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Role of Exosomes in Aesthetic Medicine

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Abstract:

Background: Exosomes are nanosized extracellular vesicles of endosomal origin that play a pivotal role in intercellular communication by transferring bioactive molecules such as proteins, lipids, and nucleic acids. Once regarded as cellular waste products, exosomes are now recognized as key mediators in tissue regeneration, immune modulation, and cellular homeostasis. Their intrinsic biocompatibility, low immunogenicity, and ability to penetrate biological barriers have positioned them as promising cell-free therapeutic tools in aesthetic medicine. Recent advances have highlighted the role of exosomes—particularly those derived from mesenchymal and adipose-derived stem cells—in skin rejuvenation, wound healing, pigmentation disorders, hair regeneration, and scar remodeling. This review discusses the biological characteristics of exosomes, including their biogenesis, isolation and characterization methods, routes of administration, and clinical applications in aesthetic medicine, while addressing current challenges, safety considerations, and future translational perspectives.

Keywords: Exosomes; Extracellular vesicles; Aesthetic medicine; Regenerative dermatology; Stem cell-derived exosomes; Drug delivery systems

Introduction:

A variety of applications of human adipose tissue stem cell-derived exosomes have been suggested as novel cell-free therapeutic strategies in the regenerative and aesthetic medical fields **(1)**.

The term exosomes refer to membrane-bound vesicles released from many cells into the extracellular matrix. The main idea is that these nano-particles are generated inside the cells, within the MVBs, by the invagination of the membrane of MVBs, which leads to the generation of intraluminal vesicles (ILVs) inside MVBs (Fig. 1) **(**2**)**.

These vesicles may be named pre-exosomes, which can be secreted out of cells following the fusion of MVBs with the cellular membrane; now there are known as exosomes. Always MVBs do not expel ILVs out of cells, rather they may fuse with the lysosomes and subsequently ILVs and their cargo are degraded for recycling and reuse for cellular homeostasis **(2)**.

In addition, there is evidence that MVBs may fuse with the autophagosomes of the autophagy pathway, and generate hybrid vesicles known as ‘’Amphisomes’’, subsequently, amphisomes may now fuse with the plasma membrane and secrete exosomes with other cargo **(3)**.

Understanding how and why MVBs fuse with different membranes has been a long-standing goal because it is critical to discriminate heterogeneity in exosomes, and relevant physiological consequences, regulate their production for clinic use and monitor pathological conditions. Various molecules and complexes are present on MVBs membrane that mediate cargo loading and sorting inward budding membrane, and pinch off newly formed ILVs into MVBs. For instance, an ESCRT-related mechanism, consists of four complexes, that mediate biogenesis and loading ILVs using ATP molecules in a regulated manner or an ESCRT-independent mechanism is involved **(**2**)**.

Many Rab proteins linked with MVBs facilitate the movement of MVBs in different ways **(**2**)**. Among them, the role of Rab7, Rab8, Rab11, Rab27, and Rab35 in regulating the exosomes pathway has been recognized. The SNARE proteins are short molecules that drive the fusion of MVBs and the cellular plasma **(**4**)**.

Upon secretion into the cellular space, exosomes interact with the target cells those either nearly located or distantly. It was suggested that three mechanisms that exosome or other EVs recruit to affect recipient cells' function comprising, endocytosis (e.g. phagocytosis and pinocytosis), receptor-ligand interaction, and direct-fusion, which cause changes in cellular and biological processes, participating in normal physiology or worsening pathological condition **(5)**.

This is an exosomes journey; however, further investigations would be needed to determine exactly how exosomes are generated for a definite purpose. Exosomes cargo comprises molecules provided from the cellular membrane, endosomal compartments, the cytoplasm, and those that come from the endomembrane system like the Golgi apparatus **(**2**)**.

Exosomes exhibit a specific biconcave or cup-like shape during the drying process, while they appear spheroid under transmission electron microscopy **(6)**. These vesicles have a density 1.08–1.19 g/ml with common exosomal markers such as CD9, CD63, CD82, CD81, Alix, and Tsg101 **(7)**.

Thousands of types of biomolecule are present within exosomes, comprising proteins, numerous RNAs, and lipids whose data are collected and presented by various databases such as Vesiclepedia, Exocarta, and a Bioinformatics lab from china **(8)**.

Understanding mechanisms that drive exosomes biogenesis and loading, as well as exosomes cargo and ways of exosomes uptake by other cells, will support scientists to achieve meticulous and efficient translational medicine. It is worthy to note that full comprehension of the nature, purity, and origin of exosomes would be critical for downstream experiments. For example, exosomes from stem cells may participate in regeneration and normal physiology, while those derived from infected or cancer cells mediate pathogenesis (Fig. 1) **(8)**.

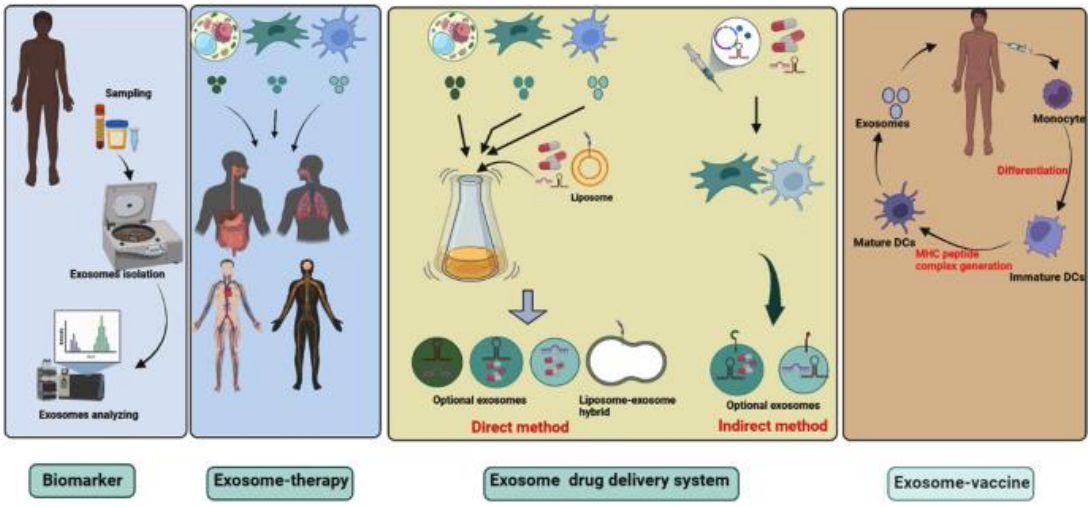

Fig 1. Clinical application of exosomes. In clinical trials, exosomes are being used as biomarkers, cell-free therapy (exosome-therapy), drug delivery system, and cancer vaccine. Exosomes from plant cells, mesenchymal cells, T cells, and dendritic cells are used for the treatment of different diseases. In addition, exosomes from these sources are promising carriers for drug delivery systems. In the direct method, exosomes are loaded with therapeutic agents, while through indirect methods, proper cells are genetically engineered or co-cultured with therapeutic agents to produce artificial exosomes **(9)**.

Formation

The initial endosomes are formed by the invagination of the cell membrane in the early stage, and then the bioactive substances begin to accumulate in the early sorting endosomes (ESEs). Then, under the control of

the endocytosis sorting complex and other related proteins required for transport, the early endosomes become late sorting endosomes (LSEs). LSEs ultimately form multivesicular bodies (MVBs) after a second indentation **(10)**.

After MVBs fuses with the cell membrane, the substances inside the cells are released to the outside in the form of vesicles. These vesicles are exosomes. The biological origin of exosomes is shown in Figure (2). The formation of exosomes is diversified. At present, more researches are on ESCRT-dependent and ESCRT-independent mechanisms **(10)**.

However, it has recently been reported that certain components, such as four-transmembrane domain proteins and lipid raft, are also involved in the formation of some exosomes. Therefore, the exact mechanism remains controversial **(11)**.

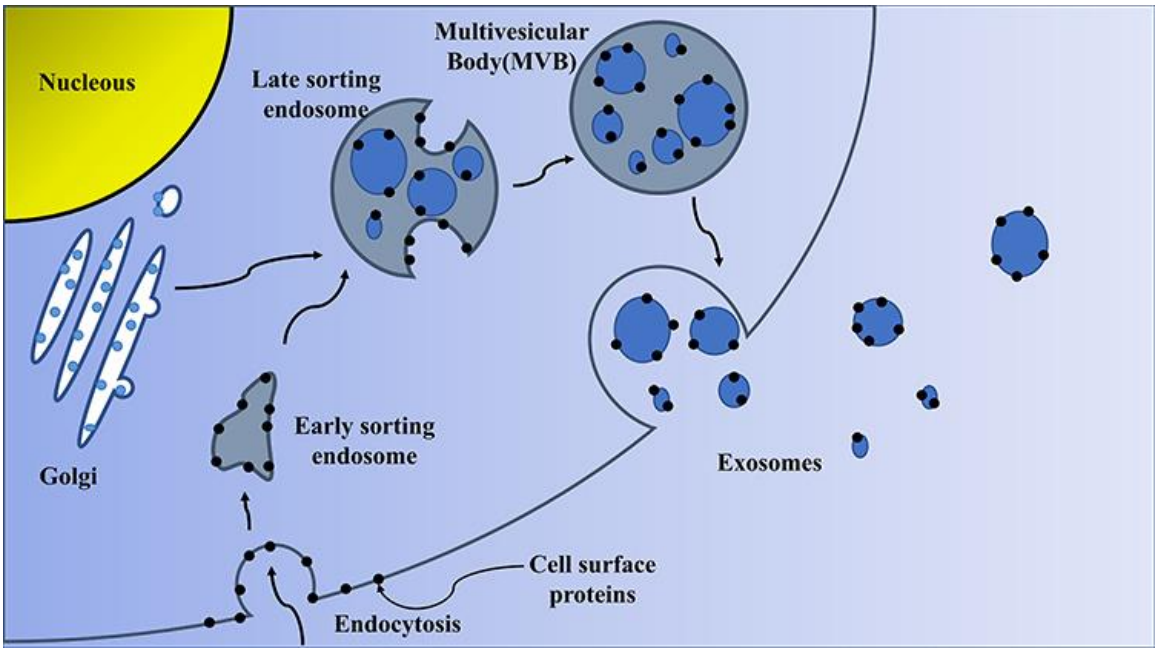

Figure (2): Biogenesis of exosomes **(12)**.

Isolation and characterisation of exosomes

Exosomes are frequently isolated using various techniques from cell culture supernatants or bodily fluids like blood, urine, and saliva. The preferred techniques for isolating exosomes are ultracentrifugation, precipitation, immunoaffinity, and density gradient centrifugation. The technique of ultracentrifugation, which yields the exosomes through a series of high-speed centrifugation processes, is regarded as the gold standard for isolation **(13)**.

Exosomes can be precipitated using procedures that rely on precipitation, such as the ExoQuick kit, which requires adding a polymer to the sample. However, each technique has pros and cons, and the choice of technique depends on the sample's characteristics **(14)**.

A recent review by Chen et al. found that combining several isolation techniques can increase the quantity and purity of exosomes and that it's crucial to confirm exosome isolation using markers and electron microscopy **(14)**.

To understand exosomes, correct characterisation is essential. Western blotting, flow cytometry, and mass spectrometry are used to analyse their size, shape, surface indicators, markers, and protein/lipid content **(15)**.

Transmission and scanning electron microscopy are used to visualise exosomes. Despite their benefits, exosome isolation methods often co-isolate other contaminants, which affect their purity. To obtain consistent

results across investigations, the process must be standardised. The International Society for Extracellular Vesicles (ISEV) recommends guidelines for the same **(16)**.

The source of exosomes is broadly divided into two categories. The first is human or mammal also known as conventional sources and the second group includes various nonconventional sources. These include animal, plant, and microbial (bacteria; parasitic and fungal) sources. Most research is on exosomes derived from conventional sources like cells, body fluids, or tissue and understanding their role in various physiological processes which further helps in exploring them as therapeutic modalities. However, nonconventional sources such as animal or plant-derived exosomes are interesting as they have a role in inter-species communication which provides alternative approaches to developing newer therapeutic agents **(17)**.

Exosomes have been extracted from lyophilised snake venom and studied using mass spectrometry, suggesting their function in the venom's cytotoxicity and offering new perspectives on developing therapeutics for envenomation **(18)**.

Recently, exosome-like vesicles (EVs) were isolated from bee glandular secretion products like honey and bee pollen. They not only have antibacterial and biofilm-inhibiting properties but also had the capacity to stimulate the migration of human mesenchymal stem cells (MSCs) which explains their role in interspecies activities. Exosomes derived from plants known as plant exosome-like vesicles or PLEVs are similar to animal-based ones in terms of both structure and function. Despite limited research, there remains huge scope for exploring them since they are easy to isolate in large quantities at a relatively low cost. Another major advantage of using them in therapeutics is their low toxicity since they are derived from natural plant parts **(19)**.

PELVs isolated from ginger protected mice from alcohol-induced liver damage **(20)**. In mouse models, PELVs derived from grapes, broccoli, and ginger were protective towards the intestine and decreased acute colitis **(19)**.

Additionally, ginger PELVs were found to have better chemotherapeutic action by enhanced delivery of agents like doxorubicin as compared to the free drug **(21)**.

Route of Administration:

The exosome delivery system has various routes of administration, among which the common routes include intravenous injection, subcutaneous injection, intraperitoneal injection, intratumoral injection, nasal administration and oral administration **(12)**.

Essentially, the route of drug administration is closely related to the therapeutic effect of various diseases, and different routes of drug administration also affect the biological distribution and rapid clearance rate of drugs in vivo. Therefore, it is necessary to investigate the influence of the routes of exosome drug delivery system **(12)**.

Applications

- **Disease Diagnosis**

Exosomes are rich in biomarkers for disease diagnosis and prognosis. They are mainly applied in cancer and have also made some progress in the fields of cardiovascular diseases, tuberculosis and central nervous system diseases. The level of exosomal microRNAs associated with cardiovascular diseases including miR-499, miR-133, miR-208, miR-192, miR-194, miRNA-34a is up-regulated in patients with acute myocardial infarction and heart failure, which provides a strong basis for their use as a diagnostic marker. It is reported that Dysferlinopathy is a kind of disease caused by the lack of dysferlin **(22)**.

Yin's team evaluated the diagnostic ability of exosomes in the serum and urine of patients with this disease, and found that there is no dysferlin in exosomes from patients, which can be distinguished from normal people for the diagnosis of Dysferlinopathy **(23)**. MiR-21, miR-29, miR-219, LRP6, REST1, caveolin1 in exosomes are differentially expressed in central nervous system diseases, showing good clinical diagnostic potential **(24)**.

❖ **Disease Treatment Through Exosome-Targeted Drug Delivery System**

Exosomes are small in size, which can effectively avoid the phagocytosis of mononuclear macrophages, and can freely cross the blood vessel wall and extracellular matrix. The expression of CD55 and CD59 on its surface avoids the activation of opsonin and coagulation factors, so it can be widely distributed and stable in the biofluids. Compared to liposomes and other nano-delivery systems which are synthesized in vitro, exosomes originate from the body, and have better biocompatibility and lower immunogenicity in theory **(25)**.

In fact, due to the heterogeneity of exosomes, they carry various proteins on the surface, which enter the cells in a variety of ways after contacting with cells. Among them, receptor-mediated endocytosis is one of the main ways of information communication between exosomes and target tissues, which optimizes the endocytosis process of exosomes and promotes the internalization of the encapsulated drug and facilitates the continuous and stable transport of the contents in the blood with high transport efficiency **(26)**.

Moreover, exosomes have strong ability to homing target tissues or cells and penetrate biological barriers (like the blood-brain barrier), so they have the advantage of natural drug delivery and are promising targeted drug carriers, which can be used to deliver genetic drugs, traditional Chinese medicine, western medicine, and so on **(26)**.

However, natural exosomes may have problems such as weak targeting and susceptible to be quickly cleared in the body, resulting in poor treatment effect. At this time, they are usually modified to form engineered exosomes. Engineered exosomes refer to natural exosomes loaded with therapeutic agents or modified. In the following part, the applications of targeted delivery system of exosomes will be explained mainly from the perspectives of drug loading and surface modification **(12)**.

❖ **Exosomes-based vaccine**

Exosomes from tumor cells have been used for therapeutics to prompt strong anti-tumor immune responses. Furthermore, exosome-based vaccines showed hopeful outcomes against several kinds of infectious diseases. Exosomes from innate immune cells and tumor cells have the potential to be used as a vaccine for cancer **(27)**.

Several active molecules on exosomes like MHC and costimulatory molecules facilitate anti-tumor responses of immune cells. Recent progress in profiling exosomes cargo has also resulted in the increase of progressively active agents that may be possibly applied in cancer immunotherapies. Based on a wide investigation into the function of exosomes in cancer immunotherapy, many pre-clinical studies have been performed with exosomes **(**28**)**.

Exosomes in skin biology

Exosomes are cell-derived nanoscale vesicles. Their diameter ranges from 40–160 nm. They can be natural or synthetic. Multiple signaling mechanisms regulate exosome biogenesis **(12)**.

Microvesical body (MVB) signaling releases exosomes. Endosomes begin as tiny intracellular bodies wrapped in intracellular fluid. Initially, the endosome is formed as a small intracellular body by wrapping little intracellular fluid. After intraluminal vesicle (ILV) formation, the early endosome becomes the late endosome, known as MVB. The MVB can release its ILVs as exosomes by fusing with the plasma membrane or degrading the contents by fusing with the lysosome **(29)**.

Exosome nomenclature and characterisation remain unresolved. The Minimal Information for Extracellular Vesicles (MISEV) addressed EV isolation/purification, characterisation, and functional research. Three positive protein indicators (CD9, CD81, CD63, Alix, Hsp70) and one negative protein marker (albumin, calnexin) should be tested. MVB fusion with the plasma membrane and multiple steps play a role in the secretion of exosomes. Exosome release involves several proteins, such as Rab, SNARE Sytenin-1, TSG101, ALIX, VPS4, and actin **(30)**.

Other mechanisms include an increase in intracellular Ca2+ and the activation of protein kinase C. Exosomes are bilayer membrane-enclosed vesicles that transport essential genetic information, including proteins, carbohydrates, lipids, and nucleic acids. Exosomes can directly enter cells via various methods, including caveolae, clathrin, lipid rafts, direct membrane fusion, receptor-ligand interaction, endocytosis by phagocytosis, and micropinocytosis **(31)**.

Exosomes were once considered vesicles that carried waste materials and were unimportant for the cells from which they came. However, mounting data shows that the vesicles and their contents play vital roles in physiological and pathological processes. Thus, exosome contents may serve as biomarkers for identifying and treating skin disorders. More importantly, stem cells derived exosomes can treat scars, pigmentation, and hair growth in regenerative medicine and aesthetics **(32)**.

Exosomes in dermatological diseases:

Introduction:

Exposure to external environmental stimuli can lead to skin aging, pigmentation, hair loss, and various immune-mediated as well as connective tissue diseases. Although conventional treatments are routinely used and favoured, they fail to achieve an adequate balance between clinical and cosmetic outcomes. Exosomes are vesicles with a lipid bilayer released by several cell types. These bioactive vesicles play a crucial role in intercellular communication and in several other physiological and pathological processes **(33)**.

They serve as vehicles for bioactive substances including lipids, nucleic acids, and proteins, making them appealing as cell-free treatments. According to studies, exosomes play a vital role in preventing scarring, and senescence, and promoting wound healing. Moreover, research on the biology of exosomes is growing, which has enabled the creation of specific guidelines and quality control methodologies to support their potential implementation in the future **(33)**.

- **Exosomes in wound healing:**

Exosomes participate in various steps of the wound repair mechanism including coagulation, migration, stem cell mobilisation, angiogenesis, extracellular matrix remodeling, and immunoregulation. Exosomes can be derived from saliva, platelets, and mononuclear macrophages. After skin trauma, Tissue factor (TF) inhibitory molecules may inhibit coagulation and prolong wound repair time. Active TF and factor VII in saliva-derived exosomes accelerate wound coagulation. Monocyte exosomes can bind to platelets and release their own TF to activate downstream cascades to promote thrombin and fibrin clot formation **(34)**.

Currently, exosomes from different tissues and cells, such as mesenchymal stem cell exosomes, endothelial progenitor cell-derived, and fibroblast-derived exosomes, influence the proliferation of skin cells. Exosomes influence the expression of growth factors or activate genes associated with the cell cycle to control cell proliferation. Exosomes can also stimulate growth factors, including vascular endothelial growth factor (VEGF), insulin-like growth factor-1 (IGF1), and interleukin-6 (IL-6) that promote the proliferation of injured skin cells **(35)**.

After skin trauma and infection, many immune cells are recruited to the lesion region. Exosomes transport pathological nucleic acids, proteins, and lipids, and participate in antigen-promoting, immune response-related receptor activation, and defense induction, arousing interest in considering exosomes as good immune-based therapeutics and vaccine candidates. Exosomes from circulating immunological cells such as monocytes can also promote the expression of MMP-1 in dermal fibroblasts by transporting 14-3-3 protein, thereby promoting cell migration to the wound area **(34)**.

- **Exosomes in the regulation of skin pigmentation**

Solar irradiation activates regulatory agents and pathways that promote melanin synthesis in melanocytes in the thin outermost skin layer. Melanocytes deliver melanin to epidermal cells and create a functioning epidermal melanin unit, which regulates pigmentation. However, excessive melanin production and uneven accumulation in skin cells after damage cause skin burning, tanning, and pigmentation, including solar lentigines, freckles, and

melasma. Epidermal keratinocytes and melanocytes affect skin pigmentation. Exosomes influence pigmentation by altering gene expression and enzyme activity **(33)**.

Cicero et al. observed that the exosomes isolated from UVB-irradiated keratinocytes significantly stimulate melanocytes **(36)**. Liu et al. suggested that exosomal miRNAs linked epidermal melanin unit keratinocytes and melanocytes. Keratinocyte exosomes overexpressed miR-330–5p and downregulated tyrosinase (TYR) expression in melanocytes **(37)**.

❖ **Exosomes for hair growth**

Hair follicles go through the anagen, telogen, catagen, and neogen stages. Pluripotent stem cells are prevalent in the hair dermal papillae. Dermal papilla cells (DPCs), and mesenchymal fibroblasts interact with multiple epithelial cell types, hair germ cells, and stem cells in the hair follicles. A few intervention techniques are readily available, such as medications like finasteride or minoxidil, as well as hair transplant surgery **(33)**.

According to Zhou et al. mice with cutaneously injected DPC-exosomes into HFs at various HF cycle phases had skin bulges that were larger, longer hair shafts, and an earlier commencement of HF anagen. Increased beta-catenin levels in the Sonic Hedgehog (Shh) pathway were the main mediators **(38)**.

Due to their short-term retention in vivoSonic, typical subcutaneous injections of exosomes sometimes require repeated administration. Combining exosomes with biomaterials or joint medication delivery holds promise for treating hair loss because it will improve the efficiency of exosome release and absorption **(33)**.

Yang et al. designed a microneedle device supported by a water-soluble hyaluronic acid (HA) patch base and integrated with MSC-exos and a small molecular drug, UK5099. It improves hair growth treatment efficiency at a lower dosage by transporting the loaded cargoes into the HF microenvironment. Besides being painless, and minimally invasive, it stimulates the telogen-to-anagen transition and improves pigmentation and hair regrowth **(39)**.

❖ **Role of Exosomes in chronic inflammatory dermatoses**

Regarding psoriasis, according to Jiang et al., exosomes produced by psoriatic keratinocytes activate the NF-B and p38 mitogen-activated protein kinase (MAPK) pathways and increase the production of IL-6, IL-8, and TNF-B by neutrophils **(40)**.

Additionally, interactions between exosomes of keratinocytes and invading immune cells have a positive impact on the epidermal microenvironment of psoriasis **(41)**.

Shao et al. demonstrated that the neutrophils of patients with generalised pustular psoriasis secrete exosomes that could be incorporated by keratinocytes, which then activate the NF-B and p38 mitogen-activated protein kinase (MAPK) pathways **(42)**.

In terms of atopic dermatitis, Shin et al. found that the subcutaneous injection of ADSC-exosomes significantly reduced trans-epidermal water loss, improved stratum corneum hydration, and markedly reduced levels of inflammatory cytokines like IL-4, IL-5, IL-13, TNF-, IFN-, IL-17, and thymic stromal lymphopoietin (TSLP) in an oxazolone-induced dermatitis model. This means that by encouraging the de novo synthesis of ceramides, ASC-exosomes successfully restored epidermal barrier functions in AD **(43)**.

❖ **Exosomes and skin tumors**

With regard to melanoma, Exosomes produced by melanoma encourage its growth and spread. MiRNA dysregulation may be related to the development of melanoma. MiR-532-5p and miR-106b expression levels were noticeably greater in exosomes isolated from the serum of melanoma patients compared to healthy controls. This study also revealed that miR-532-5p and miR-106b in exosomes could be utilised to differentiate melanoma patients from healthy people, patients with metastases from patients who have not yet developed it, and patients in earlier stages from those in later stages **(44)**.

PD-L1 and PD-1 inhibitors have been utilised to treat multiple cancers, and PD-L1 expression in tumor tissues is a marker of their use. PDL1 levels in exosomes from melanoma patients predict their responsiveness to PD-L1 inhibitor treatment. Higher basal levels of PD-1 and CD28 in T cell-derived exosomes were related to higher disease-free periods and survival in melanoma patients receiving PD-1 inhibitors **(45)**.

With regard to Squamous cell carcinoma (SCC), SCC can develop in the skin, oral cavity, esophagus, or lung and exhibit a wide range of clinical symptoms. Radiation can boost exosome uptake by recipient cells and exosome release in the head and neck SCC. Additionally, exosomes from head and neck SCC cells exposed to radiation impart a prosurvival impact on receiving cells. The upregulated proteins have functions in translation, transcription, and cell signing. TGF type II receptor-containing exosomes from stromal fibroblasts of oral SCC patients reactivate TGF signaling in SCC keratinocytes **(46)**.

Although current research suggests that exosomes may play a role in pathogenesis, their precise function and mechanism in SCC are yet unknown **(33)**.

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