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Host effects contributing to cancer therapy resistance

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ABSTRACT

There are several approaches for the management of malignant disease. However, tumor resistance to therapy is still a major challenge in the clinic. Efflux transporters, genetic responses and enzyme activity in tumor cells are examples of the main modalities that account for resistance to therapy. In addition, emerging evidence suggests that the host also plays a significant role in promoting therapy resistance. Recruitment of different host cell types to the treated tumor site occurs in response to a range of therapies, including chemotherapy, radiation and even targeted drugs. This host response may have a protective effect on the tumor cells, not only negating anti-tumor activity, but also promoting a resistant tumor. In this review, we focus on host–tumor interactions leading to therapy resistance with special emphasis on different host cells and secreted factors within the tumor microenvironment. The development of novel inhibitors that block the host response to therapy could be used as a treatment strategy to enhance therapy outcomes and survival.

1. Introduction

Tumor initiation, growth and expansion are dependent on several specific intrinsic tumor cell characteristics, such as an endless proliferation state, sensitivity to growth factors, and the ability to escape from apoptotic pathways. In addition, the tumor microenvironment has also been shown to play an important role in promoting tumor growth and spread to distant sites (Hanahan and Weinberg, 2000). For example, angiogenesis, which allows a flow of nutrients and oxygen to the tumor and removes tumor metabolic waste, is an essential process for tumor cell proliferation and spread (Folkman, 2003). Angiogenesis is achieved by the proliferation of local endothelial cells that form sprouting vessels to tumors, and also by several bone marrow derived cell (BMDC) types that are recruited into the neoplastic lesion and promote vessel formation (Patenaude et al., 2010; Kovacic and Boehm, 2009; Lamagna and Bergers, 2006). Another example for the contribution of host cells to tumor growth is related to the immune system. While tumors seem to have the ability to evade the immune system by inhibiting their mechanism of cell killing, a significant number of immune cells still infiltrate growing tumors. They include macrophages, lymphocytes, dendritic cells, and natural killer cells (NKs) which contribute to tumor growth or suppress it by various mechanisms. Myeloid-derived suppressor cells (MDSCs), for example, home in large numbers to the tumor site, and negatively regulate the immune cells which are active against tumor cells (Cavallo et al., 2011). Therefore, it is currently clear that the cross-talk between tumor cells and cells in the microenvironment highlight the diversity of functions different cell types have against and in favor of tumor.

The therapeutic management of cancer involves several approaches including chemotherapy, targeted treatment and radiotherapy used separately or simultaneously. Such treatments can efficiently kill cancer cells due to their ability to target rapidly proliferating cells and promote tumor cell death by various mechanisms. However, cancer cells have emerged ways to protect themselves from the majority of treatments thus making them resistant to therapy.

In general, insensitivity of tumors to a variety of anticancer drugs is known as multidrug resistance (MDR) involving inactivation or elimination of the drug from the target tumor cells. Overexpression of efflux transport proteins such as ABC transporters, and alterations in drug targets, enzymatic activity and genetic response have been described as processes leading to therapy resistance. These processes involve direct changes within the tumor cells which may occur before or during therapy (Higgins, 1992; Gottesman et al., 2002; Holohan et al., 2013). For example, antifolate resistance is known to be induced by alterations in influx and efflux transporters and in folate dependent enzymes (Gonen and Assaraf, 2012). Therefore, targeting folate receptor overexpressed in solid tumors is a novel evolving cancer treatment (Assaraf et al., 2014).

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Kim and Tannock provided an explanation for relapse or tumor resistance that occurs following an initial response to therapy. They postulated that at the time of the drug-free break periods between consecutive bolus acute chemotherapy treatments, tumor cells repopulate the tumor site and contribute to tumor regrowth at an accelerated cell proliferation rate (Kim and Tannock, 2005). Several mechanisms explaining this phenomenon have been suggested in the last few years, some of which are related to different cell types that are recruited to the tumor microenvironment after therapy.

In this review, we discuss collective studies describing how anticancer therapies induce a host response that, in turn, directly affects various tumor characteristics, eventually leading to therapy resistance (Fig. 1). We describe the role of different types of host cells and host-secreted factors, and discuss new possible treatment modalities based on targeting the host response.

2. Host cells promoting drug resistance

It has become clear that cancer cells clustered together as a solid tumor are able to recruit different cell types to the tumor bed. Bone marrow derived cells, such as mesenchymal stem cells (MSCs), hematopoietic cells and circulating endothelial progenitor cells (CEPs), have been shown to be recruited to the tumor site, and together with adipocytes, astrocytes and fibroblasts, they constitute the tumor microenvironment. Crosstalk between tumor cells and the different cell types in the tumor microenvironment is manifested by the secretion of growth factors, chemokines and cytokines by both tumor and host cells. Emerging evidence has revealed that stromal cells in the tumor microenvironment play an important role in regulating tumor development and progression (Bhowmick et al., 2004). In addition, they are also known to modulate the response of the tumor to therapy by cell–cell interactions or by local release of factors encouraging tumor growth (Shekhar et al., 2007; Sethi et al., 1999). Below we discuss the role of different host cell types within the tumor microenvironment in promoting tumor cell resistance.

2.1. Non-immunological cells

2.1.1. Endothelial cells and endothelial precursor cells

Perhaps one of the first studies to explore the link between angiogenesis, tumor re-growth following therapy and therapy resistance described the role of CEPs (Shaked et al., 2006). CEPs are known to specifically incorporate into the blood vessel wall of growing vessels (Heissig et al., 2005; Asahara et al., 1999; Hattori et al., 2001), but their contribution to tumor angiogenesis has been debated during the last decades. Gao et al. demonstrated that CEPs are critical for achieving progressive metastatic tumors from an avascular tumor in a mouse pulmonary metastasis model (Gao et al., 2008). Shaked and colleagues demonstrated that treatment with vascular disrupting agents (VDAs) or certain cytotoxic drugs induced an acute mobilization and tumor homing of CEPs within hours, followed by accelerated angiogenesis (Shaked et al., 2006, 2008). Inhibition of CEP mobilization, either pharmacologically or genetically, enhanced treatment outcomes and significantly delayed tumor re-growth and resistance to therapy. Importantly, the therapeutic agents also induced the mobilization of CEPs in mice lacking tumors, suggesting that the reactive host generates an influx of CEPs in response to the therapy, which then contribute to therapy resistance.

The host effect following therapy has also been documented in patients. Circulating endothelial cells (CECs) and/or CEPs were found to be increased in the blood of cancer patient's receiving several chemotherapeutic agents. These changes were observed within a few hours as well as at 7 and 21 days after the initiation of chemotherapy. The extent of this release correlated with the patient's response to treatment and predicted overall survival/progression free survival (Farace et al., 2007; Beerepoot et al., 2006; Shaked et al., 2008). These collective studies indicate that CEPs and CECs are major contributors to tumor angiogenesis following therapy and represent one aspect of how the host promotes tumor resistance.

In addition to CEPs, mature endothelial cells (EC) have been shown to respond in a similar manner to chemotherapy, and thus may also contribute to tumor aggressiveness following therapy. For example, Daenen et al. investigated the host response to chemotherapy using a lung metastasis model in which mice primed with chemotherapy were injected intravenously with tumor cells 4 days after receiving treatment (Daenen et al., 2011). In the described model, the cytotoxic agents were cleared from the blood by the time that the tumor cells were injected. In this way, the potential effect of chemotherapy on the host rather than on the tumor cells could be studied. The authors showed that pretreatment with cisplatin and paclitaxel resulted in a significant increase in lung metastasis (Daenen et al., 2011). They found that the chemotherapeutic agents enhanced the expression of vascular endothelial growth factor receptor-1 (VEGFR-1) in ECs which in turn led to increased tumor cell seeding in the lungs (Daenen et al., 2011). While this study does not necessarily discuss resistance per se to chemotherapy, it implies that following certain therapies, tumors can spread to various tissues, such as the lungs, due to host effects generated by endothelial cells.

2.1.2. Astrocytes

Astrocytes were found to protect tumor cells from chemotherapy in an in vitro brain metastatic model in which human breast or lung cancer cells were co-cultured with murine astrocytes (Kim et al., 2011). Constant and direct cell–cell contact between astrocytes and tumor cells led to an alteration in the pattern of survival gene expression in both tumor cells and astrocytes. The upregulation of survival genes reduced apoptosis in the tumor cells and therefore increased resistance to chemotherapeutic agents. This protection was seen exclusively with astrocytes and was not demonstrated with other cell types e.g., fibroblasts (Kim et al., 2011).

2.1.3. Mesenchymal stem cells (MSCs)

MSCs are mobilized from the bone marrow and are recruited to damaged sites as they are involved in tissue repair. Interestingly, MSCs have also been shown to promote resistance to chemotherapy in the damaged cancer tissue (Roodhart et al., 2011; Morigi et al., 2008). In the tumor, MSCs release growth factors and cytokines which stimulate angiogenesis, tumor growth and spread (Beckermann et al., 2008; Karnoub et al., 2007). Roodhart et al. demonstrated that circulating MSCs are activated by platinum-based chemotherapy in tumor-bearing mouse models. The activated MSCs secrete unique fatty acids that induce the release of an intermediate factor by the host tissue. This, in turn, directly prevents apoptosis of tumor cells, and thus induces chemotherapy resistance (Roodhart et al., 2011).

2.1.4. Fibroblasts

Cancer associated fibroblasts are known to enrich the tumor microenvironment in most carcinomas (Hanahan and Weinberg, 2011; Hanahan and Coussens, 2012). Recently, heat shock factor 1 (HSF1), was shown to be activated in cancer associated fibroblasts (CAFs) within human tumors (Scherz-Shouval et al., 2014). The loss of HSF1 in fibroblasts inhibited tumor growth in a xenograft mouse model suggesting that HSF1 activated in CAFs supports tumor growth. Transforming growth factor-β (TGF-β) and