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Arguments to Acknowledge the Bystander Killing effect as a Tool to Modify the Tumor Microenvironment by the Action of Antibody Drug Conjugates

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Abstract

Antibody drug conjugates have augmented the spectrum of anticancer regimens acting across various entities and active even against tumor cells expressing lower levels of relevant antigens. A bystander killing effect in the tumor environment (TME) has been demonstrated, however the definition of the targeted cells is still in discussion. Since these cells are speculated to partly mediate a tumor promoting activity, it seems worthwhile to proceed in the definition of these possibly non malignant cells however protumoral acting cells as additional drivers in the tumor microenvironment.

Keywords: Antibody drug conjugates, tumor microenvironment, hallmarks of cancer.

Abbreviations: ADC: Antibody drug conjugates; TME: Tumor microenvironment; CRC: Colorectal cancer; GC: Gastric cancer, TNBC: Triple negative breast cancer; DLBCL: Diffuse large b cell lymphoma; NSCLC: Non small cell lung cancer ; MMAE: Monomethyl auristatin E; CAF: Cancer associated fibroblasts; EMT: Epithelial-mesenchymal transition; EV: Extracellular vesicles.

Introduction

The bystander killing (BKE) effect enables substances such as antibody drug conjugates (ADC) to influence cells in the neighbourhood of the primary target. ADC` s are composed of an antibody, a linker, and a payload mediating a toxic effect. The antibody targets a structure on a relevant cell localized in a tumor or its microenvironment which may alter the course of the process. The payloads of the presently applied ADC`s are derivates of camptothecines such as irinotecan, SN-38, deruxtecan, govitecan, pamirtecan, and others or the tubulin polymerisation blocker monomethyl auristatin E (MMAE), or the pyrrolobenzodiazepine dimer tesirine. The linker technology combines the payload with the targeted substance to optimizy the release of the cytotoxic agent at the appropriate place. The combination of these components have to be adjusted to result in the desired effect.

The tumor microenvironment (TME) which structurally is rather similar in many tumor situations contains the tumor itself, hybrid cells between tumor cells and TME cells, and cells of the TME such as endothelial cells, macrophages and its subpopulations, myeloid cells and its subpopulations, stromal cells, lymphatic cells, and neuronal cells. The complex interaction of TME cells with its neighbourhood enumerates several protumoral and antitumoral acting factors summarized in the hallmark concept of cancer growth [1]. An important factor of the hallmark concept is the neoangiogenesis targetable by several already admitted drugs. The interaction of pro- and anti-tumoral acting factors results in the final outcome.

A mainly antitumoral acting substance leads to a delayed progress or longer survival, a predominantly protumoral acting situiation will end in progressing cancer or finally in death. A blockade of TME cells provides the chance to retarden tumor growth.

Several payloads have augmented the spectrum of antineoplastic treatments.

ADC relevant drugs have been approved in various entities such as trastuzumab deruxtecan for HER2 positive and low HER2 positive breast cancer, for HER2 mutant NSCLC, for HER2 positive gastric cancer [2], the anti-Trop2 antibody sacituzumab govitecan (SG) for triple negative, and HR positive, HER2 negative breast cancer [3], the anti-nectin4 antibody, coupled to monomethyl auristatin E (MMAE) for urothelial carcinoma [4], the anti-CD19 antibody loncastuximab coupled to tesirine (SG3249) for DLBCL[5]. Several ADC's are under investigations in a variety of tumor situations.

Methods

Considering the the existence of a BKE one should be aware of the possible effects of ADC- payloads on cells of the TME such as endothelial cells, macrophages, cancer associated fibroblasts (CAF), myeloid cells, and others. We searched the literature for reports on single cell sequencing of some tumor entities and the contribution of TME cells to the course of breast cancer (BC), colorectal cancer (CRC), and gastric cancer (GC).

Results

The bystander killing effect: The term „bystander effect" has already been mentioned in 1996, mediated by a cytokine cascade released by tumor infiltrating cells mainly monocytes. The term „ bystander killing effect" described the action of ADC`s on tumors with antigen heterogeneity. The concept of intratumor pharmacokinetics could be visualized in an antigen heterogeneous model by phosphor-integrated dots imaging analysis [6].

Single cell analysis of human breast cancer (CC), colorectal cancer (CRC), and gastric cancer (GC):

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Single cell and transcriptomics analysis of human breast cancers were documented analysing more than 100 000 cells by RNA sequencing and including the expression and clustering of 133 clinically and targetable receptor or ligand immunomodulation markers across all cell types grouped by clinical breast cancer subtypes (TNBC, HER2+, and ER+) [7]. Genome and transcriptome signatures of 1063 colorectal cancers yielded mutations in WNT, EGFR and TGFß pathway genes, the mitrochondtrial CYB gene and 3 regulatory elements along with 21 copy-number variations, and the COSMIC SBS44 signature correlated with survival [8]. A single-cell analysis of pre-cancerous and cancer lesions showd that intestinal and diffuse type cancer were characterized be different cell populations and described cancer associated fibroblast harbouring pro-stemness properties and malignant cells with high expression level of epithelial-myofibroblast transition which was correlated with poor clinical prognosis [9].

Effects of tumor associated macrophages (TAM) in clinical situations: An overview on the present known TAM landscape is given in a review describing the CD expression of macrophages with favourable and unfavourable prognosis and of macrophage subpopulations with inhibition or with cooperation in anti-cancer therapy [10]. In breast cancer high numbers of CD163+ tumor associated macrophages predicted poor prognosis in HER2+ patients [11]. In colorectal cancer CXCL8 induced M2 macrophage polarization and inhibited CD8+ T cell infiltration to generate an immunosuppressive microenvironment [12]. Patients with peritoneal metastasis of gastric cancer and high M2 status in CD68+CD163+ cells had worse overall survival than those with low expression [13].

Effects of endothelials cells in clinical situations: A summary describes the interaction between endothelial cells and targeted therapy in the tumor microenvironment [14]. A single-cell analysis of various cancer types revealed differences in endothelial cells between tumors and normal tissues claiming that tip-like endothelial cells are the main differential endothelial cell subcluster promoting angiogenesis and inhibiting anti-tumor responses. TIP-like endothelial cells may bo found in CRC, renal cell cancer, gastric cancer, and lung cancer [15]. In CRC endothelial cells exhibited enhanced angiogenesis. An increase in the density and proportion of tip cells correlated with crc occurence, progression, and poor prognosis. Effective PD-1 blockade reduced tip cells disrupting the VEGFA-KDR-ESM1 positive feedback loop [16].

Effects of fibroblasts in clinical situations: A cancer-associated fibroblast-derived gene signature dicriminated distinct prognoses by integrated single-cell and bulk-seq analyses in breast cancer [17]. In CRC stromal fibroblasts shape the myeloid phenotype in normal colon and CRC and induced CD163 and CCL2 expression in macrophages [18]. In gastric cancer cancer-associated fibroblasts (CAF) affected progression via the CXCl12- CXCR4 axis [19].

Role of epithelial-mesenchymal transition (EMT) in tumor growth: Aberrant reactivation of EMT was associatedwith malignant properties of tumor cells during cancer progression and metastasis. A review summarized the contribution of EMT to tumor progression [20].

Contribution of extracellular vesicles (EV) and RNA binding proteins as bystanders in tumor growth: An interaction between the TME and cancer cells is involved in CRC metastasis. EV`s have been shown to play a role in cancer-TME interaction and in cancer progression. The RNA LINC00543 was overexpressed in CRC tissues, correlates with advanced TNM stage and poorer prognosis of CRC patients. Overexpression promoted metastasis by enhancing and remodeling EMT [21].

Macrophage conversion / reprogramming: Considering the unfavourable condition of the M2 polarization status there have been attempts to alter the macrophage polarization towards a M1 status. A summary on the present landscape of macrophage– reprograming cancer immunotherapies has been reported [22].

ADC targeted constituents of the TME: Considering the BKE in conversion tumor cells may be viewed as bystander cells to TME cells elucidating the importance of TME cells in the action of ADC `s. In 2018 a tumor stroma targeting ADC of an anti TEM8 antibody and the payload MMAE was shown to trigger localized anticancer drug release resulting in the idea to apply stroma- targeting ADC`s as an alternative to cancer-targeting in cases of heterogeneous target expression [23]. The immunosuppressive contribution of TME cells has been shown in CAR-T-cell therapy [24] and the elimination of tumor associated neutrophils by ADC`s in preclinical models of cervical cancer [25].

Discussion

It is technically difficult to prove the targeting of cells possibly already removed by the targeting procedure. This may be indicated by a histologically demonstration of the lack of defined subsets of cells following therapy or the expression of apoptose markers on susceptible cells, or the modification of the activity of defined cells by the therapy. The effect of the BKE has augmented the understanding the possibilities of ADC`s. The effect of ADC's on the neighbourhood of the primary targets has been shown. The possibilities of the BKE in conversion has been demonstrated showing that targeting stromal cells in the TME resulted in a killing of the tumor. The action of one ADC on different tumors may be explained by targeting one common hallmark active in the course of different tumors.

Conclusion

Any reduction of tumor growth has to be judged with view on a at least partial contribution of TME cells. A definition of the non-tumoral cells in the tumor microenvironment modulated by ADC therapy is interesting and necessary because of a possible future resistance or intolerance of the applied ADC-therapy. The analysis of possible protumoral activities of TME cells demands further investigations. The understanding of the effects of ADC's on cells of the TME may offer an additional way to influence the course of tumor growth. It depends on an advanced definition of these cells acting as additional drivers of tumor growth. Improvement of spatial oncology permitting the allocation of exosomes to TME cells as important mediators of intracellular communication will improve the spectrum of therapeutical opportunities.

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