Cancer Cells Hijack the Genome of other Cell via Extracellular Vesicles

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Abbreviations: AR: Androgen Receptor; ER: Estrogen Receptor; EGFR: Epidermal Growth Factor Receptor; EV: Extracellular vesicles; CRPC: Castration Resistant Prostate Cancer; PSA: Prostate Specific Antigen

Introduction

Nuclear Receptors are a superfamily of transcription factors that exhibit multiple functions in health and disease [1]. These receptors play essential roles in various physiological processes; including metabolism, immunity, developmental patterning and cell proliferation [2] typically nuclear receptors are activated by steroid hormones, such as estrogens, androgens, progesterone, and various other lipid-soluble signals, including retinoic acid, oxysterols, and thyroid hormone. The ligands can cross the plasmamembrane and directly interact with the receptors in the cytoplasm, causing their translocation to the nucleus [3]. Within the nucleus, the receptors bind DNA and activate specific responsive genes. In cancer, nuclear receptors play a major role in various types of the disease, with roles ranging from oncogenic, tumor suppressor, or both, depending on the body organ they are expressed in [2]. Androgen receptor (AR) in prostate cancer and estrogen receptor (ER) in breast cancer are the most common nuclear receptors that contribute to the progression of these cancers. The two receptors or their releasing factors are targeted for the treatment of these cancers, by the hormonal therapies.

As part of the complexity of cancer it has been reported that many membrane receptors could be translocated and detected in the nuclei of tumor cells, the phenomenon associated with aggressive and therapy resistant tumors. One of the essential membraneeceptors in the progression of various cancers is the epidermal growth factor receptor (EGFR), which is either overexpressed or mutated in most of the aggressive tumors. It has been reported that there is an alternative mode of EGFR signaling, in which activated EGFR undergoes nuclear translocation, subsequently regulates gene expression, and potentially modulates cellular processes. This signaling route is distinct from the better characterized, traditional EGFR pathway, which involves transduction of mitogenicsignals through theactivation of multiple signaling cascades. The signaling pathway of nuclear EGFR is associated with increased cell proliferation, nitric oxide synthesis and accelerated G1/S cell cycle progression [4].

Several other membrane receptors found to undergo nuclear translocation such as HER2, EBR3, Fibroblast growth factor receptor 1 and 2 (FGFR1 and 2), prolactin receptor, Interferon-γ receptor (INFγ), insulin receptor, and vascular endothelial growth factor receptor 2 (VEGFR2 or FlK1/KDR) [5-10] Nuclear translocated receptors have been shown to act as transcription factors [11-13] modulating transcription by either activation or repression. Several mechanisms have been reported to explain the translocation of membrane receptors to the nucleus, including interaction with transport receptor importin β1, nuclear protein Nup358, and a host of players in endocytic internalization [14]. Although the translocation of membrane receptors to the nucleus is well documented, the underlying mechanism of nuclear translocation is poorly understood [5]. In this regard, the studies reported on the translocation of membrane receptors to the nucleus are documented. The increasing interest of the scientific community in extracellular vesicles, which includes exosomes and microvesicles as a mode of intercellular communication in cancer drive a new understanding for their role in the tumor microenvironment.

Particularly, the role of these vesicles in the intercellular exchange of receptors [15,16] which led to questioning their possible role in shuffling these receptors to the nucleus of other cells. The recent finding [17] that extracellular vesicles could transport receptors directly to the nucleus of other cells that may not express the receptor, brings our understanding of the tumormicroenviro
ment to a completely new stage. The reported mechanism is novel, as all studies to date have reported only on the translocation of endogenous receptors from the cell membrane to the nucleus of the same cell. The manuscript shows a new mechanism for the nuclear translocation of receptors such as the mutant form of EGFR, EGFRvIII, which has a truncation in the extracellular domain that renders the receptor active without the need for a ligand. The receptor is associated with aggressive tumors including glioblastoma and other cancers such as prostate cancer [18,19].

Although, the receptor has a weak signaling capacity, it is continuously signaling, which due to its impaired recycling through the endosomal pathway [20] makes it a potent oncogene. Also, the characteristic of impaired recycling makes it difficult to explain the reported accumulation of this receptor in the nuclei of the cells expressing it. The phenomenon was reported in aggressive tumors [21] it is noteworthy that nuclear accumulation of various receptors has suggested being achieved through the endosomal pathway [14]. Also, the new mechanism could explain the activation of nuclear receptors such as AR in the absence of the ligand, which represents the main cause of resistance to hormonal therapy, as well as the generation of the castration-resistant prostate cancer (CRPC). The accompanying figure demonstrates the role of extracellular vesicles in transporting AR to the nucleus of other cells and the activation of the AR responsive gene i.e. prostate specific Antigen (PSA) (Figure 1).

![Figure 1: Cancer cells shed EV containing AR receptor to be transported directly to the nucleus of AR-null cells. The transported receptor binds DNA of the acceptor cells and stimulates transcription of the AR responsive gene of PSA, and stimulate the release of PSA.](image)

The role of extracellular vesicles in intercellular exchange of membrane receptor [15,16] has captured the attention of the scientific community [22] and is considered a landmark in cancer cell biology. Transporting exogenous receptors to the nucleus of other cells to be in direct contact with the DNA of the host cell, and the induction of the receptor’s responsive genes represent a new level of understanding in cancer cell biology and establishes a new vision for the complexity of the cancer microenvironment. It shows that cancer cells can hijack the transcription machinery of other cells, which might be stromal cells. By hijacking the transcription machinery of other cells, cancer cells might have an impaired microenvironment. Also, by this mechanism, cancer cells may acquire cytoprotective characteristics to overcome the effects of various anticancer therapies, and metastatic characteristics as well [23] It is noteworthy that cancer cells may develop mechanisms similar to the ones performed by the viruses to utilize the host genome and produce their molecular components. Interestingly, there are studies suggesting that extracellular vesicles are of viral origin [24] Revealing various mechanisms adopted by cancer cells will bring us closer to understanding the challenging nature of this devastating disease. This will lead to new means to disarm cancer cells from these remarkable capabilities and mechanisms and increase their responsiveness to therapies.

References


