Extracellular Vesicles and Tumor-Immune Escape

Subjects: Others

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The modulation of the immune system is one of the hallmarks of cancer. It is now widely described that cancer cells are able to evade the immune response and thus establish immune tolerance. The exploration of the mechanisms underlying this ability of cancer cells has always attracted the scientific community and is the basis for the development of new promising cancer therapies. Recent evidence has highlighted how extracellular vesicles (EVs) represent a mechanism by which cancer cells promote immune escape by inducing phenotypic changes on different immune cell populations. In this review, we will discuss the recent findings on the role of tumor-derived extracellular vesicles (TEVs) in regulating immune checkpoints, focusing on the PD-L1/PD-1 axis.

extracellular vesicles (EVs) | cancer immune tolerance | immune checkpoints | PD-1/PD-L1 axis

1. Introduction

Tumors adopt numerous strategies to manipulate the surrounding microenvironment to guarantee and support their development. One of the more powerful strategies through which cancer cells protect their growth concerns the possibility to evade the immune system. Within tumor microenvironment (TME) several mechanisms have been described to be responsible for immune tolerance, ultimately promoting tumor proliferation and metastasis. Cancer cells can induce immune cell death via the FasL/Fas and PD-L1/PD-1 pathways, resulting in a decrease in the number of T-cells and NK cells. In addition, they also recruit the immuno-suppressive Regulatory T cells (Tregs) and myeloid-derived suppressor cells (MDSCs) that inhibit CD8+ T-cells, resulting in tumor immune escape.

2. History and Development

To deeply investigate how cancer cells can activate these immune escape mechanisms, in recent years researchers have focused on the study of extracellular vesicles (EVs), a heterogeneous group of lipoproteic structures, released from all cell types [1][2]. It has now been widely demonstrated that EVs derived from tumor cells (TEVs) can promote tumor-mediated immune suppression creating a tumor-friendly microenvironment [3][4]. Many studies are specifically focused on small extracellular vesicles (sEVs), to date also named exosomes, a well-characterized subtype of EVs playing a pleiotropic role in different key processes of tumor formation and progression; in fact, EVs are involved in tumor microenvironment (TME) remodeling as angiogenesis [5][6][7], invasion [8][9], metastasis [10][11], and resistance to therapies [12][13]. sEVsare nano-sized (40–100 nm) membrane-delimited vesicles that are secreted by almost all cell types under both normal and pathological conditions. They are usually detected in biological fluids like blood, urine, ascitic fluid and others. sEVs transport various biomolecules, such as proteins, messenger RNAs (mRNAs), microRNAs (miRNAs), and long non-coding RNAs (lncRNAs) [2][3]; common exosomal markers include HSp70, CD9, CD63, and CD81 [4][5]. The release of sEVs is a complex process that the cells execute following multiple steps in which different proteins are involved. Among those, neutral sphingomyelinase 2 (nSMase2) [14], phosphorylated synaptosome-associated protein 23 (SNAP23) [15][16] and Ras-related RAB proteins (RAB27A/RAB27B) [17][18]regulate sEV secretion from different cancer cells like breast cancer [14], hepatocellular carcinoma (HCC) [15][16], and colorectal cancer [18].

3. Findings

There is the scientific evidence showing that EVs and in particular sEVs released by cancer cells play a key role in promoting the immune escape of the tumor, specifically modulating the behavior of each cellular component of tumor immune microenvironment. Particular emphasis will be given to the role that tumor-derived extracellular vesicles (TEVs) have in regulating immune checkpoint directly activating the PD-L1/PD-1 axis.

Here we reported the evidence of the involvement of TEVs as contributors to the cancer-immune escape, highlighting their role in modulating the PD-L1/PD-1 axis. The studies discussed above suggest that the development of EV targeting strategies can improve anti-cancer immunotherapies. Some approaches are conceivable and part of the scientific community in the field is focused on these; for example, inhibiting the release of vesicles by cancer cells, or blocking their specific interaction with target cells is under investigation. However, although promising, the detailed examination of vesicle content, combined with the in-depth comprehension of the in vivo mechanisms underlying TEV-mediated immune escape, are necessary steps for the further clinical application.

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