK, PI3-K/Akt, NF-κB and STAT pathway [46]. So, in our analogy, LMP2 may also contribute to malignance conducted by exosome though there still have little researches on the bioeffect of exosomal LMP2 in recipient cells.

**3.2 Signaling proteins in EBV-associated tumor-derived exosomes**

**FGF-2 (Fibroblast growth factor-2)**

Basal epithelial cells produce FGF-2 that interacts with its receptor 2 and 3, which satisfy the need of normal epithelia growth and maintenance of connective tissue structures. However, deregulation of FGF-2 plays an important role in both pre-malignant and tumor angiogenesis. In the early stages of carcinogenesis, the expression of FGF-2 is increased, mainly of its 18 kDa isoform, which interacts with over-expressed FGFR-3. The continuous activity of FGER-3 would enhance epithelia growth and promote angiogenesis [47]. Moreover, in the study of EBV-associated exosomes, Ceccarelli S et al. [48] pointed out that LMP1 promotes FGF-2 and its 18 kDa isoform concentrating in multivesicular bodies and release through exosomes. Also, they further implicated that FGF-2 containing exosomes are responsible for angiogenesis in tumor microenvironment.

**HIF1 (hypoxia inducible factor-1)**

Secretion of HIF1 into exosomes is independent of LMP1. However, LMP1 effectively increases the content of HIF1 in exosomes. They also demonstrated that HIF1 recovered from exosomes retain DNA-binding activity and is transcriptionally active in recipient cells after integrating with exosome. The functions of HIF1 in exosomes mainly coordinate with LMP1 to downregulate E-cadherin levels and upregulate N-cadherin levels, which correlates with EMT. Thus, the HIF1 associated exosomes exert pro-metastatic effects in recipient cells, resulting in migration and invasiveness of NP cell lines [24].

**EGFR (Epidermal Growth Factor Receptor)**

David G. Meckes, Jr. et al. [39] indicated that LMP1 increases the release of EGFR into exosomes which are taken by epithelial, endothelial, and fibroblast cells. EGFR is a target for EBV that interacts with a lot of growth signals, including RAS/RAF/MAPK, PI3K and Jak/STAT [49]. Exosomes harboring activated EGFR and interact with recipient cells that notably active MAPK and Akt [50]. The exosomal EGFR enhances angiogenesis by upregulating the expression of Vascular Endothelial Growth Factor Receptor (VEGFR) [50]. On the other hand, exosomal EGFR elicits antagonism to innate antiviral immunity. Tumor derived exosomes are able to transfer EGFR into host macrophages and stimulate mitogen-activated protein kinase kinase 2 (MEKK2) which blocks dimerization of Interferon regulatory Factor 3 (IRF3). Finally, interfere the translocation of IRF3, leading to downregulate the expression of type I interferon [51].

**FasL (first apoptosis signal receptor ligand)**

The effect on promoting proliferation have been well study in EBV-infected cells and its exosomes. However, exosomes derived from both type I and type III EBV latent infected cells was shown to induce apoptosis in B-cells (BL30), T-cells (Jurkat) and epithelial cells (293T cells) in a dose- and time- dependent manner. The exosomes induce death via FasL-mediated extrinsic pathway which binds to CD95(FasL receptor) and trigger the recruitment of the adaptor protein Fas-associated death domain (FADD) in recipient cells followed by activation of caspase-3/7/8 [52]. The results also meet with the report conducted by Klinker et al. [53] who had shown that FasL and MHC-II contained exosomes induce apoptosis of CD4+ T-cells. But this phenomenon of apoptosis are not universal for all types of recipient cells, for example, Burkitt’s lymphoma-derived B-cell line BJAB was found to resistant to apoptosis when exposed to FasL contained exosomes [52]. Thus, exosomal FasL is one of the key factors in inhibition of antigen-specific immune respond in the progress of EBV+ tumor [53], which create a favorable microenvironment for both EBV infection and EBV-associate tumor.

**Galectin-9**

The expression levels of Galectin-9 in nasopharyngeal carcinoma (NPC) is enhanced after EBV infection. What’s more, EBV infected NPC release exosomes containing high amounts of Galectin-9. Further investigation demonstrated that Galectin-9 containing exosomes induce CD4+ cells to apoptosis via Galectin-9/Tim-3 pathway. Tim-3 is a membrane receptor that induce apoptosis in mature Th1 lymphocytes. Thus, EBV associated NPC derived exosomal Galectin-9 also account for the immune evasion in NPC cells [54, 55]. Interestingly, compared with immune suppress effect of exosomal LMP1, exosomal Galectin-9 has more restricted populations of immune cells [55].

**3.3 Nucleic acids in EBV-associated tumor-derived exosomes**

Exosomes released from EBV infected cells contain at least three kinds of nucleic acids, including Epstein-Barr virus-encoded small RNAs (EBERs), microRNAs (miRNAs) and message RNAs (mRNAs). Exosomes protect nucleic acids from being degraded by RNases [56, 57], which ensures RNAs traveling in extracellular space and elicits its biofunctions in recipient cells.

**EBERs**

EBERs include EBER1 and EBER2, which are abundantly expressed in EBV latent infected cells [58]. EBERs are associated with malignancy [57]. EBERs are released into exosomes and probably exist in exosomes in the form of EBER-La complex. Exosomes isolated from the same EBV-infected cells contain higher amounts of EBER1 than EBER2, which could be explained by the expression levels of EBER1 in host cells is 10-fold higher than EBER2 might account for this phenomenon [59]. In the progression of EBV-associated neoplasms, EBERs exert an effect on promoting growth in several cell types, for example, promoting NP cells proliferation via upregulating the expression levels of insulin-like growth factor 1 (IGF-1) [60], promoting Burkitt’s lymphoma growth through IL-10 induction [61] and promoting EBV-infected T cells growth via IL-9 induction [62]. Likewise, exosomal EBERs mainly play two roles in EBV-associated malignancies, including activation of growth signaling and deregulation of inflammation. Internalization of EBERs-modified exosomes into monocyte-derived dendritic cells (moDCs) leads to upregulation in both IFN-related genes and IL-6. The exosomes derived from latent-EBV infected cells contain high levels of EBER1 to induce IFN expression in recipient cells, which links to inflammation-mediated tumorigenesis. What’s more, the unbalanced proinflammatory cytokines further to activate transcriptional factors such as NF-κB, STAT3 and AP-1 in premalignant cells resulting in stimulation of cell proliferation and survival [59].

**miRNAs**

miRNA is a kind of small non-coding RNA containing about 22-25 nucleotides and EBV is the first human virus found to express miRNAs [63]. Interestingly, mature EBV-encoded miRNAs are secreted into exosomes and then elicit a miRNAs-mediated post-transcriptional regulation of gene expression for intercellular communications [56]. EBV-encode miRNAs consist of BamHI fragment H rightward open reading frame 1-miRNAs (BHRF1-miRNAs) and BamHI A rightward transcript-miRNAs (BART-miRNAs) [58]. The release of miRNAs into exosomes is under the regulation of miRNA-loaded RISC (miRISC) [64]. Exosomal miRNAs derived from EBV infected cells participate in immunoregulation and metabolic alteration after taking up by recipient cells. Haneklaus, M. et al. [65] showed that EBV miR-BART15 secreted from EBV transformed B cell line via exosomes takes up by noninfected T cells. Consequently, exosomal miR-BART15 leads to inhibition of NLRP3 inflammasome and also inhibits inflammasome producing of IL-1b. In addition, Pegtel, DM et al. [56] implicated that EBV-encoded exosomal miRNAs secrete from EBV infected B cell and inhibit translation after integrating into recipient cells. Especially, BHRF-1 target CXCL11/ITAC which responsible for immunoregulation and result in increasing of EBV load. Another function of EBV exosomal miRNAs is regulation of metabolism in recipient cells, which is similar with KSHV exosomal miRNAs. EBV transfers miRNAs into exosomes which affect mitochondrial respiration in recipient cells, resulting in metabolism changes in tumor stroma [26].

**mRNAs**

Many studies have found that mRNAs and miRNAs are both exist in the same exosomes [66, 67]. EBV associated exosomes are no exception. A lot of mRNAs loaded into EBV associated exosomes, including EBV-mRNAs coding for the latent phase proteins LMP1, LMP2, EBNA1 and EBNA2. However, the expression of miRNAs in exosomes are different greatly to host cells. mRNAs elicit their biofunctions by integrating into recipient cells, but the accurate functions of exosomal mRNAs need to be further investigated [67].

1. **Summary and Discussion**

Overall, oncogenic γ herpesvirus contribute to neoplasms mainly thought two ways: the first one is directly infection, another one is transfering biological molecules via EVs, especially via exosomes. Interestingly, the two ways draw some similar properties and functions. For directly infection, oncogenic γ herpesvirus manipulate a lot of signals and promote malignancy in infected cells. In addition, oncogenic γ herpesvirus further to release exosomes into extracellular space to manipulate microenvironment and even distant sites. In the oncogenesis of EBV, numerous virus oncogenic molecules are altered in host cells after EBV infection, including LMP1, LMP2A, EBERs, EBV-encode microRNA, which interact with extensive pathways, such as MAPK, NF-kB, JNK, STAT. Therefore, EBV infection contributes to tumor transformation in host cells [68]. To facilitate infection, EBV utilities exosome pathways to deliver bioactive molecules into recipient cells, where EBV associate exosomes exert bioeffects similarly with host cells and lead to adverse changes in microenvironment. As for KSHV, compared with the changes of molecules in KSHV infected host cells, the oncogenic molecules in exosomes seem to be simplified, which mainly about miRNAs and some host cells encode proteins. What’s more, KSHV encode proteins do not exist in exosomes. Even though, KSHV associated exosomes still have strong oncogenic effects by affecting tumor microenvironment via exosomal molecules.

KSHV and EBV are both oncogenic gamma herpesvirus and have the similar types of infection, including lytic infection and latent infection. The latent infection might have more significant contributions to malignancy due to latency is easier to compromise with immunity and further manipulate tumor microenvironment by releasing exosomes. Generally speaking, KSHV and EBV associated exosomes share the analogical bioeffects to the progress of malignancy:

1/ regulating downstream signals: KSHV derived exosomes containing massive miRNAs which regulate the genetic expression of recipient cells, including manipulation of PI3K/Akt, TGF-beta, focal adhesion and adherens junctions. These signals and pathways contribute to pathogens of KS. Besides, EBV associated exosomes contributes to malignancy also via regulation of downstream signals. Especially, LMP1 plays a center role in EBV exosomes. Exosomal LMP1 directly or indirectly interacts with PI3K/Akt, EGFR, P53, NF-κB etc. after integrating into recipient cells. What’s more, LMP1 facilitates other proteins releasing into exosomes, such as, FGF-2, HIF1, ERGF.

2/ leading to immune dysfunction: exosomes are utilized by both KSHV and EBV to secrete proteins and RNAs that associate with either inflammation or immune envision into extracellular spaces. So far, the exosomal miRNAs leading to immune dysfunction have been well investigated [69, 70]. And proteins responsible for immune dysfunction are turning up, such as IFI16 [19], Cleaved IL-1β [19], LMP1 [41], FasL [53], Galectin-9 [55]. Exosomes media the communications between immune cells and oncogenic λ herpesvirus, which domesticates immune system to compromise latent virus for building tumor environment.

3/ transforming cells: though KSHV or EBV don’t produce any virions during latency, they both continuously transform recipient cells via exosomes. What’s more, compared with virus, exosomes integration into recipient cells is independent of specific receptor. Thus, exosomes could infect more types of cells by transferring cargos. For example, KSHV associated exosomal miRNA transfer into KS cells, changing the expression levels of PI3K/Akt, TGF-beta, focal adhesion and adherens junctions, genes associate with metabolism. Similarly, EBV also utilizes exosome to transform cells by transfer exosomal LMP1, HIF1, miRNAs etc. Transformations of recipient cells facilitate proliferation, EMT, migration. Besides, the transformation of immune cells leading to immune envision.

The three biofunctions of exosomes derived from oncogenic λ herpesvirus infected host cells interrelate with each other. Immune evasion facilitates exosomes releasing into extra space where elicit the functions of regulating downstream signals and transforming cells. Also, regulating downstream signals and transforming cells are significant to immune dysfunction. Together, leading to malignancy.

1. **Prospective and Challenge**

Exosomes are promising biomarkers for diagnosis and therapy. Exosomes have been isolated from numerous biofluids including blood, urine, saliva, ascites and breast milk [71]. The contents mentioned above including EBV DNA, EBV RNA, Galectin-9 had been demonstrated as biomarkers for EBV associated neoplasms [72]. As for KSHV associated neoplasm, exosomal miRNAs also could be represented as biomarkers in KS [16]. What’s more, exosomal biomarkers could be much more robust for being protected by exosomes from degradation [57]. However, immature isolation techniques for exosomes make it hard to create a criterion for exosomal biomarkers [73].

Thus, EBV and KSHV-associated exosomes participated in neoplasm. However, exosomes are promising diagnostic markers and therapeutic targets.

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