Extracellular Vesicles in Melanoma

Subjects: Pathology

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Malignant melanoma, one of the most aggressive human malignancies, is responsible for 80% of skin cancer deaths. Whilst early detection of disease progression or metastasis can improve patient survival, this remains a challenge due to the lack of reliable biomarkers. Importantly, these clinical challenges are not unique to humans, as melanoma affects many other species, including companion animals, such as the dog and horse. Extracellular vesicles (EVs) are tiny nanoparticles involved in cell-to-cell communication. As such, they may be valuable biomarkers in cancer and may address some clinical challenges in the management melanoma.

melanoma extracellular vesicle

1. Introduction

Malignant melanoma, one of the most aggressive human malignancies, is responsible for 80% of skin cancer associated deaths [1]. Current prognostic indicators for melanoma are crude, relying predominantly upon the Breslow thickness, or depth of the tumour. However, thin melanomas, which should carry a favourable prognosis, still account for 22-29% of melanoma-related deaths [2][3]. This highlights the lack of a clear method of stratifying risk in melanoma. Whilst the early detection of disease progression or metastasis can improve patient survival [4], it remains a challenge due to the lack of reliable biomarkers. Notably, these clinical challenges are not restricted to humans, as melanoma affects many other species [5], including companion animals, such as the dog and horse. Spontaneously occurring canine dermal and oral malignant melanoma, show striking similarities with human melanomas and represent a valuable translational animal model [5][6][7].

Extracellular vesicles (EVs) are small nanoparticles released by almost all cells examined to date. They harbour a variety of macromolecules such as proteins, lipids, metabolites, DNA, RNA and microRNAs. They are involved in cell-to-cell communication and play a role in regulating physiological processes such as angiogenesis, coagulation, inflammation and immune responses [8]. They are classified based upon their size, biogenesis pathway, cell of origin and function. Importantly, EVs play a significant role in disease and are of particular interest in cancer. Their cargo can drive several specialised functions, including those implicated in the control of tumour proliferation, epithelial-mesenchymal transition (EMT), immune-evasion, and *pre-metastatic niche* formation in many cancers [9]. In melanoma specifically, it has been demonstrated that EVs play a role in tumour progression [10][11][12][13], and the ability to increase tumour cell migratory capability [14].

2. EVs as Biomarkers in Melanoma

Biomarkers are defined as a *'characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention'* [15]. However, for a biomarker to be a viable clinical tool, it must meet a number of criteria. Any cancer biomarker must be reflective of the tumour itself, with a high sensitivity and specificity, whilst its utility should be convenient, minimally invasive, reproducible and low cost [16]. Extracellular Vesicle contents reflect the cell from which they have been derived [17], reproducing both the transcriptome and proteome of the cell of origin [18]. They have been described as a potential '*liquid biopsy*' [19], due to their detection in multiple different body fluids, in several species, including in plasma, serum, urine, bronchoalveolar lavage, seroma and milk [20][21][22][23][24][25]. This allows convenient and minimally invasive acquisition. In cancer, EVs are of specific interest as they are ubiquitous throughout the body, and can be viewed as a physiological or pathological bio-print. They can offer a 'snapshot' insight into the tumour and metastatic landscape at any given moment. EVs are thought to protect their contents, such as genetic material, from degradation, improving the detection of clinically-relevant mutations[26].

In the setting of human melanoma, EVs are intimately involved in regulating the antitumour immune response, angiogenesis and *pre-metastatic niches* supportive of metastasis [27]. In order for melanoma-derived EVs to be a reliable source of biomarkers or a tool in the diagnosis of melanoma, they must first be identifiable within a chosen body fluid. As such, there have been multiple studies which have attempted to define a specific signature melanoma EV, and so allow their identification in patient serum. Multiple protein markers, such as HSP70, PMEL and Mart-1, as well as genomic markers, such as micro-RNAs, have been suggested. Indeed, combinations of these, as well as the inclusion of normalising controls, have also been published [28].

Alterations in the EV profile may potentially alert clinicians to recurrence before it is clinically evident, thereby facilitating timely interventions and so improving patient outcomes[4]. Patients with advanced disease appear to have a higher concentration of protein per particle, both in plasma [12] and exudative seromas [23]. There is also the suggestion that cargo of EVs from melanoma cells contain distinct proteins reflecting the stage of progression and metastases. Extracellular Vesicles may also be used to assess treatment response in melanoma. The impact of the removal of the primary melanoma on the EV profile has not been thoroughly researched to date. However, there is evidence that the reduction of tumour burden, via surgical resection, is associated with a reduction in the concentration of circulating EVs in humans [29]. There have also been multiple studies investigating how EVs may play a role in monitoring the patient's response to oncological treatment. *In vitro* studies have suggested that the secretion and shedding of EVs may be increased in response to chemotherapy [30], in particular of those EVs containing HSP70 [31].

3. Challenges & Conclusions

Whilst the field of EVs is developing rapidly, there are many challenges and barriers to their introduction into clinical use. Inconsistent nomenclature and wide variations in both methods of isolation and reporting standards significantly hinder comparison between studies. These issues are being addressed by the EV community, through the repeated revision of guidelines [22], and the introduction of an online database of experimental parameters EV-TRACK [32], which aims to encourage and facilitate systematic reporting on EV biology and methodology. In

addition, the majority of studies performed on EVs in melanoma have been based upon homogenous cell line populations *in vitro*. Whilst cell lines have long been used to model melanoma molecular biology, they do not replicate the *in vivo* tumour microenvironment or immune landscape, and as such, they can be a poor representation of *in vivo* pathophysiology. Melanoma cell lines, represent a valuable tumour model in terms of gene expression similarities, but also differ from their originating tumour at a transcriptional level [33]. Furthermore, EVs isolated from these cell lines represent those from a single cell clone and do not represent variations in tumour heterogeneity. This problem has been noted by those in the field, where melanoma-specific EV signatures developed *in vitro,* are not replicable as reliably *in vivo* [23][34].

Melanoma prognostication and monitoring of treatment response remain a significant clinical challenge in both human and veterinary medicine, and despite advances in treatment, the disease still carries significant mortality. Melanoma-derived EVs have been identified in the circulation, and have been demonstrated to play a significant role in tumorigenesis and disease progression. As a result, and due to the advantages they offer over other potential biomarker sources, EVs provide an attractive option for liquid biopsy in many species. In this regard, several clinical studies have attempted to define a melanoma-specific EV signature, and have shown their relevance in monitoring progression and response to treatment. As this field advances, in conjunction with standardisation of reporting and methodology, melanoma-derived EVs will likely play a key role in the clinical management and surveillance of all melanoma patients.

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