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Review

Autocrine mechanisms of cancer chemoresistance

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ABSTRACT

An ever-increasing number of studies highlight the role of cancer secretome in the modification of tumour microenvironment and in the acquisition of cancer cell resistance to therapeutic drugs. The knowledge of the mechanisms underlying the relationship between cancer cell-secreted factors and chemoresistance is becoming fundamental for the identification of novel anticancer therapeutic strategies overcoming drug resistance and novel prognostic secreted biomarkers. In this review, we summarize the novel findings concerning the regulation of secreted molecules by cancer cells compromising drug sensitivity. In particular, we highlight data from available literature describing the involvement of cancer cell-secreted molecules determining chemoresistance in an autocrine manner, including: *i)* growth factors; *ii)* glycoproteins; *iii)* inflammatory cytokines; *iv)* enzymes and chaperones; and *v)* tumor-derived exosomes.

Contents

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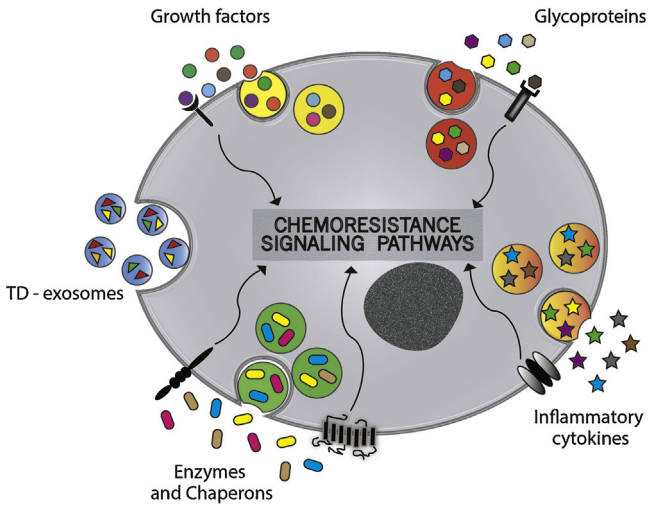

Fig. 1. A schematic summary depicting the autocrine stimulation of chemoresistance in cancer cells. Various cancer cell-secreted molecules activate intracellular signaling pathways involved in drug resistance.

1. Introduction

Recent advances in chemotherapy allowed a relevant number of cancer patients to receive treatment with substantial results. Although cancer patients generally benefit from the treatment of neoplasia with one or combination of cytotoxic drugs, resistance to chemotherapeutic drug treatment still remains a major challenge for clinicians strongly reducing the efficiency of anticancer therapies. The remarkable progresses in target-therapy lead to the improvement of treatment of cancer patients [1], but these outstanding results are compensated by the augmented occurrence of acquired or intrinsic events of chemoresistance that limit long term success of therapies. Drug resistance is a complex and multifactorial phenomenon. In the process of acquiring resistance, the tumor may become cross-resistant to a variety of chemotherapies leading to treatment failure in the large majority of patients with metastatic disease. Many factors are involved in the reduction of drug sensitivity, including: accelerated drug efflux; drug inactivation; alterations in drug target; DNA methylation; adaptation and restraint of damage induced by drugs; and evasion of apoptosis [2]. Furthermore, many pieces of evidence support the involvement of factors secreted by cancer cells stimulating drug resistance through autocrine mechanisms (Fig. 1). This article provides an overview of the recent findings of secreted factors associated with cancer drug resistance. The knowledge of these cancer cell-secreted molecules and their role in tumor microenvironment might permit to better understand the biology of the tumor and to identify novel potential serum biomarkers of drug response or novel drug targets to overcome cancer chemoresistance.

2. Secreted growth factors and chemoresistance

Growth factors and their cognate receptors are involved in all steps of tumor progression, especially in the escape from the cytotoxic effects of chemotherapy [3,4]. A clear example of the bond between cancer cell-secreted growth factors and chemoresistance is provided by the epidermal growth factor receptor (EGFR) family of tyrosine kinases, which comprises four receptors (EGFR/ERBB1/HER1, ERBB2/HER2, ERBB3/HER3 and ERBB4/HER4), and their several EGF-like ligands [5], including the low affinity EGFR ligand amphiregulin (AREG) [6]. Currently, AREG is known to stimulate the proliferation of most cell types analyzed. This effect is mainly mediated through the binding of its EGF-like domain to EGFR/ERBB1, promoting EGFR homodimerization or heterodimerization with ERBB2, ERBB3 and ERBB4 and triggering the generation of intracellular signals [6]. AREG expression has been correlated with cancer cell resistance to several chemotherapeutic agents [7]. For example, in hepatocellular carcinoma, AREG showed resistance to sorafenib, a multi-target kinase inhibitor [8]. Recently, AREG has been found secreted by cancer cells and expressed in fluids from ovarian and lung cancer patients. Furthermore, neutralizing anti-AREG antibodies inhibited growth of ovarian cancer xenografts and strongly enhanced chemotherapy efficacy of cisplatin [9].

Connective tissue growth factor (CTGF) is a secreted protein that binds to integrins and modulates the invasive behavior of cancer cells, resulting in the progression and chemoresistance of cancer [10,11]. Tsai et al. demonstrated that the overexpression of CTGF increased the resistance to cisplatin-mediated apoptosis in osteosarcoma cells and in mouse models, through promotion of MAPK survival signaling pathway and upregulation of Bcl-xL and survivin. In contrast, they observed that knockdown of CTGF enhanced the therapeutic effect of cisplatin [12]. The same authors reported that CTGF expression in osteosarcoma patients is significantly higher than that observed in normal bone tissues, increasing the resistance to paclitaxel-induced apoptosis [13]. Altogether, these studies support CTGF as a critical secreted oncogenic growth factor involved in chemoresistance in an autocrine manner.

Li et al. investigated the autocrine role of insulin-like growth factor-II (IGF-II) in esophageal cancer progression. They found that IGF-II is overexpressed in 60% esophageal cancer tissues analyzed and that autocrine IGF-II mediated the tumor progression and metastasis through activation of the PI3K/Akt pathway. Notably, IGF-IR blockade by cixutumumab monoclonal antibodies enhanced the chemosensitivity of tumor xenografts to fluorouracil and cisplatin [14]. However, despite a compelling biological rationale and promising preclinical data, clinical studies have so far failed to provide definitive evidence that IGF-IR may represent a valid therapeutic target in solid tumors. Qu et al. analyzed a total of 17 studies to evaluate the curative effects of IGF-1R inhibitors for patients with solid tumors. They concluded that anti-IGF-IR mono-antibodies, ganitumab, dalotuzumab, cixutumumab, teprotumumab and figitumumab, did not make significant differences in solid tumor prognosis (progression-free survival and overall survival) [15]. Sclafani et al. further revealed that adding dalotuzumab, an anti-IGF-IR monoclonal antibody, to the drug irinotecan and the EGFR inhibitor cetuximab did not improve survival outcome of metastatic colorectal cancer patients [16].

Proutski et al. examined the role of the divergent transforming growth factor-β (TGF-β) superfamily member, the prostate-derived factor (PDF), in regulating response to chemotherapies used in the treatment of colorectal cancer. They revealed that PDF secreted from cancer cells determined chemoresistance to a panel of drugs, as oxaliplatin, 5-fluorouracil, and SN38 (the active metabolite of irinotecan), in a PI3K/Akt-dependent manner [17]. Furthermore, elevated levels of PDF have been detected in the serum of patients with metastatic colorectal [18], pancreatic [19], breast [20], and prostate carcinomas [21], and high secreted PDF levels positively correlated with the malignant grade of tumors, indicating a critical role for secreted PDF in the development and progression of cancer disease.

Vascular endothelial growth factor superfamily (VEGF) plays a crucial role in the multistep process of angiogenesis, which is normally regulated by the local balance of endogenous proangiogenic and antiangiogenic factors. The biological relevance of VEGF in soft tissue sarcoma (STS) has been suggested by clinical studies showing impaired prognosis in patients with elevated VEGF levels [22]. Zhang et al. demonstrated that blockade of VEGFR2 signaling using anti-VEGFR2 monoclonal antibodies enhanced doxorubicin chemoresponse and suppressed the activity of matrix

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