The Breast 30 (2016) 92–100

Contents lists available at ScienceDirect

The Breast

journal homepage: www.elsevier.com/brst

Review

Tumor microenvironment-mediated chemoresistance in breast cancer

Kobra velaei [a, c], Nasser Samadi [b], Balal Barazvan [c], Jafar Soleimani Rad [a, c, *]

[a] Department of Anatomical Science, Faculty of Medicine, Tabriz University of Medical Sciences, Tabriz, Iran
[b] Department of Clinical Biochemistry and Laboratory Medicine, Faculty of Medicine, Tabriz University of Medical Sciences, Tabriz, Iran
[c] Stem Cell Research Center, Tabriz University of Medical Sciences, Tabriz, Iran

ARTICLE INFO

Article history:
Received 12 January 2016
Received in revised form
2 September 2016
Accepted 2 September 2016

Keywords:
Chemoresistance
Tumor microenvironment
Stromal cells
Breast cancer

ABSTRACT

Therapy resistance or tumor relapse in cancer is common. Tumors develop resistance to chemotherapeutic through a variety of mechanisms, with tumor microenvironment (TM) serving pivotal roles. Using breast cancer as a paradigm, we propose that responses of cancer cells to drugs are not exclusively determined by their intrinsic characteristics but are also controlled by deriving signals from TM. Affected microenvironment by chemotherapy is an avenue to promote phenotype which tends to resist on to be ruined. Therefore, exclusively targeting cancer cells does not demolish tumor recurrence after chemotherapy. Regardless of tumor-microenvironment pathways and their profound influence on the responsiveness of treatment, diversity of molecular properties of breast cancer also behave differently in terms of response to chemotherapy. And also it is assumed that there is cross-talk between phenotypic diversity and TM. Collectively, raising complex signal from TM in chemotherapy condition often encourages cancer cells are not killed but strengthen. Here, we summarized how TM modifies responses to chemotherapy in breast cancer. We also discussed successful treatment strategies have been considered TM in breast cancer treatment.

© 2016 Elsevier Ltd. All rights reserved.

Introduction

Breast cancer is the most common cancer among women and the second cause of cancer death in the world [1]. Breast cancer accounts for approximately one million new cases and leads to more than 400,000 deaths per year [2,3]. Four types of breast cancer, including Basal (also known as, triple negative), HER2 (human epidermal growth factor receptor 2) positive, Luminal A, and Luminal B [4] demonstrate phenotypic and genotypic heterogeneity, which is a common feature of breast cancer [5]. Heterogeneity is considered a dilemma for breast cancer therapy. There are recently renewed interests in investigating cross-talk between phenotypic diversity and TM [6].

Stromal cells, extracellular matrix (ECM), soluble factors and the physical states as TM can affect in a complex manner the solid tumor behavior. Therefore, TM is now considered to be a hallmark of cancer biology [7–9]. Recently, investigators have focused on TM as a target for cancer therapy. Drug responses of cancer cells are not exclusively determined by their intrinsic characteristics but are also controlled by signals derived from cells of the tumor microenvironment. Tumor stromal cells, including fibroblasts, immunoinflammatory cells and vascular endothelial cells and other component of microenvironment such as the extracellular matrix not only play a pivotal role in cancer response to anti-cancer therapies but also influence on proliferation of tumor cells, invasion and metastasis. According to a widely accepted idea, soil (microenvironment) and seed (cancer cell) hypothesis [10], tumor-microenvironment pathways [11] are a critical part of cancer therapy. The development of chemotherapy resistance is one of the most important obstacles to effective treatment of breast cancer, which can lead to disease relapse and death. Clonal expansion or Darwinian selection theory based on genetic heterogeneity, which is the consequence of mutation, could cause a failure in cancer therapy [12–14]. Another scenario is that chemotherapy-induced injury could cause responses such as epigenetic alteration, rewiring of signaling network and regulatory changes at the level of protein–protein interaction (PPI) in tumor cells [15] which all contribute to establishment of resistance to treatment [6,16]. Additionally, infrastructure of tumor microenvironment is also one of the factors could be influenced by chemotherapy. During recent years, chemoresistance seems to be partly due to interplay between tumor stroma and tumor cells. Successful cancer therapy requires

* Corresponding author. Department of Anatomical Science, Faculty of Medicine, Tabriz University of Medical Sciences, Tabriz, Iran. Fax: +98 0413334208.
E-mail address: soleimanirj@yahoo.com (J. Soleimani Rad).

http://dx.doi.org/10.1016/j.breast.2016.09.002
0960-9776/© 2016 Elsevier Ltd. All rights reserved.

more understandings of interactions between tumor cells and their microenvironment in chemotherapy. Disrupted balance of growth factors, chemokines and cytokines, as a decisive part of microenvironment, in response to genotoxic stress results in selection of a certain subset of tumor cells [17]. IL6, CSF2, CCL5, and VEGF [4] are exemplary factors, which modulate the breast cancer trait. Surprisingly, cancer-associated fibroblasts (CAMs) promote cancer stem cell (CSC) phenotype in cancer cells by secreting CCL2 [18] and CSC phenotype is one of the possible explanations to chemoresistance. And also, CXCL1/2 chemokines recruit $CDb11^{+}Gr1^{+}$myeloid cells, which protect cancer cells from apoptosis (11) and other type chemokine; CXCL12 or stromal cell-derived factor (SDF-1) support survival of cancer cells [19]. This accumulating evidence has clearly emphasized on the role of microenvironment in the response of cancer cells to therapy, which induce resistance to apoptosis. For instance, CXCL12 is proposed as a sensitizer for anticancer therapies [20].

Here we discuss the breast cancer resistance through the lens of microenvironment. Nowadays, breast cancer niche is being considered responsible for therapy failure or breast cancer recurrence. Hence, microenvironment must be taken account into breast cancer treatment. Therefore, for aiming this goal understanding interaction between breast cancer cells and their microenvironment in details is incredible during therapeutic perturbation.

Tumor-associated macrophage (TAM) and chemoresistance

Macrophages present in malignant tumors or TAM as a population of myeloid cells might be derived from or related to myeloid-derived stromal cells (MDSCs) [21]. MDSCs as immature myeloid cells are presents in tumors [22] with distinguished plasticity in different microenvironments [23]. The historical consideration of MDSCs derived macrophage phenotypes are M1 (or classically activated) and M2 (or type II alternatively activated) macrophage [24–27]. Pro-inflammatory and anti-tumorigenic M1 macrophages turn into anti-inflammatory and pro-tumorigenic M2 macrophage, which is tumor-associated macrophage. This macrophage plasticity is assumed that is a response to diversity of the microenvironment constituent [28]. Macrophages rapidly recruit in tumor bulk after anti-tumor invention, which promotes tumor progression and limits the cytotoxic effect of chemotherapy [29–31]. TAMs and their products participate to modulate behavior of cancer cells in the presence of drugs [32] and breast cancer cells could activate TAMs as well [33]. Accumulated evidence is suggesting direct therapy toward niche of cancer cells to sensitize cancer cells to anticancer therapy [17,34]. Therefore, targeting tumor-associated macrophage in combination with chemotherapy to improve chemotherapy efficacy has attracted lots of attention [35]. Recruited macrophages following cytotoxic chemotherapy can protect tumor cells from death through a cathepsin-dependent function [32]. Surprisingly, not only recruited macrophages in tumor mass but also macrophages residing in spleen can be activated by systemic DNA-toxic anti-cancer agent and induce chemoresistance through an intricate lysophospholipid signaling [36]. It is obvious that, angiogenesis is a mechanism in tumor relapse. Accumulation TAMs ($MRC1^{+}TIE2^{Hi}CXCR4^{Hi}$) around blood vessels in tumors after chemotherapy promote revascularization and relapse [37]. CCL18 from TAMs of breast cancer is responsible for encouraging endothelial cells to angiogenesis in both vitro and vivo [38]. Metastatic breast cancer is highly associated with resistance to chemotherapy [39,40]. Function of MACC1 (metastasis-associated in colon cancer 1), VEGF and Snail in establishing metastasis and chemoresistance [41–43] confirm a certain link between chemoresistance and metastasis feature of cancer. Moreover, M2-polarized macrophages enable to develop metastasis by epithelial to mesenchymal transition (EMT) phenomenon in cancer microenvironment [44]. Hence, it is highly likely that considering TAMs as a target in breast cancer therapy in combination with chemotherapy can be an answer for microenvironment mediated drug resistance puzzle. Inhibition of colony stimulating factor-1 (CSF-1) expressed by cancer cells, which is involved in recruiting macrophage in tumors could reverse chemoresistance in breast cancer cells [45,46]. Knockdown of macrophage inhibitory factor (MIF) in TAMs caused significant reduction of breast tumor growth and metastasis [47] and overexpressing of STAT3β in TAMs by regulating crosstalk between macrophages and breast cancer could suppress breast cancer growth [48]. Finally, we suggest that inhibiting the interactions between cancer cells and TAMs would be beneficial in eliminating of chemoresistance.

Chemoresistance and cancer-associated fibroblast (CAF)

A major part of breast cancer microenvironment is fibroblast cells which, are referred as cancer-associated fibroblast (CAF) or a subpopulation of fibroblasts with a modified phenotype. These cells belong to connective tissue and secret ECM [49], growth factors and chemokines [50]. ECM accumulation and fibroblast proliferation are feature of the most breast cancer types [51]. Then, it is predictable that abundant fibroblast in breast cancer can affect the breast cancer behavior in order to promote chemoresistance [52]. Moreover, it has been demonstrated that CAFs possess the diverse phenotype [53,54] which leads to the different interaction between cancer cells and finally results in diverse response to drugs in cancer cells. Breast cancer cells and fibroblasts co-culture induces proliferation of cancer cells by regulating metabolism process [55,56] such as 3-hydroxybutyrate and lactase, which is generated from aerobic glycolysis by CAFs as a hallmark of CAFs [57]. Surprisingly, normal human fibroblasts in coculture with breast cancer MCF-7 cells gain CAFs characters [58]. Fibroblast-producing HGF (hepatocyte growth factor) stimulates triple-negative breast cancer to abundantly phosphorylate Met and induces resistance to epidermal growth factor receptor (EGFR) and tyrosine kinase inhibitors (TKIs) [59]. Fibroblast phenotype easily alters in the presence of chemotherapy agent. Activated fibroblasts by treatment or CAFs with a deficiency of transforming growth factor-beta receptor-2 (TGFBR2) support the breast cancer cell survival [60] while normal fibroblasts are disable to affect breast cancer promotion. Accordingly, regarding the microenvironment subtype during treatment may improve the efficacy of therapy in breast cancer. As an example, fibroblast activation protein (FAP) vaccinated mice by targeting CAFs in combination with chemotherapy drugs exhibit prolonged survival and greater uptake of chemotherapeutic drugs in vivo [61]. Proposed mechanism for tamoxifen resistance is interplay between fibronectin, fibroblast-derived factor, and its receptor β1integrin which protect breast cancer cells from death through activation of PI3K/AKT and MAPK/ERK 1/2 pathways [62]. These pathways abundantly are active in non-response breast cancer cells to tamoxifen, and it is well-known EGFR phosphorylation acts as upstream of PI3K/AKT and MAPK/ERK 1/2 pathways. In some case, stroma-derived factors in response to drugs could potentially provide drug resistance Such as DNA-damage caused by chemotherapy in fibroblast makes them to secret the Wnt family member wingless-type MMTV integration site family member 16B (WNT16B) which promotes tumor cell survival in paracrine manner [63,64].

Nowadays, CSCs/cancer-initiating cells (CICs) have been described as possible mechanism in chemoresistance [65–68]. CSCs and their interactions with niche may underlie resistance to chemotherapy. How niches could induce either chemoresistance trait in CSCs feature in tumor cells? To shed light to this big

Download English Version:

https://daneshyari.com/en/article/3908185

Download Persian Version:

https://daneshyari.com/article/3908185

Daneshyari.com