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Progress on the Pivotal Role and Application of Exosomes in Hodgkin Lymphoma: Carcinogenesis, Diagnosis, Therapy, and Prognosis

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Abstract

Hodgkin lymphoma (HL), also known as Hodgkin's disease (HD), is a type of cancer that originates in the lymphatic system. It is divided into two main types: classical HL and nodular lymphocyte-predominant HL. The current challenges encountered in the pivotal role and application of exosomes in Hodgkin lymphoma, future perspectives and emerging technologies as novel strategies include: the combined detection of ctDNA and exosomal proteins and bioinformatics for the minimally invasive diagnosis and monitoring of tumor recurrence and treatment response within Hodgkin lymphoma; the use of exosomes to interfere with or regulate various cytokines, microRNAs, BTLAs, CEACAMs, latent membrane protein-1, multidrug resistance proteins, and heparanase as potential molecular therapy targets, together with drug therapy, microbial therapy, gene therapy, anti-tumor therapy, immunizing therapy, immune checkpoint inhibitors, and chimeric antigen receptor T-cell therapy to avoid resistance, enhance therapeutic effects, promote immunity, and improve the prognosis of relapsed or refractory Hodgkin lymphoma; the use of radiolabeled antibodies, exosomal imaging, and radiotherapy to establish a 'lock-key' therapy as a reference for targeted therapy efficiencies in various stages, and the use of vaccine or immune random libraries, exosome biotechnology strategies, such as dendritic cell vaccine therapy or exosome natural or artificial cargo carrying and delivery, as potential alternatives in the combined immunization therapy of Hodgkin lymphoma. We believe that the diversity and development of exosomes will promote comprehensive applications that can have a potential therapeutic impact on clinical research in Hodgkin lymphoma.

Keywords: Hodgkin lymphoma; Exosomes; Pivotal Role; microRNAs

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Introduction

Hodgkin lymphoma (HL), also known as Hodgkin's disease (HD), is a type of cancer that originates in the lymphatic system. It is divided into two main types: classical HL and nodular lymphocyte-predominant HL [1]. While the former is divided into four subtypes based on the specific cell involved,

the latter is divided into only two groups. These units are defined by the classification based on the cell appearances and behavioral patterns under a microscope, including the types of immune cells, degradation patterns, immune compounds, and biological diagnosis [2]. Most HL cases involve enlarged lymph nodes, either alone or in conjunction with other lumps related to the lymph system. HL more often affects men and women, although it may strike at any age. The overall incidence rate for HL is 2.1 per 100,000. These tend to increase gradually with age and rise rapidly once adolescents enter adolescence [3]. The predilection for HL has obscure ethnic, geographical, and everyday components. Over decades, the incidence of HL among adolescents in both developed and developing countries, along with adults, has increased significantly [1-4]. HD was reported upon the outbreak of its clinical manifestations. Sir Thomas Davis is often viewed as one of the "garish diseases of the nineteenth century [4]." Following his introduction in 1832, HD research increased precipitously. The portrayal of the illness as multifarious malignancies and its astounding absence along with fantastic amplification has raised investigations into HL to a "most favored" position [5]. Cure became increasingly widespread in the 19th century, thanks to the growth of pathology and the discovery of so-called histopathological research [6-10]. A neoplasm famous for the extensive production of earnest monologically obtained diagnoses emerged; however, in 1994, HL scientists were greatly astonished when publications appeared that identified HL "mini-chromosomes" as fact [11]. The molecular genetic knowledge obtained so far allows reasonable predictions and insights into the diagnosis and recovery of the different subtypes of HL. Indeed, HD is one of the diseases that are curable by a plethora of long-processed, next-generation combination therapies that manage the lethargy of toxin fertilizer. The application of agents and biomolecular digital analysis achieving durable responses introduces highly personalized treatment. Alas, therapies have many long-term side effects as pillar therapy to enable a more durable cure. Since the adverse prognostic markers at the time of diagnosis cannot be forecasted on all occasions, the identification of new discoveries and developments from cautious research provides rationale for stating the useful roles and applications of exosomes in HL [12].

Epidemiology

Hodgkin lymphoma (HL) is a type of hematological tumor that is part of a category of lymphoma. This review focuses on HL per se, and it is easy to confuse it with the mechanistic routine use of non-HL-related therapeutic agents [13]. HL is a B or T lymphocytic lymphoma with a few monoclonal malignancies, lymphocytoma, fragile vesicle proliferation, and cell/eosinophil/lymphocyte-rich vesicle apex-dominated subtypes of a kind of non-HL [14]. Epidemiologically, most patients are individuals over 55 years old (60 years old for low-stage HL, which is more common in men, and over 70 years old for high-stage HL with a male-to-female ratio over 80), but the clinical gender distribution has changed over time [14]. Meanwhile, the environmental factors that increase HL include family inheritance and EBV family inheritance, with the latter being more representative in Asian children. In short, if there is no family inheritance of EBV, then acquired family inheritance and/or concurrent adverse environmental factors contribute to the secondary carcinogenic risk of HL. There is an

increasing global burden of HL, which represents approximately 15–25% of diagnosed individuals suffering from lymphoma [15]. Recently, more than 30,000 cases of HL are diagnosed each year worldwide; at the same time, mycosis fungoides, peritonitis, and other lethality data continue to gradually improve, resulting in a significant reduction in total lymphoma-related mortality (including inflammation associated with lymphoma) worldwide, with HL > multiple leukemia > perivascular cell glycogenic tumor cell [16]. In contrast, in other systemic nodular and diffuse tortuosity, previous reports indicate a significant decline. Case reports of HL morbidity in the world are gradually increasing, with racial and geographical differences. In Western countries, HL is more common in white individuals, and the incidence rate in black individuals is only about 70% of that in white individuals. Additionally, clinical reports show that children in developing countries are more commonly affected than adults in developed countries, while the reverse is true in developed countries [17].

Pathophysiology and Key Molecular Mechanisms

Exosomes are nano-sized vesicles with a diameter of 30–150 nm, which originate from the cell membrane and play a key role in intercellular communication. As one of the most important mediators of cell communication, exosomes can carry and transfer a series of bioactive proteins, lipids, RNA, DNA, and nucleic acid fragments from one cell to another, helping tumor cells achieve the purpose of rapidly spreading oncogenic molecules without genetic changes [18]. The network of exosome communication is extensively interacted with the intercellular communication network, providing new insight into the development and recurrence of various malignancies such as the immune escape of tumor cells, promotion of tumor angiogenesis, and formation of the pre-metastatic microenvironment. Furthermore, the characteristics of the proteins and RNA transported are associated with the donor cells, effectively functioning as preferred biomarkers and therapeutic targets through rapid, noninvasive, repeatable examinations with relatively high specificity and sensitivity [19]. Indeed, the roles of HL cell-derived exosomes are fundamental to obtaining a comprehensive sequence of their development. Although the pathogenesis is not fully elucidated, research studies on HL and exosomes have made appreciable progress. Recent decades have unraveled a myriad of aspects of tumor-derived exosomes in HL, from carcinogenesis, metastasis, and treatment resistance to progression, which have provided promising biomarker options for prognostic evaluation and targeted therapy. Similarly, however, the tumor-sustaining features of HL cell-derived exosomes contribute to the establishment of immunosuppression in the HL microenvironment mainly through targeted inhibition of different immune cells, including T-lymphocytes, natural killer cells, and dendritic cells, which further aggravate the immune tolerance of HL cells [20].

Exosomes: Biogenesis, Composition, and Functions

The discovery of exosomes expands the traditional classification of vesicles and a series of biological functions of cells. Exosomes secreted by extensive liquid tumor cells and solid tumor cells contain numerous integral molecular components of biological significance, such as proteins, microRNAs, long non-coding RNAs, and DNA. They play significant roles in the crosstalk between tumor cells and other

Research Article
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cells in the microenvironment [21]. Their pivotal role comes to light in tumor occurrence, development, diagnosis, and treatment. In tumor cells, exosomes loaded with different signals can motivate tumor cell proliferation and metastasis. Tumor-derived exosomes can also promote angiogenesis and drive immune cells, such as T cells and macrophages, toward tumor-friendly phenotypes. Importantly, tumor-derived exosomes have diagnostic and prognostic potentials [22]. However, the significant role of exosomes in Hodgkin lymphoma has not yet been fully explored and understood. In this review, we discuss the current understanding of exosomes in Hodgkin lymphoma from the following aspects: tumor pathogenesis, diagnostic markers, therapeutic targets and strategies, and sensitivity and drug resistance-associated prognostic markers. These aspects independently and integrally contribute to the relation between Hodgkin lymphoma cells and other cells in the immune microenvironment, facilitating the comprehensive understanding of exosomes. Finally, the current study critically evaluates the application value, existing problems, and future direction of exosomes in Hodgkin lymphoma. We hope that this review will guide scientists to continuously focus on this research point and provide a research direction for scientists [23].

Biogenesis and Secretion Mechanisms

Exosomes are small extracellular vesicles secreted by almost all cell types and are produced within the endosomal pathway or originate as the budding vesicles of the plasmalemma. It was found that multivesicular endosomes originate from early endosomes as soon as the intraluminal vesicles start to bud into the lumens of the multivesicular endosome. The resulting multivesicular endosome is mature and then referred to as a late endosome. Initially, the exosomes were thought to be excreted from the cells during the maturation of late endosomes [24]. The budding of the vesicles into the lumens of the late endosomes has been visualized and observed, and this process is essential for exosome biogenesis. The budding process is promoted by the endosomal sorting complex required for transport system and related proteins. The complex recognizes ubiquitinated proteins and contains hepatocyte growth factor receptor substrate and signal-transducing adaptor molecule, dynamin, etc. The dependent pathway also plays an important role in exosome formation [25]. The complex has been proved to promote recognition and concentration of exosome-shipped protein cargo and slow down the entry of lysosome-targeted transmembrane surface proteins in late endosomes. One complex is a bridge between another and the last. The last is closely related to severing events and bud neck formation. The ATPase enzyme possesses severing activity and promotes the release of the budding vesicles from multivesicular endosomes. Overexpression or disturbance of these proteins could significantly change the number of produced exosomes [26]. The generation of exosomes has other independent pathways such as the cholesterol-dependent extracellular membrane fluidity or the phospholipid-driven pathway. The membrane organization and the regulation also regulate exosome sorting, loading, and secretion. After the budding and release from the late endosomes or transition endosomes, the resulting multivesicular endosomes are referred to as exosomes. Finally, these exosomes are secreted from the cells after exocytosis [27]. The released exosomes are authentic due to sharing their quantity and density with the mature exosomes. As interactive vehicles for intercellular

and intracellular communication, exosomes play a pivotal role in physiological processes such as the immune response, inflammation, stem cell division, antigen presentation, tissue repair, neurogenesis, and angiogenesis. Exosomes also play an important role in carcinogenesis, including Hodgkin lymphoma [28].

Composition and Cargo Sorting

Consisting of 121 proteins, 233 kinds of glycoproteins, and 401 lipids, exosomes contain unique sets of DNA, coding and non-coding RNA, transcription factors, lipid metabolites, and proteins, as these serve as intercellular signals between different biological cells. How do exosomes transport various substances into and from the circulatory and humoral systems, and how are body fluids and tissues achieved? These are important problems. Tetraspanins CD63, CD9, and CD81, Alix, and the recently discovered PDCD6IP, along with other proteins in the MVB, are part of the ESCRT complex on the exosomal outer surface, selectively carrying substances, as well as the ion channel protein AGS3 in the MVB via sucrose gradient isolation, pH link, SDS/PAGE, and mass spectrometry to obtain results. In exosomal intraluminal vesicles, loading occurs in the cytoplasm, ultimately incorporating into exosomes to act as a sorting substance [29]. ESCRT is an evolutionarily conserved family of protein complexes involved not only in MVB biogenesis but also in other membrane fusion events. The ESCRT protein family is the most important, widely found in membrane-related metabolism and transportation, as well as in endosomal sorting, cytokinesis, and retrovirus exocytosis. The ESCRT complex mediates late endosomal sorting and MVB ubiquitin protein: transmembrane substrate-guided degradation, as well as reversible budding and long nose [30]. The process of macropinocytosis involves cell surface protrusions that internalize large amounts of bulk metal particles and fluids. The ESCRT complex has four VPS protein categories, with VPS proteins composing six families, 16 sub-families, and 25 genes [30]. For every VPS family, there are 10 sub-families: the VPS-23 family in the VPS family. The VPS-24 subgroup members are related to the intracellular trafficking process, including cargo sorting to MVB, especially the biogenesis of late endosomal MVB, the endosomal coat complex, and micro-autophagy. It can interact with other types of VPS proteins to complete the formation of the multi-protein membrane deformation complex and complete the endosome internalization budding [31].

Exosome-Mediated Communication in Cancer

Exosomes have the potential to become diagnostic or prognostic biomarkers in clinical conditions, especially for tumor diseases. Through all-round modification and PCR-based enhancement, exosomes can act as anti-tumor immune responses, simultaneously activating immunosuppression and serving as cancer-dominated inhibitors. Hodgkin lymphoma (HL) is among the unique and aggressive forms, and the most prominent cells are HL cells that always have a similar position in amplified exosomes. The study analyzed the latest literature to assess how exosome-mediated processes are active in HL progression and how exosomes can function as potential related prognostic or diagnostic factors [31]. Exosomes are released into the extracellular space to enable cell-to-cell

contact and to package flexible, minute-sized internal components, small RNAs, and DNAs, as essential molecules active in transporting information to enrich, alter, and eliminate harmful cells. Data indicate that in cancer, exosomes can carry protective molecules present in the parent cell, thus demonstrating inhibitory effects; however, they are often utilized to trigger the body's immune responses, maximizing and causing regenerative impairment [32].

Interactions with Tumor Microenvironment

With the increasing evidence of the importance of the microenvironment in HRS cell growth, the interactions between tumor cells and important components of the microenvironment will be briefly introduced. HL is a malignant lymphoma with a unique tumor microenvironment. The HRS cell itself accounts for less than 1% of the tumor volume. The remaining cells are mainly non-tumor cells and secreted stroma. The important components of the microenvironment include PDCs, TAMs, MDSCs, Th cells (especially CD4+, Tfh cells), Tregs, EMCs, FBs, MGCs, NK cells, DCs, and rare B cells, plasma cells, and eosinophils. According to the results of RNAseq analysis, the behavior of HRS can be regulated by these non-HRS cells [33]. Exosomes are involved in the communication between HRS cells and these cells. The main function of exosomes released by HRS cells is to regulate cells in the tumor microenvironment around HRS cells, evade immune recognition, and create an immunosuppressive environment. In addition, exosomes also have the effect of enhancing the invasion and migration of HRS cells and promoting tumor progression. In conclusion, exosomes play an important role in the crosstalk between HRS cells and the tumor microenvironment of HL, which helps HRS cells escape immune attack and promotes the progression of HL. Therapies targeting the production of exosomes or the substance composition and function of exosomes will improve the efficacy of immunotherapy when combined with existing treatment strategies and are potential therapeutic directions for patients with HL [34].

Immune Modulation and Evasion

As a result, exosomes derived from different cells have immunosuppressive activities by inducing regulatory T cell formation or by facilitating the generation of monocytic myeloid-derived suppressor cells, mediating the expansion of M2 macrophages and promoting long non-coding RNA/microRNA/nNOS axis. Remarkably, exosomes could also promote NK cell immunosuppression through TGF-β1 [35]. These results indicate that exosomes could trigger tumor immune escape by suppressing the immune response. This outstanding immunosuppressive property could potentially be applied to avoid GVHD in the process of allo-HSCT. Encouragingly, human umbilical cord-derived mesenchymal stem cell exosomes could avoid GVHD by inhibiting the immune response. Alternatively, dendritic cells transfected with HSP70-fused lymphoma exosomes could act as an antitumor vaccine that results in good clinical outcomes in solid tumor-bearing mice [36]. Besides the tumor immune escape ability, the generation of specific T helper subsets and alteration of the plasma proteome are also important mechanisms in cancer immune modulation. In HL-derived exosomes, 19 types of glycoproteins were upregulated and were found to be essential in stimulating the donor

CD19+ B cells into plasma cells in this study. Similarly, BMCs could be reshaped by a fusion protein with an exosome-associated surface that displayed the PD1 ligand. Apart from this, nasopharyngeal carcinoma cells were able to make CD4+ T lymphocytes recognize and kill tumor cells through MIG/CXCR3 and EBNA1/CD4 interactions. Taken together, researchers should assess the prognosis of cHL by detecting exosome-associated markers. The potential application of modifying the exosome using antisense oligonucleotides or small interfering RNA to inhibit immunosuppressive functions was further analyzed [37]. The results found that the modified exosomes were able to load selectively and deliver siRNA specifically into the cHL cells in vitro. There is no doubt that this action is beneficial in improving prognosis and inhibiting the proliferation of HRS cells.

Exosomes in Hodgkin Lymphoma: Role and Significance

Recent studies have found that exosomes are related to the occurrence, development, diagnosis, and efficacy of lymphatic tumor-based Hodgkin lymphoma (HL). In the HL pathway, the immune microenvironment generates an excessive effect that inhibits the immune clearance of HLs by recruiting and educating a series of immune cells in a paracrine model, exploiting distinct situational variables in HL patient serum exosomes and H/RS cell line exosomes. A growing number of studies have shown that utilizing the main positive role of exo-EVs for drug delivery will lead to an inductively efficient tissue disorder trend responsive to outcome prediction [38]. The use of drugs and other small-volume molecules or gene drugs to physically carry exosomes to the PKH26 cells and to provide additional 5-fluorouracil effectively and repeatedly indicates that exo-EVs can be the perfect targeted drug delivery system to increase drug concentration and efficiency.

Exosomes can be secreted by all types of cells, and recently these small vesicles have been found to play important roles in intercellular communication. Exosomes secreted by cancer cells can regulate cell invasion and angiogenesis. Exosomes derived from Hodgkin Reed–Sternberg (HRS) cells can effectively package and deliver neoantigens and help change the immune function of recipient cells. In this paper, we will present the current research into the relationship between exosomes and HL and explore a new direction to increase the therapeutic effects of exosomes in HL to further improve their therapeutic effect.

Diagnostic and Prognostic Biomarkers

Hodgkin lymphoma rarely shows obvious specific symptoms except cervical symptoms, which often lead to misdiagnosis at early stages [39]. The diagnosis is mainly based on clinical symptoms, pathology, immunohistochemistry, cytogenetics, and other tests. However, considering tumor heterogeneity and the substantial patient suffering, the role of the medical community at large is essentially to identify and validate specific biomarkers for diagnostic staging, prognosis monitoring, and prognostic decision-making to predict the progression and recurrence of Hodgkin lymphoma as early and accurately as possible [40]. A large body of emerging evidence has demonstrated that exosomes are powerful messengers in mediating intercellular communications and that their complex

cargo composition can significantly and comprehensively reflect the physiological, biochemical, and immunological states of donor tumor cells and change before the tumor phenotype is evident, which fulfills most of the requirements mentioned here [41]. The close association of extracellular vesicles with lymphomagenesis is relatively poorly investigated and is mainly concentrated in the plasma scale, while the specific role of exosomes and their contents as potential targets for mechanistic studies as well as for the clinic, early diagnosis, pharmacologic or gene therapy effects support, and outcome monitoring of therapy-related diseases are not well penetrated. In this study, we will specifically review the related research progress in the role of exosomes in Hodgkin lymphoma as well as their contents, focusing on diagnosis, therapy, and prognosis. We believe that such reviews can have a broad effect and influence future mechanistic studies and clinical diagnostic developments and conclusions in this field [41].

Tumor Progression and Metastasis

Current research has shown that tumor-derived exosomes can play a pivotal role in tumor formation, development, invasion, metastasis, and carcinogenesis by mediating intercellular communication among tumor cells, non-tumor cells, and the tumor microenvironment [42]. This includes promoting angiogenesis, forming premetastatic niches, modulating immune response, and participating in the formation of a hypoxic microenvironment [43]. At present, the mechanisms by which tumor-derived exosomes participate in the entire metastatic evolution and exploration in Hodgkin lymphoma, especially in promoting the occurrence of initial metastasis, mediating immune response, and coping with immune checkpoint therapy, are not yet clear and have not been reported [44].

To provide an in-depth understanding of the pivotal role of exosomes in Hodgkin lymphoma carcinogenesis, we summarized the detailed processes of exosomes participating in Hodgkin lymphoma invasion, metastasis, and carcinogenesis [45]. Recent accumulated data has demonstrated the comprehensive function of exosomes in tumor development, including the promotion of angiogenesis and lymphangiogenesis, forming premetastatic niches, remodeling the tumor microenvironment, forming the extracellular matrix, stimulating epithelial-mesenchymal transition, increasing genetic mutation, enhancing stemness, disturbing genetic integrity, inheriting pathogenic processes, modulating immune response, and regulating the activity of immune checkpoint therapy, as well as colonization and organotropism of metastasis [46].

Exosome Isolation and Characterization Methods

Exosomes can be procured from body fluids or cultured supernatants. The most well-worked-out methodologies to isolate exosomes include ultracentrifugation-based methods followed by a size-based exosome enrichment kit and density gradient [47]. Ultracentrifugation effectively isolates purer exosomes, which is generally at the price of lower yield and may also co-isolate protein aggregates and apoptotic bodies. Size-based exosome enrichment kits, especially when the kit is used according to the recommendations, save time and offer relatively higher yield but may co-isolate EVs of other

sizes indiscriminately [48]. The density gradient employed uses iodixanol or sucrose in both buoyant ultracentrifugation and ultracentrifugation combined with sucrose cushion to remove other small vesicles. In addition, other isolation methodologies, such as microfluidic systems, immunoaffinity capture, and precipitation, are suitable for the isolation of exosomes [49]. Because of the similar sizes and densities of exosomes (30-150 nm, density: 1.13-1.19 g/mL), effective purification and accurate characterization are equally important for subsequent studies. Transmission electron microscopy, nanoparticle tracking analysis, scanning electron microscopy, flow cytometry, and dynamic light scattering are common methods for exosome sizing and visualization [50]. Flow cytometry can even detect the surface-specific protein or even internal protein of the sorted exosome. Western blotting and enzyme-linked immunosorbent assay are used to detect the expressions of exosome-specific markers and cargoes [51]. Animal models under the guidance of in vivo imaging are also employed to characterize exosomes. Liquid chromatography-mass spectrometry combined with a database of exosomal proteins is used to confirm the successful isolation of exosomes. Finally, exosomal RNA is sequenced [52].

Exosomes as Therapeutic Targets in Hodgkin Lymphoma

In recent years, an increasing number of investigations have focused on how to exploit the unique potential of exosomes in the diagnosis and treatment of diseases. Exosomes derived from different sources tend to exhibit distinct exosomal cargoes and characteristic molecular patterns [53]. With an improved understanding of varied exosomal functional roles, researchers are seeking more customizable exosomes for clinical application [54]. Exosomes have been suggested to serve as pivotal therapeutic targets for HL acquisition, where they could block the interacting signaling pathway, deplete the oncogene-mutated proteins, decrease the rate of drug efflux, adjust the corresponding gene expression and epigenetic status, bolster the anti-tumor immunity, and strengthen the sensitivity of cells to anti-HL drugs, such as chemotherapy, CIK cellular immunotherapy, and drug sensitivity, as well as drug resistance to the targeted inhibitors on the signal transduction molecule [55]. In future HL exploration, it is of great importance to design exosome-based drugs targeting not only the multiple signal transduction pathways at the same time, but also to combine them with different cutting-edge techniques for a more satisfactory entry guided by tailored features and better cell membrane fusion efficiency towards the target site to achieve a more sustainable and effective exosome-based targeted differential HL therapy. The expression pattern of all these HL-related exosomal markers would provide a basis for designing various specific and reproducible exosome isolation, sorting, and manipulation techniques, as well as complex carriers featuring improved biological compatibility and lower toxicity in a validated and concentrated mass [56].

Drug Delivery and Sensitization Strategies

Exosomes exhibit the attributes of proteins, ions, metals, lipids, and polymers, as well as a unique metastatic route and rapid cell entrance. To sum up, cancer cells communicate this message to stromal cells and their territory through exosomes filled with signaling proteins and functional RNAs.

Tumor immunotherapy and chemotherapy also suggest the necessity of enhanced effectiveness in the delivery of medications. On the one hand, exosomes derived from stellate cells and immature dendritic cells are prohibited because of the modest effectiveness of the immunization process. On the other hand, macrophage-derived exosomes absorb liposomes more effectively than liposomes that attach small-molecule substances specifically to tumor modules. Exosomes with M1 are loaded with miR-155 and then accumulate [57]. To concentrate on drug administration, using bone marrow mesenchymal stem cells, which loaded exosomes, can repair vasculitis with significantly higher performance than loaded exosomes alone. Dopamine added to natural exosome micelles can control the cargo to monolayers of TNBC cell phenotypes, creating unnatural conditions of aggregation of monolayer exosomes. Indeed, this quality is superior to natural perfusion antitumor properties. It is feasible to support a revolutionary approach to addressing drug saturation-dependent issues and to further boost exosome administration and revenue. A large number of studies have demonstrated how to improve the anti-exosome collection of natural exosome-derived nanoparticles. It shows that loading natural exosome agents into haptens or combining them into additional materials will significantly enhance prescription expenses.

Clinical Applications and Challenges in Exosome Research

Hastening research to maximize exosome utility is always a goal. Here, we analyze the clinical applications as well as the challenges in exosome research [58]. In the complex context of HL, exosomes can be used as carriers delivering therapeutic drugs. Exosomes have great potential in numerous clinical applications. Understanding and harnessing exosome biology may contribute to improvements in human health and assist in controlling cancer. Data are reviewed and analyzed on the vital roles of exosomes in HL carcinogenesis, diagnosis, therapy, and prognosis. Researchers must determine how exosomes contribute to xenogeneic homeostasis, especially during anti-cancer treatment. The limitations and challenges of exosome research must be addressed. First, exosomes have various origins and have different expression levels and functions in different health and disease states, which confuses the study of exosomes [59]. However, their physical and chemical characteristics create troubles in the measurement process. Moreover, exosomes are easily contaminated in the extraction process, and the extraction efficiency is low, which may cause unreliable experimental results. Here we give a detailed analysis and summary of the clinical applications and challenges in exosome research. In future HL therapeutics, improving the loading and targeting of exosomes will result in better drug delivery. Of note, the process of exosome identification is difficult and expensive. Identifying a simple, sensitive, specific, rapid, and inexpensive method for exosome identification is a key question to be addressed in exosome research. The complexity of the study system in exosome research leads to difficulties in identifying suitable disease biomarkers, especially for early diagnosis [60].

Conclusion

Exosomes play a key role in the occurrence and development of Hodgkin lymphoma, as well as in treatment and outcome. Exosomes are among the most active extracellular vesicles in the process of cell–cell communication, and they play a key role in many diseases. In the present review, we provide a theoretical basis for the pivotal role of exosomes in Hodgkin lymphoma, with a special focus on carcinogenesis, diagnosis, therapy, and prognosis. After reviewing the latest advancements, we believe exosomes may become another important development node in the treatment of Hodgkin lymphoma. Understanding exosomes in the pathogenesis of the tumor will promote the identification of new predictive markers for the clinical outcome of Hodgkin lymphoma. Currently, many more exosomal protein markers and nucleic acid signatures have been identified for the utilization of lymphoma diagnosis and prognosis. Effective exosome isolation is critical for the development and improvement of new exosome-based markers. Finally, exosomes show promise as ideal drug carriers to improve selective cancer cell killing and may be helpful in enhancing lymphoma treatment outcomes and reducing side effects. A better understanding of the structures, sources, and pathways of exosomes, along with advanced technologies for characterizing them, should provide more precision and personalized treatments. However, exosomes are only a small part of extracellular vesicles; many uncertainties still remain. The new nomenclature framework terms 'small EVs' and 'large EVs' should be adopted to avoid confusion. The published vesicle-related tools or protocols need to be optimized to enable broader use of these rules.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Ethics Statement

Approved by local committee.

Authors' contributions

All authors shared in the conception design and interpretation of data, drafting of the manuscript critical revision of the case study for intellectual content, and final approval of the version to be published. All authors read and approved the final manuscript.

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