Chapter 7
Mechanisms and Modulation of Tumor Microenvironment-Induced Immune Resistance

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Abstract In the quest for developing more effective immune therapy strategies for cancer, to date, unraveling and successful modulation of the mechanisms of tumor escape in the microenvironment became an urgent challenge. While immune suppression is considered an important mode of immune escape, this overview will deal with another important mechanism of immune escape in the tumor microenvironment: the microenvironment-regulated resistance of tumor cells toward the cytotoxic machinery of immune effector cells. We have recently studied the impact of the microenvironment to the development of immune resistance in multiple myeloma (MM) and will outline the backgrounds and current knowledge about the mechanisms and modulation of this type of immune escape.

Keywords Cytotoxic T cells • Cancer immunotherapy • Bone marrow • Microenvironment • Apoptosis • Drug resistance • Immune resistance • Multiple myeloma

Abbreviations

BM	Bone marrow
BMSC	Bone marrow mesenchymal stromal cells
CTL	Cytotoxic T cell
MM	Multiple myeloma
MSC	Mesenchymal stromal cells
NK cell	Natural killer cells

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7.1 Introduction

Eradication of malignant cells through the cytotoxic machinery of immune cells such as cytotoxic T cells (CTLs) and natural killer (NK) cells is the ultimate aim of cellular immunotherapy of cancer. Starting from the early applications of allogeneic stem cell transplantation, followed by successful donor lymphocyte infusions, clinicians and immunologists have witnessed and appreciated the potential power of cellular immunotherapy in the battle of hematological and non-hematological malignancies [1]. Over the past two decades, the rapid identification of tumor-associated antigens [2, 3], development of new technologies such as T cell receptor (TCR)-gene transfer [4] and recently the remarkable successes of virus-specific T cells [5], tumor infiltrating lymphocytes (TIL) [6] and chimeric antigen receptor (CAR)-engineered T cells [7–9] in the treatment of various hematologic cancers, have elevated cancer immunotherapy to a new level, with high expectations. Nonetheless, despite the optimal activation and infiltration of abundant numbers of tumor-reactive CTLs or NK cells at tumor sites, human cancers, mainly due to genetic heterogeneity as well as micro-environmental influences, display various mechanisms to evade the immune attack [10, 11]. To date, the unraveling and the successful modulation of the mechanisms of tumor escape in the microenvironment became the most urgent challenges to achieve the next level of success in the immunotherapy of cancer [12, 13].

Currently, most scientists consider immune suppression as the main mechanism of immune escape in the tumor microenvironment [14–17]. There is, indeed, a large body of evidence that the tumor microenvironment is a suppressive inflammatory niche [18, 19], with the presence of several immune suppressive soluble factors, such as IDO, Arginase, INOS or TGF-β [20–22], secreted either from tumor cells [23], accessory cells (vascular endothelium, stromal cells, fibroblasts) [24] or from suppressive immune cells such as regulatory T cells [25], tumor associated macrophages [26], and myeloid derived suppressor cells [27, 28], many of which are recruited or induced in the microenvironment through crosstalk with tumor cells and tumor stroma [29]. This immune suppressive milieu also involves the strong upregulation of the immune checkpoint molecules PD1 on T cells and PD-L1/2 on tumor cells [30–35], and in some reported cases through interaction with stroma [36].

This chapter will, however, deal with another, entirely distinct mechanism of immune escape in the tumor microenvironment: the microenvironment-regulated resistance of tumor cells toward the cytotoxic machinery of immune effector cells. This resistance of tumor cells against cytotoxic attack, although extensively documented in the melanoma setting, and may be as important as "immune suppression", has not received sufficient attention yet, probably because it has not been seen as a microenvironment-mediated phenomenon. We have recently studied the impact of the microenvironment to the development of immune resistance in multiple myeloma (MM) and will outline below the backgrounds and current knowledge about the mechanisms and modulation of this type of immune escape.

7.2 MM the Model for Investigating the Role of the Microenvironment in Human Cancers

MM is the malignant disorder of antibody producing clonal plasma cells [37]. It is the second most common hematological malignancy worldwide. Despite four exciting decades of drug development, MM remains incurable by chemotherapy due to the induction of drug resistance [38, 39]. Although experimental and clinical studies indicate the immune competence of MM cells and possibility to treat the disease with cellular immunotherapy [40–42], the overall outcome of allo-SCT, DLI or other experimental immunotherapies in MM is at most moderate, underscoring the ability of MM cells to evade the cellular immune attack.

Traditionally, the biology of MM and its therapy-response is studied preferably in the context of the microenvironment [43–46] because MM, especially in the initial phases of the disease, is entirely dependent on its natural habitat, the bone marrow (BM). Over the past decades, it has been extensively documented that the BM provides MM cells an ideal sanctuary by the production of several survival cytokines such as IL-6 and IL-8, VEGF, SDF-1 and many others, and by interactions of MM cells with extracellular matrix and BM accessory cells, in particular with stromal cells (BMSCs) and vascular endothelial cells (VECs) [47, 48]. In fact, once taken out of this natural niche, primary human MM cells rapidly die, and are very difficult to engraft even in the BM of immune deficient mice [49–51].

7.3 Importance of the Tumor Microenvironment in Drug Resistance

Investigations aiming at understanding the molecular basis of drug resistance of MM have demonstrated that the many soluble factors produced in the BM microenvironment not only provide proliferative and survival signals to MM cells, but also -individually or collectively- contribute to the development of drug resistance [52]. Perhaps, more important is the induction of drug resistance through the (integrin-mediated) adhesion of MM cells to BMSCs and VECs. This type of environmentally, thus epigenetically, regulated drug resistance, which is generally known as “Cell Adhesion-Mediated Drug Resistance” (CAM-DR), has originally been demonstrated for MM cells in the late nineties [53], and has subsequently been described also for several other hematological and non-hematological malignancies [54–58]. While integrins were initially shown to play a key role in this type of drug resistance, another important molecule appears to be NOTCH [59–61]. The relation of this environmentally regulated drug resistance with immune resistance will become obvious upon outlining the molecular nature of both types of resistance mechanisms.

7.4 The Apoptotic Pathways: Immune Resistance Meets Drug Resistance

Studies have shown that the molecular basis of CAM-DR is the cell adhesion-dependent triggering of a complex series of signaling events resulting in the transcriptional or posttranscriptional regulation of intracellular molecules involved in apoptotic signaling for programmed cell death [45, 46]. This ability of the microenvironment to modulate apoptotic pathways was, in fact, for us a major reason to start studying the relation of the microenvironment with immune resistance, because not only drugs, but also cytotoxic immune cells kill the tumor cells via the induction of apoptosis.

In general terms, apoptosis involves a complex cascade of molecular events that can be initiated inside the cell or by external dead signals. Accordingly, two main apoptotic pathways have been described: the intrinsic or mitochondrial pathway and the extrinsic or death receptor pathway [62, 63] (Fig. 7.1). Several pro-apoptotic anticancer drugs are designed for activating either of these pathways [64–71]. While immune cells can trigger the extrinsic death receptor pathway [72], a major mechanism of tumor cell lysis by CTLs and NK cells is the apoptosis induced by the degranulation of granzyme/perforin from the cytotoxic granules upon engagement with the target cells [73]. This specific mechanism has traditionally been defined as a separate pathway, although it is also initiated by external signals. As will be outlined below, more important is the considerable overlap between these pathways. All three signaling pathways eventually converge and mediate the execution phase of apoptosis via the activation of caspase-3. Hence, although immune cells may in some cases kill drug resistant tumor cells, specific drug resistance mechanisms may overlap with immune resistance mechanisms, with potentially important clinical consequences.

7.5 The Modulation of Intrinsic, Extrinsic and Granzyme/Perforin Mediated Pathways of Apoptosis by the Microenvironment

The intrinsic apoptosis pathway, which involves mitochondrial depolarization, is initiated with the activation of pro-apoptotic proteins BAX and BAK, by BIM and BID, respectively [74] (Fig. 7.1). Oligomers or multimers of activated BAX and BAK engage with the mitochondrial membrane [75], induce the formation of mitochondrial pores and cause the release of cytochrome-c and SMAC/Diablo from the mitochondria into the cytosol [76]. By binding to the APAF-1 protein, cytochrome-c generates a large cytoplasmic complex, the apoptosome [77]. This complex binds and activates caspase-9, which in turn can activate several executioner caspases including the caspase-3 [78]. Several members of the BCL-2 family of proteins are important regulators of this pathway. Briefly, the mitochondrial

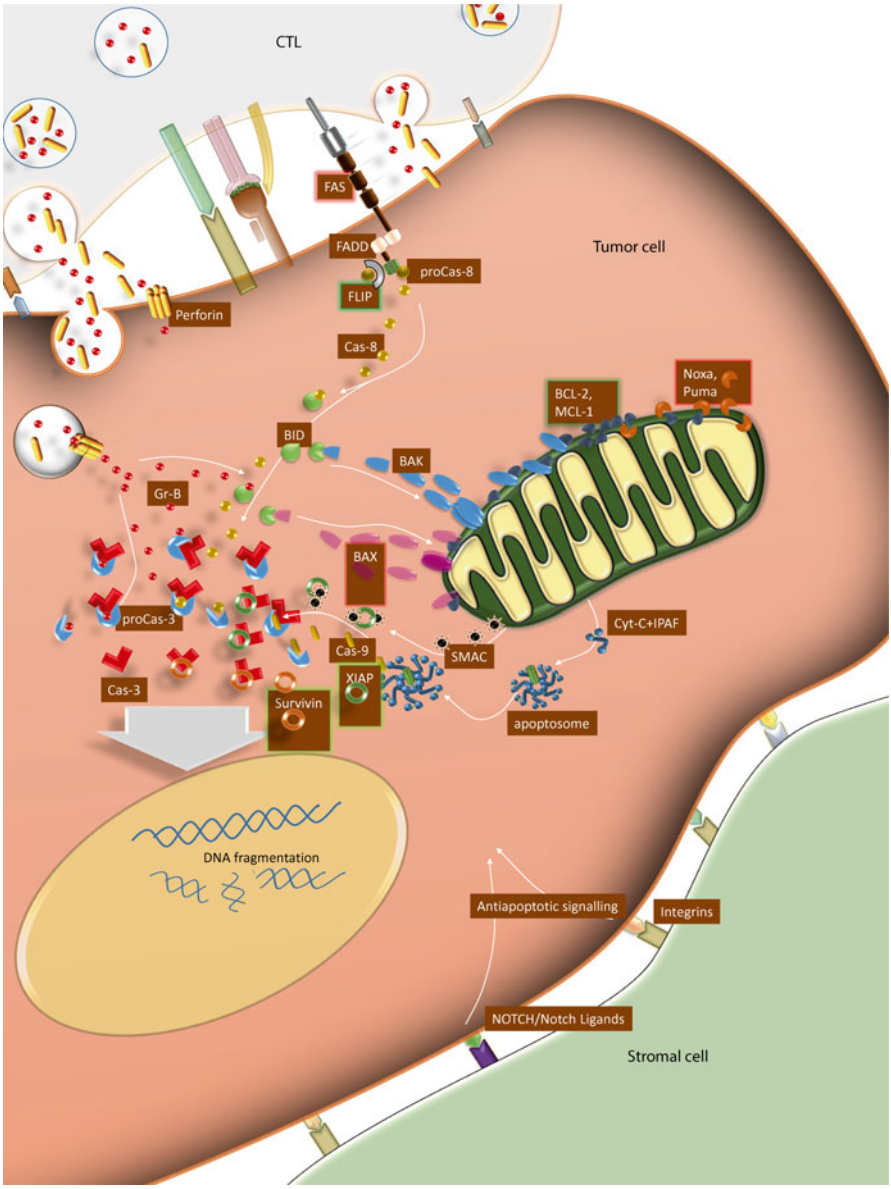

Fig. 7.1 Apoptotic pathways activated by immune effector cells (CTLs/NK cells) and their regulation by the microenvironment. The simplified scheme demonstrates the key molecules and the overlap between the intrinsic, extrinsic and granzyme pathways of apoptosis. Also note the convergence of these pathways at the level of caspase 3 (Cas-3). The molecules that are known to be modulated by the stroma-tumor interactions are indicated with *red* (downregulated) and *green* (upregulated) boxes. *Cas-3* caspase 3, *Cas-8* caspase 8, *Cas-9* caspase 9, *Cyt-C* cytochrome C, *Gr-B* granzyme B

membrane-associated BCL-2, BCL-2A1, BCL-W BCL-XL and MCL-1 proteins protect the cells form apoptosis by inhibiting the oligomerization of BAX and BAK. In contrast, the other members, such as PUMA and NOXA, improve the oligomerization of BAX and BAK via competitive binding to the former anti-apoptotic members of the BCL-2 family of proteins [79]. It has been extensively demonstrated that the mediator and regulatory molecules of the intrinsic pathway are significantly influenced by stroma-derived soluble factors and adhesion. For instance, IL-6, through activation of STAT3 upregulates the transcription of BCL-XL [80], induces adhesion of MM cells to stroma, downregulates BIM [81, 82] and BAX [83] and upregulates the anti-apoptotic BCL-2 proteins [83], especially of MCL-1 [44, 84]. Upregulation of MCL-1 and BCL-2 importantly contributes to drug resistance in MM, acute myeloid leukemia and B-cell acute lymphoblastic leukemia [85, 86]. Several studies indicate that not only integrins but also Notch signaling can have a major impact on the protection of tumor cells from apoptosis via modulation of the intrinsic pathway [59–61].

The signaling of the extrinsic apoptosis pathway involves the triggering of the tumor necrosis factor (TNF) family of death receptors including FAS (CD95), TNF-related apoptosis-inducing ligand-receptor 1 (TRAIL-R1), TRAIL-R2 and TNF receptor apoptosis-mediating protein (TRAMP). CTLs, especially of the CD4+ phenotype, frequently trigger FAS to activate the extrinsic pathway [87–93]. Triggering of death receptors activates FADD and then caspase-8, which in turn either directly activates caspase-3 or cleaves BID to signal via the intrinsic pathway [94]. In this pathway, the FLICE-like inhibitory protein FLIP can inhibit recruitment and activation of caspase-8. Soluble factors produced by BMSCs have been shown to upregulate FLIP expression [95]. In addition, integrin-mediated adhesion inhibits activation of caspase-8 due to increased cellular redistribution of FLIP [96]. In addition, we have recently shown that MM cell-stroma interactions significantly downregulates MM cell surface FAS expression [97].

Finally, the Granzyme/perforin pathway, which is exclusively utilized by CTLs and NK cells, is initiated by the degranulation of the preformed cytotoxic granules containing granzymes, perforin and serglycin into the immune synapse upon engagement of immune effector cells with target cells. Perforin, with its complement-like structure, generates membrane pores in the target cell to enable the cytotosolic entry of granzymes, which are the key molecules to induce signaling for cytotoxic cell-mediated apoptosis [98]. Among the 12 granzymes described until now, the granzyme B is the most abundantly present one in cytotoxic granules. It cleaves proteins after aspartate residues and can directly activate caspase-3 to trigger apoptosis. But, similar to caspase 8, granzyme-B can also trigger the intrinsic pathway of apoptosis through the activation of BID [98]. This clear overlap between the intrinsic pathway and granzyme-mediated lysis may have important consequences: for instance, melanoma cells that have been made resistant to CTL killing display signatures for hyperactivation of the NF-κB pathway, and overexpression of BCL-2, BCL-XL, and MCL-1 [99]. In fact, the efficacy of (CAR) T cell therapy can be significantly upregulated by inhibition of BCL-2 family of proteins [100, 101].

Thus the above described microenvironment-mediated drug resistance mechanisms of intrinsic pathway, may very well influence the outcome of CTL therapy.

In human cells, granzyme B can be inhibited by the proteinase inhibitor-9 (PI-9) [102]. The expression levels of this molecule in pediatric ALL cells correlate with their resistance against immune cell mediated lysis [103]. In the clinical setting, PI-9 expression is an important predictor of disease-free survival in melanoma patients treated with immunotherapy [104]. Interestingly, PI-9 gene expression can be induced by NF-κB signaling [105] as well as by hypoxia [106], which is a typical feature of the bone marrow microenvironment and has been shown to induce resistance against NK mediated lysis of MM cells [107].

Since all major apoptotic pathways converge at the level of caspase-3 activation, the (microenvironment-mediated) signals that regulate the activity of this executioner caspase may contribute to the development of both immune- and drug resistance. A specific group of molecules that regulates the activation of caspases is the IAP family of proteins [108–110]. XIAP, one of the best characterized IAPs, inhibits the activity of caspase-3, -7, and -9. Survivin (BIRC5), another well-known IAP, is frequently expressed in human tumor cells, and inhibits caspase-3 and -7. The activities of these molecules can be controlled, in turn, by the proapoptotic protein SMAC/Diablo, which is released upon mitochondrial depolarization [111, 112]. IAPs are indeed important in mediating both drug and immune resistance: for instance, in a recent study, cis-platinum resistant human ovarian cancer cells were found less susceptible toward NK-cell mediated killing than the parental cells partly due to the upregulation of cIAP-1 and -2 [113], Also survivin-3B, an alternative splice variant of survivin, was recently associated with chemotherapy resistance as well as with resistance to FAS-mediated immune cell toxicity [114]. Taken together, these and some earlier studies [115] demonstrate that drug resistance mechanisms show substantial overlap with the documented mechanisms of immune resistance. Unfortunately, however, the impact of the microenvironment on the induction of immune resistance has not been widely studied, except for MM.

The first indirect evidence for the microenvironment-mediated immune resistance in MM was provided by a study in which BM stroma conferred resistance to Apo2 ligand/TRAIL induced lysis in part by regulating c-FLIP [95]. In this case, soluble factors were found responsible for immune resistance. Using mainly an in vitro co-culture system, which was originally developed to study BMSC-induced drug resistance [44], we and other investigators have recently questioned whether the BM microenvironment can also cause a CAM-DR like immune resistance. Indeed, MM cells were protected against NK cells by co-culture with autologous BMSCs [116]. Subsequently, we have reported in vitro and in vivo evidence that MM cells are protected from CD4+ and CD8+ CTL-mediated lysis upon direct cellular interactions with VECs and BMSCs derived either from MM patients or from healthy individuals [97]. In our study, the protection of MM cells by accessory cells could be observed in the absence of immune suppression; hence, analogous to CAM-DR, we designated this type of cell adhesion-mediated immune resistance as CAM-IR. In further analysis, we discovered that MM cell-stroma interactions significantly downregulated MM cell FAS surface expression, but correction of FAS

expression by bortezomib, did not entirely abrogate CAM-IR. By contrast, upregulation of survivin/MCL-1 appeared a central mechanism of CAM-IR, since we could entirely neutralize the immune resistance, in vitro as well as in a recently developed MM model in vivo [51], by combining T cells with the small molecule YM155, a suppressant of survivin and MCL-1 [117, 118]. Although we have not elucidated the entire mechanisms of CAM-IR yet, we have observed that CAM-IR, like CAM-DR, can be inhibited by interfering with integrin binding on intact cells, but unlike CAM-DR, cannot be induced by sole binding of MM cells to fibronectin, vitronectin, or laminin. Signals initiating CAM-IR are therefore most likely triggered by the collective action of integrins with other receptor-ligand systems. A possible candidate is the NOTCH signaling pathway, since we have recently observed that CAM-IR could also be abrogated by inhibition of the NOTCH pathway by gamma secretase inhibitors (GSI) (unpublished observations).

7.6 Towards the Design of Immune-Chemotherapy Strategies to Overcome Microenvironment-Mediated Immune Resistance

Our findings as well as evidence provided from other studies underscore the notion that the interactions between tumor cells and the cells of the microenvironment can induce resistance toward the cytotoxic machinery of immune cells through upregulation of anti-apoptotic molecules such as survivin, BCL-2 and MCL-1. Thus, successful anti-tumor immunotherapy may rely not only on eliminating the immune suppressive factors from the microenvironment, but also on modulation of the mechanisms that induce or mediate immune resistance. Among several theoretically conceivable strategies, specific attention needs to be paid for modulating the target molecules/pathways without compromising T cell function. With this respect, neutralizing survivin/MCL-1 with YM155 is a suitable strategy as we have not observed any T cell compromising effects of YM155. Several other pathways such as the PI3-K/AKT pathway, that are activated by microenvironmental influences play important roles in tumor development, survival, proliferation and drug resistance through induction of anti-apoptotic molecules [119]. The modulation of these pathways may be beneficial but need to be cautiously explored as these pathways may also play essential roles in T cell activation. For instance, the popular MEK inhibitors appear to impair T cell functions and are probably not suitable candidates to combine with immune therapy. On the other hand, selective inhibitors of BRAF were shown to enhance T-cell recognition of melanoma without affecting lymphocyte function [120]. More practical choices may be the general regulators of epigenetic mechanisms, such as histone deacetylase (HDAC) inhibitors as they have been shown to modulate drug resistance as well as to improve CTL-mediated lysis of tumor cells through upregulation of death receptors [121], and downregulating intracellular c-IAP-2 and BCL-XL expressions [122].

Among all these choices, however, the most appealing strategies may be disrupting the tumor-stroma interactions. Since T cells require integrins to generate a proper immune synapse, targeting integrin-mediated adhesion may not be feasible. However, in the BM an effective disruption of stroma-tumor interactions may be achieved using CXCR4 inhibitors, which induce mobilization of stem cells and myeloma cells from the BM. Such a strategy has already been shown to successfully overcome stroma-mediated activation of STAT3 [123] and HGF/MET [124] pathways, and to prevent the drug resistance of myeloma cells induced by BMSCs [125]. Furthermore, disturbing the stroma-tumor interactions may also prevent the upregulation of immune checkpoint molecules [36]. Finally, since NOTCH signaling also seems important in the microenvironment-mediated drug resistance and similarly may induce immune resistance, its modulation can also be explored. Nonetheless, more investigation is required on NOTCH, as there are conflicting reports on its role, especially on the cytotoxic activity of T cells [126–128].

7.7 Concluding Remarks

The appreciation of the role of the microenvironment, not only in the induction of immune suppressive events but also in the protection of tumor cells against cytotoxic T cell attack, will stimulate the research and encourage the scientists and clinicians to combine immunotherapy not only with agents that can modulate immune suppression but also with those that can eliminate the resistance mechanisms induced by the microenvironment. Furthermore, the increasing consciousness that drug resistance may in several cases also cause immune-resistance may stimulate the discussion whether heavily pretreated and multidrug resistant patients are suitable candidates for clinical testing of cellular immunotherapy strategies.

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