Molecular Pathways: Involving Microenvironment Damage Responses in Cancer Therapy Resistance

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ABSTRACT

The armamentarium of therapeutics used to treat cancer patients relies heavily on ionizing radiation and chemotherapeutic drugs that severely damage DNA. The responses of tumor cells to these treatments is heavily influenced by their environment: physical contacts with structural elements such as extracellular matrix, associations with resident and transitory benign cells such as fibroblasts and leukocytes, and interactions with numerous soluble endocrine and paracrine-acting factors all modulate tumor cell behavior. Importantly, this complex tumor microenvironment is not static and dynamically responds to a variety of stimuli. Here, we describe emerging data indicating that genotoxic cancer treatments activate highly conserved damage response programs in benign constituents of the tumor microenvironment. These damage signals, transmitted via master regulators such as NFkB, culminate in a powerful and diverse secretory program that generates a pro-angiogenic, pro-inflammatory microenvironment. Constituents of this program include Interleukin (IL)-6, IL-8, hepatocyte growth factor, amphiregulin, matrix metalloproteinases, and other factors demonstrated to promote adverse tumor cell phenotypes including enhanced resistance to treatment and rapid tumor repopulation. A detailed understanding of these survival signals induced in the context of genotoxic stress provides a platform to develop combinatorial strategies to improve outcomes that consider malignant cells, the tumor microenvironment, and the dynamics exerted by the treatment itself.
BACKGROUND

Therapy Resistance.

Since the advent of modern cancer therapeutics that involve the administration of drugs and ionizing radiation to eradicate neoplastic cells, both de novo and acquired resistance have been recognized as major barriers to cures. Most cancer-directed therapeutics fall broadly into three classes that exploit differential vulnerabilities in malignant tumors relative to benign tissue counterparts. The most commonly deployed therapies inflict substantial damage to nuclear DNA or cell division machinery resulting in genotoxic catastrophe or the engagement of damage response mechanisms that halt cell proliferation. However, the lack of specificity of these interventions limits doses due to collateral damage to normal tissues. A second category of cancer therapeutic has emerged through a detailed understanding of oncogenic pathways that direct targeted inhibition of key drivers such as kinases, growth factors and growth factor receptors. A third approach to treat cancer exploits mounting information implicating the important contribution of the microenvironments within which tumor cells develop, proliferate, and in the case of metastasis, colonize and occupy distant sites. Such strategies include inhibiting new vasculature and augmenting immune system responses.

Each of the above categories of cancer treatments includes agents capable of markedly suppressing tumor growth, but each also suffers from failures due to the engagement or selection of resistance programs. Tumor cell autonomous or ‘intrinsic’ resistance mechanisms such as the activation of multi-drug resistance efflux pumps, activation of bypass signaling pathways, and secondary mutations in drug targets are well-established, and therapeutics have iteratively evolved to exploit these molecular alterations. Less well-studied are factors contributing to cell non-autonomous or ‘extrinsic’ mediators of therapy resistance, such as those provided by non-malignant cells and structural constituents of the tumor microenvironment. Recent work has defined niches within tissues and organs that offer sanctuary to tumors and activate therapy resistance programs. In several notable instances, exploiting these tumor-host dynamics has led to successful clinical translation to impact patient survival. Here we discuss mechanisms by which tumor and host interactions in the microenvironment influence treatment resistance, with an emphasis on reactions and responses induced by cancer therapeutics themselves that have the potential to attenuate treatment lethality and paradoxically promote tumor cell survival.
THE TUMOR MICROENVIRONMENT.

Neoplasms arise and grow in complex and dynamic ecosystems. For most types of solid tumors, the microenvironment is comprised of numerous resident benign cell types derived from distinct developmental lineages, as well as non-resident cells types that may be transient or may persist to become permanent components of an evolving interactive bionetwork. A structural framework provided by insoluble matrix proteins and gradients of diffusible growth factors, hormones, oxygen, reactive oxygen species and nutrients provide a further complexity.

Importantly, many facets of the tumor microenvironment (TME) are capable of profoundly influencing the behavior of pre-neoplastic and overtly malignant cells. Compared to fibroblasts derived from benign tissues, cancer-associated fibroblasts (CAFs) can augment the growth of pre-neoplastic cells and influence invasive tumor behavior in a number of organs including the prostate, breast, and stomach (1-3). Likewise, inflammatory cell components, such as B-cells, T-cells and macrophages, can promote adverse cancer phenotypes within the skin, breast and other tissues (4, 5). The existence of a temporally dynamic microenvironment is evident in studies such as those demonstrating that a ‘normal’ young liver microenvironment is tumor suppressive whereas a ‘normal’ aged liver microenvironment is permissive for tumor establishment and progression (6). Similarly, detailed studies of tumor hypoxia, pH, angiogenesis, and rigidity, have clearly shown that these and other microenvironment attributes produce major changes in tumor phenotypes.

While there is an emerging emphasis on the importance of studying tumor characteristics such as proliferation and invasion in the context of the multi-dimensional influences exerted by the TME, there is less information concerning the roles played by the microenvironment on resistance to cancer therapeutics. However, it is well-recognized that *ex vivo* assays of chemotherapeutics poorly recapitulate *in vivo* effectiveness (7). In part these differences clearly reflect drug delivery issues related to vascular access, interstitial pressures, and metabolism (8). However, other elements of the TME can impact tumor phenotypes to augment drug resistance. Distinct microenvironments can provide niches that contribute substantially to tumor cell survival and eventual relapse and therapy failure. A few examples serve to illustrate the variety of ways by which the context provided by the TME impacts tumor resistance to therapeutics (for reviews, see (8-10)).
Therapy resistance mediated by soluble factors. As with chronic myelogenous leukemia (CML), Philadelphia chromosome-positive acute lymphocytic leukemia (Ph+ALL) is driven by the BCR-ABL fusion protein and is sensitive to the Abl tyrosine kinase inhibitor imatinib (11). In a series of experiments reported by Williams et al, a mouse model of Ph+ALL was developed that exhibited resistance to imatinib, though Abl kinase activity was inhibited by drug treatment (12). However, tumor cells isolated from this model were still sensitive to imatinib in vitro, supporting the hypothesis that components of the host microenvironment, in this case the hematopoietic microenvironment, promoted resistance. Through further experimentation, host cytokines, including IL-7, were determined to promote growth despite imatinib (12). Other studies have implicated galectin 3 (Gal-3) induction in CML by the bone marrow microenvironment as a contributing factor to drug resistance and long-term lodgment of leukemic cells in the bone marrow niche (13). Further evidence for this mechanism of therapy resistance, described below, involves the role(s) of cancer therapeutics themselves in promoting the production of microenvironment-derived soluble factors.

Therapy resistance mediated by physical barriers: Cancers arising from pancreatic duct cells are highly lethal with quite limited responses to radiation or chemotherapy. However, cell lines and xenografted tumors derived from pancreatic cancers do exhibit responses to many chemotherapeutic drugs including gemcitibine, an agent used commonly to treat pancreatic cancer patients with modest efficacy (14). In a series of insightful studies using the KDM genetically-engineered model of pancreatic cancer, Olive et al found a marked difference in responses to chemotherapy between cancers arising within the environment of the in situ pancreas, and tumor cells grafted into subcutaneous sites (15). A major contributor to these differential tumor responses was found to be the limited vascularization and poor perfusion which constrained drug penetration within the pancreas. The efficacy of chemotherapy was substantially enhanced through the use of IPI-926, a sonic hedgehog pathway inhibitor that depleted tumor-associated stromal tissue, increased tumor vascularity, increased intratumoral chemotherapy concentrations, and consequently inhibited tumor growth (15).

Therapy resistance influenced by cell adhesion: Physical interactions between multiple myeloma (MM) cells and structural constituents of the bone marrow have been shown to profoundly influence de novo and acquired resistance to chemotherapy (16). Mechanisms contributing to adhesion-mediated resistance include tumor cell binding---through integrins and other compo-
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Consequent therapy resistance occurs through several pathways including the redistribution of the anti-apoptotic proteins CASP8 and FADD-like apoptosis regulator (FLIP) from the cytoplasm to cell membranes, induced proteasomal degradation of the pro-apoptotic protein BCL2-interacting mediator of cell death (BIM), and transient post-translational upregulation of the cyclin dependent kinase inhibitor p27 (17, 18). Importantly, drug sensitivity can be augmented through agents that disrupt adhesion. In preclinical studies, a blocking antibody to α4 integrin reduced tumor burden and increased overall survival in a mouse model of the multiple myeloma, and dramatically augmented myeloma responses when used in conjunction with melphalan, a drug in common clinical use for the treatment of multiple myeloma (19). Importantly, knowledge of key relationships between myeloma cells and the bone marrow microenvironment led to a series of rationally-designed clinical trials that co-targeted tumor and microenvironment interactions. Lenalidomide, an agent shown to decrease tumor cell binding to bone marrow components, among other effects, and Bortezomib, a proteosome inhibitor that among other effects, downregulates adhesion molecules on both tumor cells and bone marrow stroma, were both shown to substantially improve overall survival (20), and these agents are now part of routine clinical management of patients with multiple myeloma.

Microenvironment Reactions to Cancer-Directed Therapeutics.

It is important to consider that most cancer-directed therapeutics do not have effects entirely restricted to neoplastic cells, but also interact with---and alter---benign cells in local and distant host microenvironments. The potential for such effects are particularly relevant for non-specific treatments involving ionizing radiation and genotoxic drugs. Highly conserved damage and stress-response programs have evolved to prevent the propagation of oncogenic genetic damage to progeny by temporarily arresting cell growth for DNA repair, or irreversibly arresting growth through senescence or apoptosis.

DNA Damage Response. The DNA Damage Response (DDR) is a complex and coordinated process engaged following breaches in the integrity of DNA (21). The DDR likely evolved to protect the host from cells that sustain irreversible genomic damage resulting from exposure to exogenous and endogenous genotoxins. The DDR culminates in the elimination of those cells where damage cannot be reconstructed. Common routine environmental insults and byproducts...
of cellular metabolism produce in excess of 1 million individual DNA lesions per cell per day (22). To deal with this assault, repair mechanisms are in continual operation, and the rate of repair is sufficient to manage the rate of damage. However, exposure to genotoxic cancer therapeutics produces damage that far exceeds the capacity of the repair process to maintain DNA integrity. Alkylating agents produce DNA interstrand cross-links, which promote DNA double strand breaks. Topoisomerase inhibitors produce several effects including the generation of inter-strand cross links, the creation of free radicals, and the stabilization of DNA with consequent inhibition of proper DNA replication and a consequent damage response signal. Platinum drugs induce DNA adducts and double strand breaks, while the antibiotic bleomycin induces direct double strand breaks. These and other chemotherapeutics engage the DDR to initiate fail-safe programs that result in permanent growth arrest—senescence, or the execution of cell death--apoptosis.

The DDR is enacted by the Mre11-Rad50-Nbs1 (MRN) mediator complex which denotes specific sites of damage, followed by a second phase that propagates the recognition signal to ultimately influence repair and cellular phenotypic responses. The DDR progresses through a signaling cascade that includes ATR and ATM (23). In the context of DS breaks resulting from chemotherapy, ATM autophosphorylates at multiple sites, self-activates, and instigates reactions that assemble checkpoint proteins such as p53BP1 and BRCA1 at the break site to promote damage repair (24-26). Concurrently, ATM activates CHK2 leading to the stabilization and accumulation of p53, a pivotal mediator of either pause and repair, or permanent growth arrest and cell death. Though tumor cells commonly inactivate key components of the DDR program, benign cells of the TME are fully capable of robust responses to genotoxic stress. It has recently become apparent that in addition to the cell autonomous components of the DDR that influence the damaged cell itself, the DDR also promotes a cell non-autonomous program of secreted factors capable of impacting numerous cell types comprising the tumor microenvironment, including those tumor cells that have survived the first salvo of chemo/radiotherapy.

**DNA Damage Secretory Program.** The secretory phenotype of damaged cells was first reported in the context of cellular senescence, a state of permanent growth arrest. Cellular senescence, described by Hayflick and Moorehead (27) in the context of replicative exhaustion, is associated with characteristic morphological features encompassing enlarged flattened cell bodies with increased cytoplasmic granularity. Though growth arrested, senescent cells remain viable and metabolically active (28). The mechanism behind replicative exhaustion involves the pro-
gressive erosion of telomeres after many replication cycles with the consequent induction of a DDR-like response culminating in the induction of the CDK inhibitors p21 and p16 and permanent growth arrest (29). Subsequently, several other inducers of senescence have been identified including oxidative stress and reactive oxygen species, activation of specific oncogenes such as RAS and BRAF (30, 31), and profound levels of DNA damage such as those encountered in the context of chemo/radiotherapy.

Detailed studies of senescent cells found that this state was accompanied by the production and secretion of a remarkable spectrum of cytokines, growth factors, and proteases, many with documented roles in promoting tumor growth and invasion (32-34). Collectively, these secreted factors have been termed a Senescence Associated Secretory Phenotype (SASP) (35) or Senescence-Messaging Secretome (SMS) (36). However, it appears that a full senescence phenotype is not required for components of this secretory program to be engaged, but rather cell stress and DNA damage are central initiators, thus broadening the overlapping descriptions of these largely overlapping programs to include Acute Stress-Associated Phenotype (ASAP)(37) or DNA Damage associated Secretory Program (DDSP). Deep discovery-driven analyses of transcript and protein responses to genotoxic stress induced by cancer therapeutics have identified several hundred factors derived from benign cells comprising the tumor microenvironment (32, 38-40). The DDSP composition is complex, and includes pro-inflammatory cytokines such as Interleukin (IL)-6 and IL-8, extracellular matrix-altering proteases, pro-neurogenic factors, angiogenic growth factors and epithelial mitogens that include agonists for the epidermal growth factor receptor (EGFR) such as amphiregulin and epiregulin (38, 40). These cell non-autonomous effectors of the stress-response program likely evolved to propagate a tissue damage signal locally and distantly in order to enhance the elimination of damaged cells through immune clearance and hasten repair through angiogenesis and the migration and proliferation of epithelial and stromal cells. However, in the setting of a malignancy, where neoplastic cells co-opt such microenvironment cues, the effects may have adverse consequences. Individual components of the DDSP can suppress apoptosis and enhance the proliferation of premalignant and malignant epithelium (34), stimulate migration and invasion(38, 40), and transition epithelial cells to acquire mesenchymal phenotypes (38) with augmented resistance to chemotherapy and radiation (41) (Figure 1).

Several preclinical studies support the concept that treatment-induced microenvironment damage can promote adverse tumor outcomes. Recent reports using modern tools of molecular
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biology recapitulate insightful studies carried out in the 1950s by Revesz and colleagues whereby the growth of transplanted allogeneic and syngeneic tumors was found to be enhanced by combining lethally-irradiated tumor cells with non-irradiated tumor cells (42). This ‘Revesze Effect’ was shown to be due to the metabolic activities of the irradiated cells through the production of diffusible factors which conditioned the tumor microenvironment (43, 44). More recently, using a mouse model of breast carcinoma, Nguyen et al. determined that ionizing radiation acting on the breast microenvironment accelerated the development of aggressive p53-null breast cancers (45). The development of these tumors was found to be influenced by TGFß signaling and exhibited distinct molecular programs involving estrogen receptor and stem cell activity. Similar results were reported in studies of myogenic cells whereby implanted cells rapidly progressed to poorly-differentiated tumors in irradiated muscle microenvironments relative to cells implanted into non-irradiated muscle (46). Tumorigenicity was also found to be dependent on the dose of pre-irradiation and varied depending on the host genetic background. Whether these damaged microenvironments would also promote therapy resistance has not been tested.

Studies using genotoxic chemotherapeutics have extended these observations to demonstrate that treatment-induced damage to the microenvironment can promote a chemoresistance niche of residual disease that subsequently serves as the nidus for relapse. Experiments reported by Gilbert et al using doxorubicin to treat the Eµ-Myc model of transplantable lymphoma determined that surviving metastatic tumor cells were exclusively localized to the thymus (37). Detailed molecular analyses of damage responses in different lymphoid tissues and of individual cell types comprising these tissues identified IL-6 and Timp-1 as prosurvival factors secreted selectively by thymic endothelial cells. Tumor cell resistance was shown to be due to the paracrine production of IL-6 and Timp-1, and inhibition of these factors, or the upstream signaling pathway operating through p38 MAP kinase, enhanced the effectiveness of subsequent chemotherapy treatment (37). In addition to providing proof-of-principle that damage induced by cancer therapeutics to residents of the TME can influence tumor behavior, in this case therapy responses, this study demonstrated that different tissues, and indeed distinct cell types comprising these tissues have varied damage responses, a finding that has important implications for designing clinical trials to exploit these results.
CLINICAL-TRANSLATIONAL ADVANCES

Therapeutic Context.

The development and application of treatment strategies to modify the tumor microenvironment or interrupt interactions between tumor cells and microenvironment components is attractive from several perspectives. First, there are demonstrated successes in several malignancies exemplified most strikingly in multiple myeloma where co-targeting the TME is now a mainstay of the overall treatment paradigm (20). Second, there are many potential ways to impact the TME for more effective tumor cell killing that span mobilizing tumor cells, for example through CXCR4/CXCL12 axis blockade (47), to breaking down desmoplastic barriers for more efficient drug penetration (15). Third, since the TME targets are generally derived from benign cells involving well-conserved developmental pathways, they are unlikely to be subject to mutation and resistance. Fourth, most TME targets represent a non-crossreactive feature of the tumor that may not contribute substantially to toxicity.

In treatment-induced therapy resistance, it is important to consider that context is critical: treatment itself can unmask or induce new opportunities for intervention. The standard regimens currently deployed to treat most solid tumors are unfortunately ideally suited to promote microenvironment-mediated resistance. Most chemotherapeutics are dosed in a sequence of treatment cycles which are generally designed to allow normal host tissues and organs to recover and avoid major morbidity and host lethality. Radiotherapy is similarly administered in a series of fractionated doses at intervals spanning days to weeks. Initial cycles of treatment eliminate a substantial percentage of the tumor cell mass, but also induce a damage response in cells comprising the TME (Figure 1). Tumor cells surviving the first salvos of therapy are thus exposed to the high levels of growth factors, cytokines, and proteases that comprise the DDSP which are capable of bolstering the remaining tumor cells to survive subsequent treatment cycles. As well-documented in the murine lymphoma studies described previously (37), key pro-survival factors such as IL-6 and Timp-1 emerged as therapeutic targets only in the context of treatment, whereas without genotoxic stress, suppression of these factors was not relevant. The pro-growth, pro-survival, and pro-angiogenic components of the DDSP may also underlie the accelerated tumor repopulation kinetics that have been observed during the intervals between treatments and that account for rapid tumor repopulation, an important cause of treatment failure (48).
Co-Targeting Specific Microenvironment Effectors.

The robust induction of growth factors and cytokines by DNA damaging therapeutics may be a contributing factor in the limited responses observed in clinical studies of targeted therapeutics such those designed to inhibit angiogenesis or suppress EGF signaling. Following genotoxic treatments, small molecule inhibitors and receptor-directed antibodies must contend with very high local treatment-induced concentrations of ligands for these receptors, such as VEGF, amphiregulin and epiregulin. Recognizing that multiple distinct ligands may activate redundant signaling programs to resist these targeted treatments is an initial step in designing the appropriate clinical studies to confirm effective pathway suppression. Although remarkably diverse (38, 49), the secretory program induced by DNA damage and attendant cell stress is not unlimited, and it is likely that only a subset of the program effectively contributes to therapy resistance. Further, components of the DDSP may assist in controlling tumor growth through host damage response signaling that attracts inflammatory cells and engages other tissue repair processes. Thus, a reasonable strategy is to identify and co-target only the key DDSP factors responsible for inducing a therapy-resistant phenotype.

Co-Targeting the Collective DNA Damage Secretory Program.

An alternative to targeting individual resistance-promoting components of the DDSP---which may require multiple drugs deployed in combination to effectively suppress particular paracrine interactions, involves inhibiting ‘master regulators’ that transduce the DDR signal to modulate the expression of large subsets of effector proteins. Though complex and incompletely understood, current knowledge of the DDR suggests several nodes that could be evaluated (Figure 1). For example, inhibition of p38MAPK has been shown to suppress the secretion of most stress-responsive secretory proteins in fibroblasts (50), primarily through NFkB, itself also an attractive target in the context of regulating DDR-induced responses. Poly(ADP-ribose) polymerase (PARP-1) has been shown to be activated in response to DNA damage and propagate a signaling cascade that includes the production of a secretome with protumoral and prometastatic properties (51). Thus, PARP-1 inhibitors, currently in clinical trials for the treatment of breast and ovarian cancers, could be repurposed for inhibiting the microenvironment DDSP in the context of genotoxic tumor therapy. IL1α, itself a component of the damage-associated program has been shown to promote the secretion of several key pro-inflammatory cytokines via interaction with
cell surface IL1R and consequent activation of NFkB (52). It is likely that additional master regulators of the DDSP will be identified as knowledge of the signal transduction program matures.

**Future Directions**

Many questions remain regarding the optimal strategies required to effectively suppress the prosurvival microenvironment induced directly by cancer therapeutics. It is unclear the extent to which damage-associated secretory responses vary between different organs, different cell types within tissues, and between different individuals—and how this variation is controlled. Such information may be quite important when considering microenvironment targets in different primary tumor locations and sites of metastatic disease. Systemic effects of DNA damage responses also likely influence the resistance of tumor cells to treatment. The duration or persistence of damage-associated paracrine activity has also not been established, and this may be quite important for designing clinical trials that sequence genotoxic agents with those inhibiting microenvironment factors, and for understanding therapy resistance niches and tumor cell dormancy and reactivation. Intuitively, suppressing the damage response prior to genotoxic treatment would be ideal. Sequencing microenvironment agents between intervals of genotoxic therapy is also reasonable and are analogous to metronomic designs where cytotoxic agents are alternated with cytostatic drugs to inhibit rapid tumor repopulation (53).

It is becoming clear that context, in this case, the microenvironment, profoundly influences tumor cell behaviors including treatment resistance. Importantly, this bionetwork is dynamic, and for every action, such as exposure to genotoxic stress, there are reactions and consequences throughout the micro and macrosystem. Defining the interactions between tumor cells, benign constituents of the tumor, and the influences of treatment will likely yield more effective combinatorial strategies that improve upon conventional approaches that here-to-for have focused primarily on the neoplastic cell.

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FIGURE LEGEND

Figure 1. Therapy resistance is promoted by genotoxic treatment-induced damage responses in the tumor microenvironment. The local environment in which most neoplasms originate is a complex ecosystem comprised of cancer cells, benign resident cells and transient cells---such as inflammatory cell types, and includes additional structural and soluble components. Genotoxic cancer therapeutics induce DNA damage in tumor cells which can lead to cell death or senescence, but also exerts genotoxic stress in benign cells such as tumor-associated fibroblasts comprising the tissue stroma. DNA damage and other stressors initiate damage response programs, for example the DDR, with several effector arms including the generation and secretion of a diverse spectrum of cytokines, growth factors, and proteases here denoted the DNA Damage Secretory Program (DDSP). Individual components of the DDSP are well-known to promote inflammation, angiogenesis, epithelial-to-mesenchymal transition, tumor cell proliferation, and augment resistance to cancer therapeutics. Targeting individual DDSP components or key upstream master regulators (e.g. NFκB, p38MAPK, PARP) may enhance the effectiveness of commonly used anti-neoplastic agents by suppressing microenvironment-derived resistance mechanisms.

CC, Cancer Cell; RCC, Resistant Cancer Cell; SC, Stromal Cell; EC, Epithelial Cell; IC, Inflammatory Cell; BV, Blood Vessel; DDR, DNA Damage Response; DDSP, DNA Damage Secretory Program.
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