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The mesenchymal tumor microenvironment
A drug-resistant niche

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Abbreviations: CAM-DR, cell adhesion-mediated resistance; ECM, extracellular matrix; EM-DR, environment-mediated drug resistance; nab-paclitaxel, paclitaxel delivered through nanoparticles conjugated to albumin; TAFs, tumor-associated fibroblasts (also known as carcinoma-associated fibroblasts or CAFs); SDF-1, stroma-derived factor 1

Drug and radiation resistance represent a challenge for most anticancer therapies. Diverse experimental approaches have provided evidence that the tumor-associated microenvironment constitutes both a protective shell that impedes drug or radiation access and a permissive or promotive microenvironment that encourages a nurturing cancer (i.e., cancer stem cell) niche where tumor cells overcome treatment- and cancer-induced stresses. Better understanding of the effects of the tumor microenvironment on cancer cells before, during and immediately after chemo- or radiotherapy is imperative to design new therapies aimed at targeting this tumor-protective niche. This review summarizes some of the known mesenchymal stromal effects that account for drug resistance, the main signal transduction pathways associated with this resistance and the therapeutic efforts directed to increase the success of current therapies. Special emphasis is given to environment-mediated drug resistance in general and to cell adhesion-mediated drug resistance in particular.

Introduction

Cancer cells use diverse strategies to decrease their sensitivity to drug therapy including alteration in drug-induced apoptosis, reduction of proliferation rates, expression of new drug-efflux pumps and failure to initiate DNA repair responses.[1] These strategies largely rely on the ability of tumor cells to acquire a series of genetic changes that confer a survival advantage. Nevertheless, this genetic resistance takes a relatively long time to develop, whereas other "less permanent" or durable types of resistance mechanisms come into play earlier in treatment with a given drug. Following a selection of mutations, tumor cells become permanently resistant to the specific drug and to additional drug families because the selective pressure leads to new gene expression patterns that differ substantially from the expression patterns of the drug sensitive parental tumor cells.[2]

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Ideally, cancer treatment would eliminate all malignant cells in order to avoid relapse and the increased aggressiveness that is often associated with tumor recurrence. However, even after "complete responses" evidenced by absence of macroscopic lesions, a small but significant number of cancer cells often survive chemotherapy.[3] These surviving cells constitute minimal residual disease and represent a valuable diagnostic test to predict therapeutic outcomes, especially the probability of relapse. For instance, in acute lymphoblastic leukemia, the levels of these cells constitute the most important prognostic factor.[4] Despite the clinical correlation between levels of minimal residual disease and probability of relapse, the mechanism whereby these cells escape the damaging effects of chemotherapeutic agents remains unclear.[5]

The presence of resistant subpopulations within the tumor mass and their subsequent selection and enrichment after treatment highlight the role of the genetic variability of these resistant cells. It has been proposed that cancer stem cells can divide asymmetrically producing the heterogeneous array of cells that compose a tumor while maintaining a resistant population of stem-like cells through self-renewal. In other words, it is possible that cancer stem cells may be the source of this heterogeneity, and thus the stem cells constitute the so-called "resistant population."[6] An alternative model suggests that cancer cells can undergo an epithelial-mesenchymal transition leading to the acquisition of stem cell properties.[7] In this context, epithelial to mesenchymal transition may comprise epigenetic and/or a genetic change resulting in altered gene expressions. The difference between these two events is that epigenetic changes arise by alterations in RNA or protein expression independently of changes in the DNA sequence, while a genetic event originates from an alteration in the DNA sequence.[8] For instance, epigenetic changes caused by extrinsic (i.e., microenvironmental), persistent or temporary cues may induce DNA methylation changes or alteration in some chromatin binding proteins leading to modifications in gene expression patterns that facilitate tumorigenesis and/or to drug resistance.[9] In this case, gene expression changes, due to either microenvironmental regulation (i.e., epigenetic) and/or to mutations (i.e., genetic), convey alterations in gene expression that confer selective survival advantages.[10,11] These statements are consistent with the traditional hypothesis of acquired resistance;

however, this classical view solely considers resistance that is genetic.[12,13] In contrast, new approaches to the study of drug resistance also consider microenvironmental influenced epigenetic changes.

The above-mentioned mechanisms require a complex interplay between environmental signals, gene mutations and selection pressures. Some models propose that a stepwise acquisition and accumulation of mutations take a long time,[14-16] suggesting that cells destined to develop genetic alterations first require a sustained protection from the toxic effects of the drug through a non-genetic mechanism such as an altered tumor microenvironment prior to the acquisition of a resistant phenotype. Alternatively, a small population of cells within the drug naïve tumor could already possess specific genetic or epigenetic predispositions, which will be selected for during the drug treatment. Hence, the drug-resistant population will in time present a different gene expression pattern from the one seen in the original drug naïve tumor. Under this time required scenario, it seems possible that the resistant cell population is protected by the tumor microenvironment (or selected for by the environmental pressures during treatment) providing a nurturing niche in which the cells could undergo mutagenesis or epigenetic changes. In both cases, the microenvironment is expected to play a role in assisting these cells to survive until the tumor becomes effectively drug resistant. In summary, newly genetic mutated, epigenetically modified or existent pre-disposed cells could all persist and regenerate resulting in what is known as an "acquired resistance" to therapy.[2,17]

It is important to note that de novo resistance could also include a microenvironmental protection mechanism or physical barrier that would limit the distribution (or the penetration) of an anticancer agent to tumor cell populations shielding cells from potential damage imparted by the drug.[18,19] Note that this aspect of protection was reviewed elsewhere and therefore does not constitute a major discussion point.[18,19] Nonetheless, several factors present in the tumor microenvironment induce gene transcription or activate post-translational modifications that reduce toxic drug effects. As this is considered a possibly transient and reversible type of resistance, therapeutic efforts to target these shielding environmental factors constitute an attractive approach to better access the tumor and to attempt to eliminate the cells that constitute the above-mentioned minimal residual disease. Consequently, it has been proposed that blockage of environment-mediated drug resistance (EM-DR) will lead to elimination of relapse or at least extend the time to disease relapse.[20]

The tumor-associated microenvironment that epithelial cancer cells often encounter during tumorigenesis (i.e., renal[21] and ovarian[22] cancers) and/or invasion (i.e., breast and other cancers[23]), consists of a rich assortment of cells (i.e, endothelial cells, plasma cells, macrophages, adipocytes and fibroblasts), extracellular matrix (ECM) fibers and stromal-derived soluble factors that contribute to the tumor-microenvironment interactions.[24] De novo EM-DR falls into two broad categories: soluble factor-mediated resistance and cell adhesion-mediated resistance or CAM-DR. These two forms of resistance interact in a cooperative way. For instance, soluble factors may induce the expression of cellular adhesion molecules initiating a positive feedback loop and amplifying the resistance. A combination of both mechanisms may contribute to minimal residual disease making it difficult to separate one process from the other.[25] In this review, we discuss aspects of CAM-DR in terms of its significant biological effects and list some promising therapeutic interventions aimed at counteracting these effects. Nevertheless, since soluble factors play an important role in facilitating, amplifying and strengthening CAM-DR, we will refer to selected factors whenever they significantly enhance this type of EM-DR.

Stages of EM-DR

A strong example of development of EM-DR is observed within the bone marrow microenvironment. Hematologic malignancies are established in the bone marrow while many solid (i.e., non-hematologic) tumors metastasize to the bone marrow. This compartment is rich in interleukins, especially IL-6 (see **Table 1** for a list of drugs targeting this and many other EM-DR factors), and fibronectin both known to contribute to the acquisition of drug resistance.[26] According to models that include tumors of primary bone origin or tumors metastatic to bone, bone marrow-like drug resistance develops in three discrete stages (see provided figure for representative example): homing, de novo resistance (including soluble factor mediated resistance and CAM-DR) and acquired resistance.[27]

Stage I. Homing, the first stage of EM-DR, normally refers to the adhesion of tumor cells to bone marrow hosted cells and/or to its ECM.[27] Nevertheless, this step may not be necessary in solid tumors, while an alternative microenvironment, such as the lung, may play the same homing role during the metastatic establishment of tumors.[28] Both normal and malignant hematopoietic cells and many epithelial solid tumor cells express a G-protein coupled receptor, CXCR4. CXCR4 is believed to be upregulated in response to pro-inflammatory factors often seen during tumor development and progression such as tumor necrosis α and IL-6.[29] CXCR4 binds to ligands such as stroma-derived factor 1 (SDF-1) also known as CXCL12. This factor is believed to attract cells to the homing tissue (i.e., bone marrow or lung), retain them within this niche and stimulate their survival.[27,30,31] In contrast to hematopoietic cells, solid tumor cells with greatest CXCR4 expression are those likely to metastasize favoring tumor cell migration, invasion and metastasis. These responses are believed to be triggered by the secondary metastatic tissue-derived SDF-1/CXCL12 known to be expressed by a predetermined secondary niche at the resident stromal location.[28,30,32,33] Hence, the CXCR4-SDF-1/CXCL12 axis may constitute a general mechanism of tumor-stroma interaction that attracts neoplastic cells to the stroma, which can subsequently foster development of EM-DR.

Increased CXCR4 expression in clinical specimens seems to be predictive of poor prognosis in pancreatic cancer.[34] In experimental systems, stromal-produced SDF-1/CXCL12, together with additional factors such as IL-8, not only attract pancreatic cancer cells to the experimental stroma (i.e., fibroblasts) but also increase tumor cell survival favoring migration and invasion.[35]

Table 1. Examples of targets that could decrease tumor microenvironment-mediated drug resistance

Target	Therapeutic agent	Model and references
IL-6	Monoclonal antibody (siltuximab)	Ovarian cancer xenografts and clinical trial[149]
CXCR4	Plerixaflor (AMD3100)	Myeloid acute leukemia cells[140]
		Glioblastoma and medulloblastoma xenografts[142]
		Breast cancer cells and xenografts[146]
	AMD 3465	Glioblastoma and medulloblastoma cell lines and xenografts[143]
	CTCE-9908 Inhibitory peptide	Transgenic mouse model of breast cancer[144]
	siRNA	Immunocompetent mouse model and cells for papillary epithelial ovarian cancer[141]
Integrins	Integrins (i.e., fibronectin synergy domain) antagonist penta-peptide (ATN-161)	Clinical trial (solid tumors)[120]
	Anti β_1-integrin monoclonal antibody (AIIB2)	Breast cancer xenografts[124]
	General β_1-integrin and natural HMG-CoA reductase inhibitor (Simvastatin)	Head and neck squamous cell carcinoma cell lines[151]
	$\alpha_V\beta_3$-inregrin: etaracizumab	Clinical trials (melanoma and advanced solid tumors)[121,122]
	$\alpha_4\beta_1$- and $\alpha_4\beta_7$: shRNA	Multiple myeloma cells[127]
	Monoclonal anti α_4-integrin antibody (Natalizumab)	Multiple myeloma cells and mouse model[128]
Cholesterol biosynthesis-dependent CAM-DR	Statins, inhibitors of HMG-CoA reductase often through a Rho pathway inhibition manner (i.e., cerivastatin, simvastatin, lovastatin and fluvastatin)	Breast cancer cells and xenografts[152] Multiple myeloma cells[153] Murine melanoma cells and xenografts[156]
Hedgehog	IPI-926 (oral smoothened inhibitor)	Murine pancreatic cancer models[69]
SPARC/ostenectin	SPARC analog N-terminal peptide	Human colon, breast and pancreatic cancer cells and xenografts[139]
	Nanoparticles conjugated to albumin that specifically binds to stromal SPARC (i.e., nab-paclitaxel)	Breast cancer models and clinical trials[131,132,137,138] Prostate cancer clinical trial[133] Pancreatic cancer clinical trial[134]

Note that additional (not listed) reagents may be available. The relevant targets, therapeutic agents and models used are provided.[11]

CXCR4 positive cells show increased activation of Akt/PKB and ERK pathways in response to SDF-1/CXCL12 thus leading to Bad phosphorylation, which translates into resistance to gemcitabine (the current preferred drug approved for the treatment of advanced pancreatic cancer) induced apoptosis. In this context, the interaction between CXCR4 and SDF-1/CXCR12 may constitute clinical relevance since it elicits resistance to gemcitabine. The study in question did not directly show that gemcitabine induces pancreatic cancer CXCR4 or stromal SDF-1/CXCL12. Nevertheless, the study shows that a small-molecule antagonist to CXCR4 desensitizes cells to gemcitabine by an effect on apoptosis.[36]

Interestingly, the CXCR4 and SDF-1/CXCL12 axis has other biologic effects that are relevant to the development of drug resistance, which do not necessarily seem to be related to homing. For example, glioblastoma cells (which usually remain in the brain and almost never metastasize) express both CXCR4 and CXCR7, which result in Erk 1/2 phosphorylation that also mediate anti-apoptotic responses.[37] In fact, stromal cells harvested from lymph nodes promote drug resistance in human colon cancer cells through a CXCR4-SDF-1/CXCL12 dependent mechanism.[38] Moreover, epithelial CXCR4 and stromal SDF-1/CXCL12 have been shown to regulate various normal and pathologic processes such as development, organogenesis, tissue regeneration and tumorigenesis.[31]

Stage II. In the second stage of EM-DR, tumor cells also engage the microenvironment. In turn, the engaged microenvironment secretes well-defined soluble factors and provides a specific adhesive milieu for the cancer cells to establish growth (see **Fig. 1**). In this stage, soluble factors and adhesive substrates can lead to drug resistance, while multiple interactions between the two amplify the cells' responses leading to a rapid yet reversible resistance to therapies.[27] For example, stromal cells in the bone marrow are known to secrete IL-6, which stimulates myeloma cells to produce vascular endothelial growth factor known to activate endothelial (stromal) cells resulting in angiogenesis and stroma nourishment.[39] In addition, IL-6 stimulates secretion of additional factors such as fibroblast growth factor, which is known for its stromal mitogenic effects thus promoting stromal fibroblast proliferation and activation. This reciprocal stimulation generates an amplifying loop in which stromal and tumor cells together acquire increased ability to proliferate and survive.[39-41]

CAM-DR involves the adhesion of integrins and other receptors with components of the ECM: various types of collagen such as collagen I and III, splice variants of fibronectin such as ED-A, as well as other proteins such as vitronectin, tenascin-C, SPARC and osteopontin. Drug resistance is associated with anti-apoptotic and anti-proliferative cues. Both strategies render cells insensitive to chemotherapeutics that stimulate apoptosis or that target

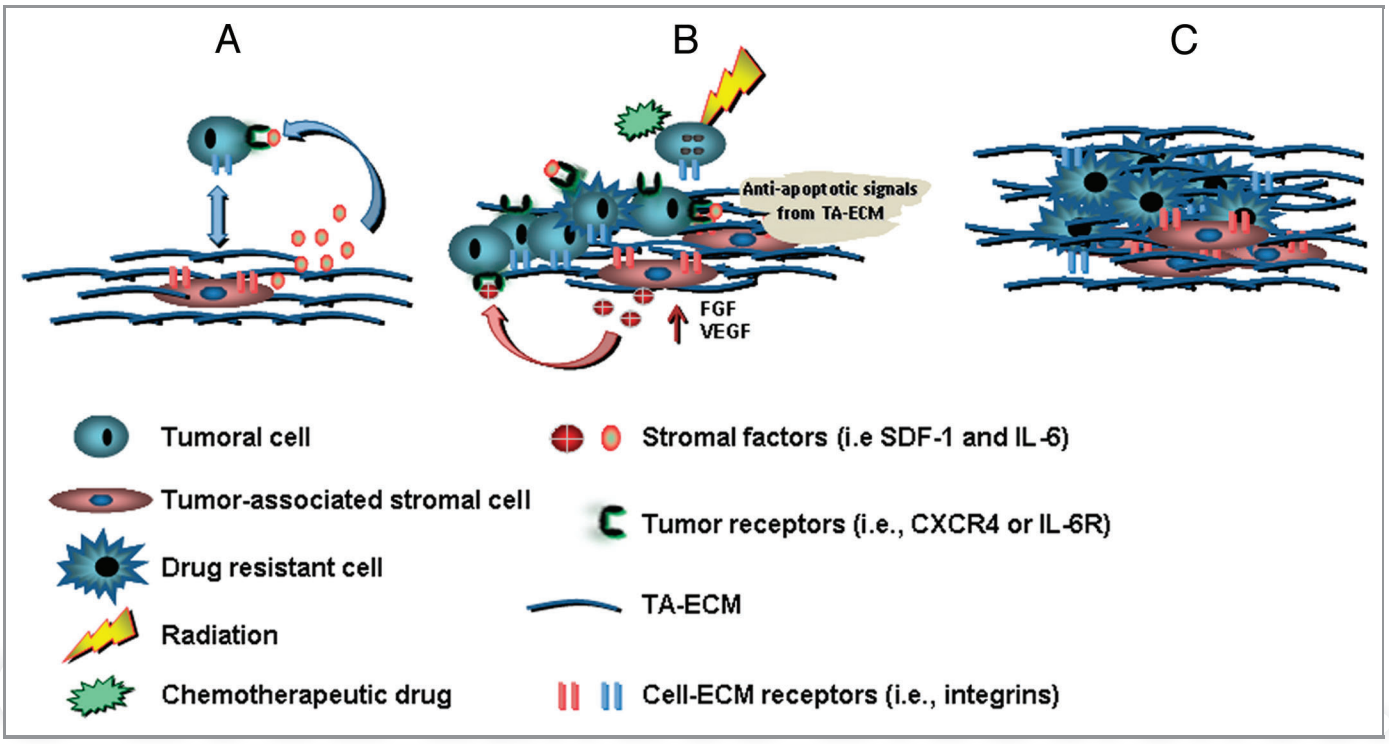

Figure 1. Stages during the development of environment-dependent drug resistance. (A) Homing or attraction. This first step requires specific cell-cell or cell-extracellular matrix interactions. Soluble stromal factors, such as SDF-1 and IL-6, and receptor-mediated adhesion contribute to attract tumor cells to the stromal niche where the tumor will be established. This first step is necessary in many hematopoietic malignancies,[27] as well as in the establishment of secondary (i.e., metastatic[28]) tumors. Although homing is often seen in primary bone marrow tumors as well as in secondary tumor establishments, this step may not be necessary during primary solid tumor development. (B) De novo resistance. In this second stage (first stage for primary tumors that are not established in the bone marrow), the main stress from the treatment is applied to the, until then, drug naïve tumor. This step is characterized by a series of cell responses and the modification of the composition of the ECM creating a positive feedback loop that amplifies the pro-survival and anti-apoptotic signals. (C) Acquired resistance. This stage is commonly regarded as being environmental-independent, yet the microenvironment still plays an important role; for example, it can act as a barrier that physically or biochemically prevents the effective access of drugs to the tumor cells (see ref. 18 for review). Note the presence of a small amount of cancer resistance cells at early stages of development of drug resistance. This small cell population in what sometimes is regarded as the first stage (i.e., environment-dependent) and represents the possibility of a predisposed (i.e., cancer stem) resistant cell or, alternatively, one that has undergone a drug resistant mutation, will be selected during the stress period rendering a genetically different tumor signature compared with the drug naïve tumor population.

pathways that are preferentially active in rapidly dividing cells. Although several integrins have been implicated in this process, a special emphasis has been placed on $\alpha_4\beta_1$-integrin, especially in bone marrow metastases. This receptor seems to play a crucial role in the acquisition of de novo resistance,[42-45] supported by evidence that adhesion via β_1-integrins decreases drug-induced DNA damage, apoptosis and/or cell cycle arrest in small cell lung,[46] breast[47] and hematopoietic cancers.[48] Inhibition of apoptosis and increased cell proliferation can also be triggered by the binding of tumoral Notch-1,[49] with Jagged, which is often expressed as a membrane bound ligand by bone marrow stromal cells.[50] Interestingly, inhibition of the Notch axis has been proposed as a possible approach to induce pancreatic cancer apoptosis, while inhibition of Notch interplaying factors such as Hedgehog have been suggested for enhancing drug delivery to this highly desmoplastic tumor.[51] Moreover, Hedgehog transcriptional target ABCG2 is well known for its stroma-dependent drug tolerance in lymphoma.[52] The expression of these types of stromal factors and their role in protecting cancer cells against toxic therapies support the notion that the mesenchymal tumor microenvironment promotes development of CAM-DR. Interestingly in a classic experiment, Teicher et al. produced resistant mammary carcinoma cell lines by treating cells with four anti-neoplastic alkylating agents and passing cells through four groups of animals where cells were orthotopically injected. Treated tumor cells were isolated and sequentially transferred to fresh animals. The resultant tumors that developed in vivo acquired resistance to the drugs.[16] Strikingly, the resultant cells lost their resistance after several passages of culture in vitro indicating that the mechanisms responsible for the resistance were not only reversible but strictly dependent on in vivo conditions.[16]

Stage III. During EM-DR, the tumor microenvironment protects cells from harsh therapeutic conditions providing anti-apoptotic signals that help cells resist drug-mediated DNA damage and apoptosis.[43,53-55] In addition, it has been suggested that the mesenchymal stromal anti-proliferative cues can prevent cells from being targeted by growth inhibitory therapies.[56] Hence, it is possible that stressful conditions promote the acquisition of

transient reversible resistance in tumor cells that enables them to gain time and set in motion a complex process of DNA mutation (and/or epigenetic changes) that will ultimately lead to a state of what is believed to be an irreversible resistance. This third stage of EM-DR is known as acquired resistance (see **Fig. 1**), and, as decades of experience demonstrate at this stage of drug resistance development, cells become particularly difficult to treat.[20,57]

Biological Effects of CAM-DR

Four decades ago, Durand and Sutherland demonstrated that, compared with single cells in suspension, CHO cells grown as 3D spheroids in which cells establish close contact with one another were more resistant to the toxic effects of radiation.[58] While the authors used spheroids exclusively composed of epithelial cells without a stromal component, this seminal work illustrated the importance of cell-cell adhesions in drug resistance. Building on these observations, we recently utilized a discrete cell culture model in which we were able to differentiate between responses of cancer epithelial cells to drug exposure determined by cell-cell vs. cell-ECM interactions (Cukierman and colleagues, unpublished results). These types of tissue engineered in vitro experimental models should assist in better understanding mechanisms responsible for some aspects of CAM-DR and facilitate development of pre-clinical screens for agents that can modulate CAM-DR.

In contrast to classical two-dimensional cell culture systems, animal models provide the complex stromal network (including altered ECMs) and permit the study of stromal influences.[23] In addition, various three-dimensional culture systems also recapitulate some of the in vivo biological properties observed in the tumor stroma.[59-61] Culture of a myeloma cell line on fibronectin provided the first indication that resistance to chemotherapeutics may develop through cell adhesion molecules.[62] Damiano et al. has long established that CAM-DR can arise from the interaction between $\alpha_4\beta_1$-integrin expressed by the tumor epithelial cells and the ECM protein fibronectin expressed by stromal cells.[62] This adhesion elicits post-translational modifications such as phosphorylations resulting in activation of survival signals such as activation of IκB kinase and others tending to inhibit or counteract drug-induced apoptosis.[63] In addition, β_1-integrin was shown to play an Akt/PKB-independent role in the observed mesenchymal matrix protective effects seen under cytotoxic drug treatments in a plethora of cancer cells cultured onto fibroblast-derived 3D ECMs in vitro.[64] A recent study suggested that tumor ECM can impart resistance to drugs due to β_1-integrin, talin and FAK-dependent nuclear activation of NFκB.[65] Another study suggested that a combination of specific splice variant forms of fibronectin together with $\alpha_5\beta_1$-integrin play a pivotal role in resistance to radiation in breast cancer and that inhibiting this specific fibronectin-integrin axis can be instrumental in ensuring a better response to radiation treatment.[66] In addition, $\alpha_5\beta_1$-integrin has been implicated in chemoresistance in pancreatic cancer.[67] In addition, CAM-DR can result in reduced availability of pro-proliferative signal molecules and mitogenic activity favoring a quiescent state that protects cells from current cell cycle-dependent therapies.[68] Moreover, inhibition of epithelial-stromal signals (i.e., by inhibiting the Hedgehog pathway) has been shown to induce increases in chemotherapy delivery using a murine model of pancreatic cancer.[69] It is well established that tumor-associated fibroblasts (TAFs, also known as carcinoma-associated fibroblasts or CAFs) produce a tumor-altered ECM that differs from that associated with normal, nonmalignant ECMs.[23,59,60,70-73] In fact, it has been suggested that TAFs are responsible for resistance to epidermal growth factor inhibition in lung cancers with epidermal growth factor receptor-activating mutations[74] and TAFs have been blamed for supporting tumor growth and drug resistance in some cancers (i.e., melanoma[75]).

Strikingly, the resistance observed in CAM-DR proved to be similar to the so-called acquired cell-derived drug resistance (de novo resistance of cells maintained in suspension). Using a human myeloma cell line, Hazlehurst et al. showed a significant increase in resistance to the alkylating agent melphalan when cells were cultured on fibronectin (i.e., CAM-DR) and compared these levels with levels of resistance imparted upon cells grown in suspension (i.e., acquired to melphalan cell-derived resistance). The levels of resistance on these two cultures were comparable. Only 69 genes were differentially expressed in CAM-DR (e.g., cultured on fibronectin) with respect to the cells grown in suspension. Among these CAM-DR 69 genes, the resistance mechanisms most frequently observed were related to decreased melphalan-induced mitochondrial depolarization and impaired caspase activation. These results highlight not only the magnitude of CAM-DR but also its reversible nature, since both the polarization state of the mitochondrial membrane and the activation of an inactive protein can be reverted using appropriate agents.[15] Furthermore, the limited number of genes activated during CAM-DR suggests that therapies directed against relevant cell-matrix interactions could successfully target cancer cells administered alone or together with other anticancer agents.

Cancer cells may alter the composition of the ECM to modulate cell-matrix interactions accelerating the acquisition of CAM-DR. For example, collagen VI, a microfibrillar collagen associated with proliferation,[76] is highly expressed in advanced metastatic ovarian cancer[77] and cisplatin-resistant ovarian cancer cell lines. On the other hand, an ovarian cancer cell line, A2780, proved to increase its resistance to cisplatin when grown onto collagen VI. In this context, ovarian cancer cell lines favoring the acquisition of resistance synthesize ECM components that provide proliferative and adhesive advantages in the presence of cisplatin. The expression of collagen VI increases the adhesion to decorin, a component of the ECM, providing a specific binding to stromal components facilitating the adhesion of ovarian cancer cells to distant sites and favoring metastasis. Yet again, collagen VI decreases the expression of Bax, a pro-apoptotic protein, increasing cell survival. This paracrine mechanism initiated by alteration of the ECM by the tumor cells establishes a self- amplifying loop between the stroma and the tumor cells.[78] Interestingly, it is important to highlight that different stromal cells and stromal ECMs can induce alternative cancer cell behaviors/phenotypes, which in turn are believed to be important in the manner that cancer cells respond to drug treatments.[79]

The notion that the degree of change in the stromal components of a tumor may be predictive of tumor behavior and also of response to treatment, leads to the concept of "stromal staging."[23,59,64,80-82] To this end, work has emerged in various types of cancers such as pancreatic[82] and renal[59] cancers demonstrating the potential clinical utility of stromal staging (see **Fig. 2**).

Signaling Pathways Associated with CAM-DR

As stated before, the interaction between the tumor cells and the stroma initiates post-translation mechanisms that confer a survival advantage. Hence, CAM-DR does not only function as a mere attachment of the tumor cell to the stroma but also as a powerful stimulus that triggers several signal transduction pathways leading to decreased sensitivity to apoptosis and, in some cases, inhibition of cell proliferation. Inhibition of cell proliferation (i.e., dormancy) may render cells resistant to anti-cancer therapies that target the cell cycle.[3,83] Moreover, epithelial cancer cell signaling is likely to differ when engaged with the microenvironment.[84] Therefore, the implication will be that amplification loops are not only initiated by the tumor microenvironment, but unique signals are educed within cancer cells under stimuli from both the soluble and physical microenvironment.[84]

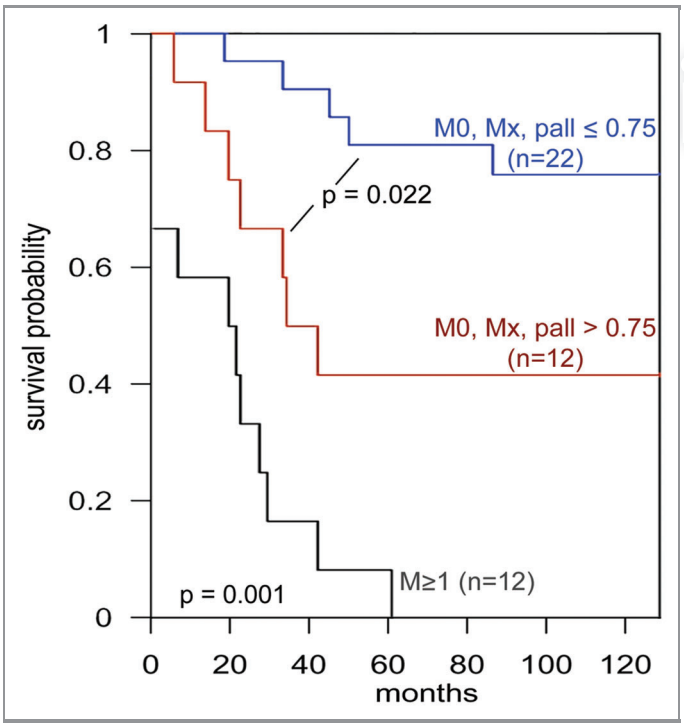

Figure 2. Activated stroma comprises a risk factor in non metastatic renal cell carcinoma. Multivariate CART-based sorting of a cohort where non metastatic patients (M0, Mx) were sorted by their stromal palladin expression levels representing non-activated (stromal palladin ≤ 0.75) vs. activated (stromal palladin > 0.75) stromal levels and were compared with metastatic patients (M ≥ 1) in a Kaplan-Meier curve showing time-scale (in months) at the x-axis and corresponding survival probability (e.g., survival fraction) at y-axis. The corresponding p values are provided. This figure was adapted from reference 59.

Integrins and their downstream signaling pathways have often been implicated in cancer growth and invasion. Moreover, direct integrin inhibition or blockade of integrin-dependent pathways have been shown to assist in vitro to overcome drug resistance or to better drug treatments.[47,64,85] In myeloma[68] and in colon cancer[86] cell lines, adhesion of $\alpha_4\beta_1$- or $\alpha_5\beta_1$-integrins to fibronectin results in increased levels of expression of $p27^{Kip1}$, which inhibits the activity of the cyclin A and cyclin E associated kinases. Inactivation of these kinases decreases the activity of cyclins and leads to arrest in G1 phase. Interestingly, the levels of $p27^{Kip1}$ return to normal (i.e., low) basal levels within two hours after disruption of a specific fibronectin-integrin interaction.[68,86] This rapid response to cell-ECM adhesion relies on post-translational processes rather than on transcriptional activation of $p27^{Kip1}$. In fact, adhesion of these integrins to fibronectin activates the ubiquitin ligase complex APC-Cdh1 increasing the ubiquitinilation and subsequent degradation of Skp-2, a negative modulator of $p27^{Kip1}$.[87,88] Decreased levels of Skp-2 results in increased $p27^{Kip1}$ stability leading to its accumulation in the nucleus[89] where it drives growth arrest in myeloma and lymphoma cell lines.[90] A similar mechanism has been proposed for $\alpha_2\beta_1$-integrin mediated cell growth arrest in a metastatic melanoma.[91] Adhesion of melanoma cells to polymerized fibrillar collagen I results in cell growth arrest.[91] As suggested above, growth arrest represents a useful strategy to decrease sensitivity to drugs that target the cell cycle. However, in solid tumors and in the context of drugs that promote apoptosis, β_1-integrin engagement exerts the opposite effect: it overrides cell cycle arrest, decreases caspase-3 activation and prevents cells from undergoing apoptosis.[92,93] Again, in this context, the ECM plays a crucial role since it provides the ligand/substrate for engaging integrin activities.

Increased and/or altered production of ECM proteins such as fibronectin, collagen IV, tenascin C and others predict poor prognosis in small cell lung carcinoma, a malignancy characterized by a good initial response to therapy but a high incidence of relapse indicative of CAM-DR.[94] In fact in this malignancy, increased proliferation and survival play an important role in the aggressiveness of stromal rich tumors.[94] Moreover, small cell lung carcinoma expresses different combinations of β1-integrins known for their abilities to bind and to respond to changes in collagen, laminin and fibronectin. This type of lung carcinoma expresses increased and differential spliced forms of fibronectin potentiating the effects of signal transduction pathways and, hence, of tumorigenic cellular responses.[94] Others have shown that the normal response to etoposide and ionizing radiation increases levels of negative regulators of the G2/M checkpoint including $p21^{Cip1}$ and $p27^{Kip1}$, which leads to decreased stability of cyclins A, B and E and to reduced phosphorylation of CDK2 with the net effect of cell cycle arrest.[46] By contrast, increased adhesion of β1-integrins to the tumor ECM triggers the activation of the non-receptor and integrin-dependent tyrosine kinase FAK, which in turn activates PI3 Kinase, Akt/PKB and GSK3β. These events trigger an increase in cyclin and a decrease in both p21 and p27 stability thus resulting in bypass of the G2/M checkpoint and eluding the pro-apoptotic effects seen following

treatment with the combination of etoposide and ionizing radiation.[46]

Other signal transduction pathways driven through PI3 Kinase lead to resistance to apoptosis. Adhesion of β_1-integrins activates the PI3 Kinase recruiting Akt/PKB to the membrane and leading to Akt-mediated pro-survival signals such as inactivation of the pro-apoptotic proteins Bad, Bim and Noxa,[95,96] or to matrix-induced resistance to paclitaxel treatment.[47] Some of the above-mentioned pro-apoptotic proteins were shown to be ubiquitinilated for degradation (BcL-2, Bim) while others were phosphorylated.

Cells can also evade apoptosis by decreasing the proteolytic-dependent activation of caspase 8, a post-translational modulator of caspase 3. For example, in multiple myeloma cells grown in suspension, the death receptor CD-95 can be found to be associated with the adaptor protein FADD. In turn, this complex attracts and tethers the procaspase 8 to the plasma membrane where it is activated by a limited and specific proteolysis. In turn, activated caspase 8 cleaves and therefore activates caspase 3 which promotes apoptosis. When cells bind to fibronectin, cFLIPL is released from the endo-membrane system to the cytoplasm competing with procaspase 8 for FADD binding. In this case, reduced binding of procaspase 8 to the FADD results in decreased activation of this pro-apoptotic enzyme and, thus, to ECM-dependent increased survival.[97]

Therapeutic Interventions

Once cells acquire resistance to a drug, relapse of the disease seems inevitable thus making it imperative to change treatment. Unfortunately, each time an individual develops a specific resistance to a given drug (or drug family) and relapse is observed, the relapse-free time decreases and the possibility of patient benefit diminishes.[20,98] In order to prevent or delay the acquisition of drug resistance, several therapeutic approaches have been proposed.[99] These include: (1) interference with direct tumor-stromal interactions,[51] (2) impairment of cell-ECM interactions,[100-102] (3) hampering of both expression and activity of paracrine factors secreted by stromal cells,[103,104] (4) inhibition of stromal nuclear receptor super-family molecules (i.e., ligand-activated transcription factors known to regulate lipid metabolism and other processes[105]) or (5) general blockade of tumorigenic signaling pathways.[48,68,90,106-108]

Integrin inhibitors have been in clinical use for two decades, for example, in prevention of $\alpha_{II}\beta_3$-dependent platelet aggregation in patients with acute coronary thrombosis.[109] Other anti-integrin antibodies with efficacy in the treatment of psoriasis, Crohn disease and multiple sclerosis target the α_4-integrins. Unfortunately, these agents were associated with progressive multifocal encelopathy and were withdrawn from the market.[110] However, one of these antibodies, natalizumab, was eventually reintroduced for clinical use because of its effectiveness in decreasing the rate of relapse in subjects with multiple sclerosis. Despite this initial low level of success, new understanding of the function of integrins,[111-114] and the development of less toxic drugs points to a brighter future for these therapies. Hence, integrin inhibitors are even being considered as tumor-stromal interaction inhibitors to attempt targeting dormant cancer cells.[115]

Integrins play a crucial role in tumor development, angiogenesis and survival, as well as cell-cell and cell-ECM interactions.[116-119] As such, several inhibitors of integrin function have been developed to stop tumor progression, and some of these are being tested in the clinic.[120] Etaracizumab, a monoclonal antibody specific for $\alpha_V\beta_3$-integrin, is under clinical development for the treatment of advanced metastatic melanoma[121] and for additional solid metastatic tumors.[122] Downstream effectors of integrin activation such as FAK also constitute novel therapeutic targets.[123] The mechanism of action of these inhibitors includes inhibition of angiogenesis, migration and survival of the epithelial cells. However, the growing awareness that this interaction (i.e., that regulate integrin-ligand communications or affect integrin functional conformational changes) leads ultimately to the acquisition of CAM-DR makes it essential to consider the biology of cell-ECM interactions for the development of new drugs.

Cilentigide, a cyclic peptide that blocks the pro-angiogenic actions of $\alpha_V\beta_3$-integrin, proved to be non-toxic stimulating investigators to search for new therapeutic approaches that target the interaction between integrins and their ligands. Inhibition of the β_1-integrin activity by means of the use of the AIIB2 monoclonal antibody resulted in increased sensitivity to ionizing radiation in breast cancer cell lines.[124] Furthermore, abrogation of β_1-integrin signaling increased sensitivity to trastuzumab, pertuzumab and lapatinib in 3D but not in 2D environments despite the similar levels of β_1-integrin expression in these environments[125,126] suggesting an important role for in vivo-like microenvironmental settings in pre-clinical drug testing.[61] As further evidence of microenvironmental influence, cells grown in 2D conditions showed changes in proliferation and apoptosis through Akt/PKB and MAPK pathway signaling in response to HER2-targeting agent exposure. Strikingly, cells shifted to a predominantly pro-proliferative behavior in 3D environments pointing to their ability to adapt to different microenvironments.[126] These results validate integrins from the β_1 family as valuable targets for future therapeutic interventions. Multiple myelomas are known to express α_4-integrins such as $\alpha_4\beta_1$ and $\alpha_4\beta_7$. Therefore, knockdown expression of α_4-integrins in multiple myeloma cells constitutes an effective way to sensitize these cells to bortezomib, a proteome inhibitor drug often used in multiple myeloma patients.[127] To this end, natalizumab, a novel small adhesion molecule inhibitor that interferes with $\alpha_4\beta_1$- and $\alpha_4\beta_7$-integrins, is believed to prevent multiple myeloma cell interactions with both stromal cells and stromal ECM as well as indirectly interfere with VEGF secretion and insulin-like growth factor induced signaling in the bone marrow where it increases sensitivity to bortezomib and dexamethasone.[128] These observations point to the potential clinical use of natalizumab for patients with relapsing multiple myeloma and other malignancies.[129,130]

Alternative strategies today utilize specific ECM proteins to target drug treatments. For example, after a series of clinical trials, the use of paclitaxel delivered through nanoparticles conjugated to albumin "nab-paclitaxel" has been approved for treatment of breast cancer.[131] Albumin binds efficiently to osteonectin/SPARC,

which is commonly upregulated in the activated (or desmoplastic) stroma of many cancers such as breast,[132] prostate[133] and pancreatic[134] cancers where its upregulation is also associated with bad prognostics.[135,136] In a metastatic breast cancer model, nab-paclitaxel showed synergy when used in combination with bevacizumab, a monoclonal antibody known for blocking angiogenesis.[137] To this end, the combination of adjuvant dose-dense doxorubicin plus cyclophosphamide followed by dose-dense nab-paclitaxel was recently found to be safe for use in women with early-stage breast cancer.[138] Interestingly, it has also been suggested that SPARC may be a stromal tumor suppressor protein which conveys resistance to therapies. In fact, a recent work demonstrated that a peptide analogous to SPARC has tumor-regressing and chemo-sensitizing activities in vitro and in pre-clinical animal models.[139]

Soluble factors involved in de novo acquired drug resistance such as SDF1/CXCL12 represent alternative targets for cancer therapy. In lymphoblastic leukemia cells, a CXCR4-SDF1/CXCL12 antagonist decreased the adhesion of cancer cells to their tumor microenvironment resulting in decreased survival and increased differentiation.[140] In another preclinical model, treatment of intraperitoneally xenotransplanted ovarian cancer cells with a selective CXCR4 antagonist resulted in decreased tumor proliferation, increased sensitivity to drug-induced apoptosis and enhanced activity of cytotoxic activity of T-lymphocytes.[141] This strategy has been implemented in a series of preclinical tumor models and cells such as in oral squamous cell carcinoma,[36] glioblastoma[142,143] and breast cancer[144-146] models with similar positive results. IL-6 is another stromal soluble factor that is typically upregulated during inflammatory diseases and stromal implicated cancers (i.e., desmoplastic or containing activated stromal cancers).[147] A small molecule inhibitor of the pleotropic serine/threonine kinase CK2 known for its regulation of IL-6 expression in inflammatory breast cancer was currently assessed in a small clinical trial where it was shown to effectively reduce IL-6 in plasma.[148] Moreover, in a platinum-resistant ovarian cancer phase II clinical trial, it was recently demonstrated that use of the anti-IL-6 antibody siltuximab is effective in downregulating IL-6 induced stromal factors such as CCL2, SDF1/CXCL12 and VEGF.[149]

An alternative approach considers downstream pathways activated in CAM-DR. For example, genes involved in cholesterol biosynthesis are upregulated in CAM-DR and in acquired drug resistance.[15] Simvastatin, one of the 3-hydroxy-3-methylglutaryl (HMG)-CoA reductase inhibitors, was shown to decrease tumor cell proliferation and induce cell cycle arrest at G1/S phase.[150] Simvastatin resulted in decreased expression of β_1-integrin, impaired FAK phosphorylation and detachment of tumor cells from the ECM leading to cell death in several head and neck squamous cell carcinoma cell lines.[151] Furthermore, inhibition of cholesterol biosynthesis resulted in decreased activity of the small GTPases Rho, Ras and RAP 1[152,153] resulting in weaker focal adhesions while decreasing the affinity of integrins for their ligands.[154-155]

Inhibition of Wnt, Notch and Hedgehog pathways is considered a promising therapeutic approach because each is implicated in tumor-stromal interaction and may contribute to the protection of cancer stem cells by the microenvironment.[157] Some investigators are considering Notch blockage as a CAM-DR inhibition strategy[51] while Hedgehog pathway inhibitors have already gone through massive translational research considerations.[158] Also, the feasibility and pharmacokinetics of the Hedgehog pathway inhibitor GDC-0449 were demonstrated in a basal-cell carcinoma phase I trial[159] while a single medulloblastoma case study showed a temporary regression of the disease.[160] Another novel approach involves the use of low, less toxic concentrations of naturally occurring stromal cytokines such as gamma interferon in combination with blockade of NFκB, a stromal-induced epithelial cell survival factor. This combination has been found to induce cancer necroptosis in vitro.[161]

Conclusions

Drug resistance represents a challenge to any therapy. Unfortunately, once a cell acquires a drug resistance mutation and the change becomes irreversible, readjusted doses are no longer sufficient and alternative therapeutic approaches are needed. Alternatively, and often by means of epigenetic changes, tumor cells can eventually overcome the toxic effects of chemotherapeutics through evading apoptosis and other treatment-derived toxic effects. To this end, the stroma in general and the tumor-associated ECM in particular provide a permissive environment that stimulates pro-survival pathways and an effective barrier against many of these chemotherapeutics. Therefore, the tumor microenvironment is considered a nurturing setting that protects tumor cells from drug exposure and reduces cytotoxicity. In conclusion, inhibition of tumor-stromal interactions could be a useful approach for preventing drug resistance and improving cancer treatment.

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