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Proliferation and Survival Signals in Exosomes as Biomarkers for Colorectal Cancer

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Abstract

Colorectal Carcinoma (CRC) is the second most common cancer as well as a major leader in cancer associated deaths worldwide. While early diagnosis correlates with a high 5-year survival rate, late-stage CRC is often untreatable, leading to a less than 5-year survival in approximately 85% of cases. Our lab, and many others, believes that cancer-derived exosomes contain tumor factors important for diagnosing and prognosing CRC. Cancer-derived exosomes can be isolated from blood plasma early in tumor development and can be used for frequent screening with rapid results. Of note, proliferative and survival signals found in exosomes are conserved across CRC, as well as many other tumor types, and can be used to easily discriminate from non-cancerous patient-derived exosomes. For this reason, we believe that exosomal proliferative and survival factors, in the form of proteins, genetic material and/or metabolites, are the key to developing biomarkers for this clinical achievement.

Keywords: Proliferation; Survival; Exosomes; Biomarkers; Colorectal cancer

Introduction

Colorectal Cancer (CRC) is the second most common cancer in the world today [1]. With 147,950 new cases and 53,200 deaths projected for 2020 alone, it is also ranked2ndfor most cancer deaths in the United States [1]. It is estimated that 4.4% of men and 4.1% of women will develop CRC within their lifetime [1]. Statistics from 2019 indicate that 5-year survival correlates with tumor state at the time of diagnosis. Patients have a 90%, 5-year survival rate if CRC is diagnosed as a local disease which drops to 14% if CRC is diagnosed at a distant-stage [1]. Researchers have shown that early detection and frequent screening significantly decreases the probability of developing an advanced stage tumor [2]. Therefore, there is an urgent need to develop an early diagnostic tool for CRC.

A promising candidate for early diagnosis is the exosome. Exosomes, which facilitate intercellular communication, antigen presentation, and shuttling of biological agents, were initially thought of as the cell's garbage disposal system [3-7]. We are now beginning to understand their potential role in the diagnosis and therapy of several diseases, including cancers [8]. Exosomes can deposit cellular cargo directly into nearby cells or interact with cells by surface receptor interactions [9]. Proteins, mRNAs, non-coding RNAs, and metabolites can all be packaged into exosomes [3,4,6]. Additionally, parent cell surface proteins can be expressed on their membrane [5]. Various studies over the decades have signified the role of exosomes in different stages of cancer development [10]. Exosome cargo can change drastically based on tumor type and progression [6,11]. They can also be isolated from patient blood samples [12], which can be screened for tumor biomarkers to discriminate between Tumor Derived Exosomes (TDEs) and normal tissue exosomes [5]. Many potential biomarkers for CRC have been studied in vitro, but their use in the clinical setting is still being explored [13]. Many of CRC's most common oncogenic mutations are proliferative and/or anti-apoptotic [14], giving rational for looking at modulators of these pathways specifically as biomarkers for this disease. Additionally, tumor cells emit up to 10 times more exosomes than healthy tissue [15], suggesting that TDEs could reach a detectable concentration in the blood at early stages of development [16]. Therefore, the connection between exosomes and proliferation/survival signaling is vital to develop, so that biomarkers can be identified for an earlier diagnosis of CRC.

Proliferation

Several studies show that exclusive factors within CRC cell-derived exosomes are involved in the growth and anti-apoptotic signaling of CRC. The specific ways and mechanisms, however, have not entirely been elucidated. CRC-derived exosomes have been shown to increase the proliferation

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of endothelial cells, which could stimulate growth and development in tumor vasculature [11]. CRC-derived exosomes have also been shown to induce a tumor-like behavior in colonic mesenchymal stem cells as well as regulate immune cells [17,18]. Because of this careful growth enhancement within the tumor microenvironment, the effect of exosomes on all cells within the tumor microenvironment has become a significant focus of cancer research. Most recently, studies found that exosomes are more efficiently taken up by cells similar to the parent cells than non-parent cells [19,20]. In addition, information trafficking between a tumor and tumor cells not in contact with the tumor of exosome origin is also an important condition for cancer progression, and, as a communicator, tumor-derived exosomes may be involved in the communication between the primary tumor and its distant metastases [21]. Matsumoto et al. [22] found that after B16BL6-derived exosomes were intratumorally injected in mice, most exosomes were taken up by B16BL6 cells, with a significantly increased growth in these B16BL6 cells. Another study showed that incubating Hep3B cells with Hep3B-derived exosomes increased the number of Hep3B colonies in soft agar [23]. These studies indicated that tumor-derived exosomes have a paracrine signaling potential that stimulates proliferation and progression.

Incidentally, many potential biomarkers linked to proliferation have already been identified. Non-coding RNAs are currently a hot topic in cancer biology today, especially to be used as biomarkers. A recent study showed an example of this in CRC-derived exosomal miR-424-5p, which is both a positive proliferation effect or and a potential early-stage predictor of CRC [24]. Additionally, CRC-derived exosomal LINC02418, which also can increase proliferation, was found to discriminate between healthy and cancer tissues with high predictive confidence [25]. GPC1, a surface protein on exosomes linked to proliferative signaling, has been discussed for years as a predictor of early-stage pancreatic cancer [26]. Li et al. [27] years later discovered that GPC1+ exosomes are not only elevated in early CRC, but also packaging within these specific exosomes is altered, changing both the exosome function, and solidifying their diagnostic potential. Interestingly, the down regulation of anti-proliferative factors found in exosomes, such as lncRNA ADAMTS9, which targets the downstream APC target pathway, Wnt/β-catenin, can be used to discriminate between healthy and CRC cells [28].

Survival

In addition to proliferative factors that can be used as biomarkers for CRC, many anti-apoptotic components in exosomes can also be used to predict CRC with high confidence. Cells undergoing hyper proliferation require mechanisms to inhibit apoptosis induced by cellular or genetic stress. In this way, many survival signals are correlated with proliferation in cancer. Survivin is a well-known anti-apoptotic and pro-proliferation molecule in cancer cell [29]. Not only is survivin found in almost every cancer [30], but it is also emitted extra cellularly *via* exosomes [31]. Its use as a cancer biomarker has been well discussed [30,32] and remains a promising candidate for early detection of CRC. Another well discussed biomarker for cancer is miR-21 [33], which targets several tumor suppressors, namely PTEN [34] and PDCD4 [35], regulators of proliferation and apoptosis respectively. miRNA-21 is notably up-regulated in exosomes at every TNM stage of CRC [10], marking it another promising biomarker for early detection of CRC. Another potential goldmine for CRC biomarkers is linked to p53, a gene commonly mutated in CRC [36,37]. This mutation has been documented to affect exosome packaging in CRC [38], which could be used to identify additional biomarkers of CRC.

Conclusion

Of the exosome factors listed above, none of them have been clinically used as early diagnostic biomarkers. While many of these factors can distinguish CRC from healthy tissues, the lack of uniformity in the development of CRC warrants the need for more testable and accurate biomarkers to be identified. Because alterations in proliferative and survival signals are common in CRC, they remain the most promising category for finding early distinguishable biomarkers. Therefore, a deeper understanding and development of exosomes and their role in proliferative and survival signaling could lead to additional early developmental biomarkers to diagnose CRC.

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