Chapter 17

Role of Tumour Microenvironment in Chemoresistance

Yong Wei and Jessie L.-S. Au
College of Pharmacy, Ohio State University, Columbus, OH 43210, USA

Abstract: Preclinical and clinical findings indicate multiple tumour micro-environmental factors, including growth factors, cytokines, cell-cell and cell-matrix adhesion molecules and hypoxia, protect solid tumours from therapeutic interventions. Experimental evidence have defined some of the resistance mechanisms, which have led to the development of innovative approaches aiming at specific targets. While some of these newer approaches have yielded therapeutic benefits in selected tumour types, considerable challenges remain in the management of the majority of patients with solid tumours. This chapter reviews the various tumour microenvironmental factors that contribute to drug resistance. These factors exert their effects through direct promoting resistance effectors and/or indirectly modulating other environmental factors. Furthermore, cooperative regulation, cross-talk and redundancy at different levels of signaling cascades affect the tumour progression and drug resistance, and can diminish the effectiveness of the single target therapeutic approach. A better understanding of the intersecting resistance pathways has the potential of leading to new therapeutic paradigms aiming at multiple targets, in order to overcome the microenvironment-conferred survival advantage to tumour cells.

Key words: Drug resistance, clinical drug resistance, solid tumour, microenvironment, soluble factor, epidermal growth factor, fibroblast growth factor, insulin-like growth factor, hepatocyte growth factor, scatter factor, transforming growth factor-β, interleukin 4, interleukin 6, interleukin 10, cell adhesion molecule, integrin, E-cadherin, hypoxia, HIF1, redundancy, cross-talk, therapeutic implications

1. INTRODUCTION

Since the first demonstration of antitumour activity of aminopterin (4-aminopteroyl-glutamic acid) in childhood acute leukaemia patients by Farber and colleagues in 1948 (1), considerable efforts have been spent on developing effective cancer chemotherapeutic agents. Curative or survival benefits have been achieved in a few selected tumour types (2). However, clinical drug resistance remains a major obstacle in most cancers, especially adult solid tumours (2). Studies using monolayer-cultured cells have defined several genetic mechanisms of drug resistance. Examples include (a) activation and/or overexpression of cell membrane drug efflux transporters (e.g., P-glycoprotein and other ATP-binding cassette transporters such as multi-drug resistance-associated proteins), breast cancer resistance protein, and lung resistance-related protein (3-8), (b) altered expression or activation of detoxifying enzymes such as glutathione S-transferase (9, 10), quantitative or qualitative alterations of drug targets (11-15), and (c) defects in apoptosis regulatory proteins (16-18). In spite of the promising preclinical data indicating therapeutic advantages by reversing these genetic resistance mechanisms, the clinical results of these experimental approaches have been largely disappointing (19). On the other hand, there is growing evidence suggesting that

G. G. Meadows (ed.), Integration/Interaction of Oncologic Growth, 285-321.

epigenetic factors or proteins present in the tumour microenvironment play important roles in clinical drug resistance.

Teicher and colleagues (20) demonstrated that repeated administration of alkylating agents to mice bearing syngeneic mammary tumours yielded subclones which, when reimplanted in other recipient mice, showed cross-resistance to alkylating agents. They further showed that this acquired resistance was exhibited only *in vivo* but not in monolayer cultures of the disaggregated tumour cells. Hoffman and colleagues developed a surgical orthotropic implantation technique (OIT) (21), where patient or animal tumour fragments are implanted into the tumour-originating organs. These orthotropic implants maintain clinically relevant tumour properties including progression, metastasis and chemosensitivity. For example, the orthotropic human small cell lung cancer in mice showed a clinically relevant chemosensitivity profile (i.e., sensitive to cisplatin and resistant to mitomycin C), whereas the same tumour implanted in subcutaneous sites shows the opposite profile (22). Similar results were obtained for colorectal cancer (23, 24), fibrosarcoma (24) and renal cancer (25). Our laboratory similarly found that lung and lymph node metastases lost their chemoresistance when reimplanted in subcutaneous sites (26).

Organ-specific chemosensitivity is also observed in patients. Table 1 outlines the various tumour types displaying different sensitivity to chemotherapy. For example, breast, colorectal, testicular and ovarian cancers usually are responsive to chemotherapy initially (2). In contrast, patients with renal, pancreatic and oesophageal cancers show very low initial response rate (2), even though the tumour cell lines derived from these cancers are equally sensitivity to chemotherapy as cell lines derived from the other more chemo-responsive tumour types (27).

These earlier studies suggest a critical role of tumour microenvironment on preclinical and clinical chemosensitivity or chemoresistance. In solid tumours, cancer cells are surrounded by vasculature and stromal tissues. The tumour-stromal interaction results in tumour-specific expression of soluble factors and extracellular matrix components, some of which promote tumour growth and invasiveness. Dysregulated tumour progression promotes active but abnormal angiogenesis and higher hypoxia level in tumours, which also affect tumour progression and chemosensitivity.

Table 1. Organ specific responses to chemotherapy. adapted from (2).

Curable by chemotherapy
Acute leukaemia
High grade non-Hodgkin's lymphoma
Hodgkin's disease
Choriocarcinoma
Germ cell tumours
Wilms' tumour
Ewing's sarcoma
Osteosarcoma
Neuroblastoma
Chemotherapy improves survival
Breast cancer
Ovarian cancer
Small cell lung cancer
Bladder cancer
Colorectal cancer
Gastric cancer
Modest survival improvement: Tumour symptomatic response only
Non-small cell lung cancer
Metastatic cancer of unknown primary origin
Endometrial cancer
Soft tissue sarcoma
Carcinoids
Head and neck cancer
Pancreatic cancer
Brain tumours
Mesothelioma
Esophageal cancer
Poorly sensitive to chemotherapy
Prostate cancer
Adrenocortical cancer
Melanoma
Renal cancer
Thyroid cancer

This chapter focuses on the effects of tumour environmental factors on sensitivity to chemotherapy and/or radiotherapy, with special emphasis on growth factors, cytokines, cell adhesion molecules and hypoxia. The information on each factor is discussed in the following order, (a) general information, (b) distribution and/or expression status

in cancer patients, (c) association with disease progression and/or resistance in preclinical models and cancer patients, (d) resistance mechanisms, and (e) current status as a therapeutic target and development of modulators.

2. CHEMORESISTANCE INDUCED BY SOLUBLE FACTORS

Multiple growth factors and cytokines cause resistance to anti-cancer drugs in cell culture and animal tumour models. In keeping with the focus of clinically relevant resistance, we will discuss the soluble factors that satisfy the following criteria, (a) inducible by chemotherapy, (b) associated with chemotherapy outcome or patient prognosis, (c) affecting the efficacy of chemotherapy *in vitro* and/or *in vivo*, and/or (d) useful targets for achieving chemosensitization. Table 2 shows the growth factors and cytokines that satisfy these criteria. The receptors for these growth factors and cytokines, which are integral components of the corresponding intracellular signalling pathways, are also discussed. Note that some of these factors may cause either chemoresistance or chemosensitization depending on the experimental systems.

2.1 Growth factors

2.1.1 Epidermal growth factors/ Epidermal growth factor receptors

Aberrant activation of epidermal growth factor receptor (EGFR) or human EGFR family members, e.g., EGFR and human EGF receptor 2 (HER2), either through overexpression of receptors and/or elevation of cognate ligands, e.g., EGF and transforming growth factor-α, promotes tumour cell proliferation, survival, invasion, metastasis, and angiogenesis, resulting in enhanced tumourigenesis and progression (28-30). Other mechanisms independent of EGFR/HER2 expression, e.g., constitutively active mutation of these receptors, transactivation by other receptors including G-protein coupled receptors, interleukin receptors, estrogen receptors and cell adhesion molecules, can also cause aberrant activation of EGFRs (28-31).

In patients, higher expression of EGFR family proteins and/or cognate ligands is associated with worse prognosis, shorter survival, and resistance to radiotherapy and chemotherapy in multiple solid tumour types (28, 29, 32-39).

In vitro and *in vivo* preclinical studies have shown that activation of EGFR and HER2 leads to activation of the downstream Ras/Raf/ MAPK, STAT3/7 and PI3K/AKT pathways, resulting in modulations of apoptosis regulatory proteins and thereby protecting tumour cells from cell death and causing resistance to several classes of antitumour drugs (28, 29, 40, 41). The protective effect mediated by EGFR activation is more pronounced in anoikis, or apoptosis due to loss of cell attachment, suggesting a link between EGFR-mediated survival pathways and adhesion molecules (40, 42).

Paradoxically, studies in several experimental tumour models have demonstrated that activation of EGFR and HER2 (a) reduces cell adhesion and thereby enhances apoptosis (43, 44), (b) inhibits DNA topisomerase II and thereby promotes DNA damage (45), and (c) accelerates the cell proliferation rate and thereby increases the sensitivity of tumour cells to chemotherapeutics (46-49). In patients, several studies on node-negative and node-positive breast cancer patients show that the efficacy of doxorubicin-containing adjuvant therapy is dependent on HER2 status, with higher response rate and longer survival in patients with higher HER2 expression (50-54). Similarly, in patients with advanced urothelial carcinoma, patients with HER2-positive tumours are more likely to respond to paclitaxel and show lower death rate (55, 56).

Additional preclinical studies have demonstrated that EGFR-targeting approaches, by using either monoclonal antibody or small molecule tyrosine kinase inhibitors (TKIs), enhance the antitumour activity of chemotherapy and radiotherapy *in vitro* and *in vivo* (28, 57). These encouraging preclinical results have led to significant efforts to develop and evaluate HER2 and EGFR modulators in patients, as monotherapy or in combination with standard radiotherapy or chemotherapy (28, 58-60).

Table 2. Clinical relevance of soluble chemoresistance factors. Abbreviations are: BC, breast cancer; BLC, bladder cancer; CC, cervical cancer; CRC, colerectal cancer; GBM, glioblastoma; GC, gastric cancer, GLM, gliomas; HC, hepatocellular carcinoma; Mel, melanoma; MM, multiple myeloma; NSCLC, non-small cell lung cancer; OC, ovarian cancer; PaC, pancreatic cancer; PC, prostate cancer; RCC, renal cell carcinoma; SCCHN squamous cell head and neck cancer; SCCOP, squamous cell cancer of the oropharynx; SCLC, small cell lung cancer; TC, thyroid cancer; UC urothelial carcinoma. If the tumour type is not specifically mentioned, the association is found in most of the common solid tumour types. ND, not studied or not reported.

Factors/Receptors	**Disease prognosis with elevated expressions/levels**		**Usefulness as therapeutic targets**	
	Tumour progression	**Treatment outcome**	**Preclinical models**	**Patients**
EGFs/EGFRs	Worse: carcinogenesis, advanced stages, increased metastasis, angiogenesis, shorter survival	Resistance: radiatherapy in SCCHN and GLM Chemotherapy in many solid tumours *Favourable: HER2 favourable for adjuvant chemotherapy in BC and taxane based therapy in UC*	EGFR tyrosine kinase inhibitors and EGFR antibody improve effectiveness of chemotherapy and radiatherapy in multiple solid tumours	Same agents have activity as single agent and/or improve effectiveness of chemotherapy in advanced NSCLC, SCCHN, CRC as 2nd or 3rd line treatments
FGF2/FGFRs	Worse: advanced stages, increased metastasis, angiogenesis, shorter survival *Favourable: in primary BC, OC, advanced GLM*	Resistance: chemotherapy in SCLC	Improve effectiveness of chemotherapy in PC, BC, RCC, PaC, BLC, CRC by a non-specific inhibitor suramin	In phase II evaluation, suramin improve effectiveness of chemotherapy in advanced NSCLC
IGFs/IGFR1	Worse: carcinogenesis, increased metastasis, shorter survival	Resistance: chemotherapy and radiatherapy in BC	Improve effectiveness of chemotherapy in multiple solid tumours	ND
HGF/SF/c-Met	Worse: carcinogenesis, advanced stages, increased metastasis, angiogenesis, shorter survival	Resistance: radiatherapy in SCCOP, chemotherapy in MM	ND	ND
TGFβ	Worse: advanced stages, increased metastasis, angiogenesis, shorter survival *Favourable: Suppressive in early stage of solid* tumours	Resistance: chemotherapy and radiatherapy in CC	Improve effectiveness of chemotherapy in BC, GC, PC, HC	ND
IL4	Worse: shorter survival in RCC	Resistance: chemotherapy in TC	ND	ND
IL6	Worse: advanced stages, increased metastasis, shorter survival	Resistance: chemotherapy in PC, BC, RCC, GBM	Improve effectiveness of chemotherapy in PC, RCC, MM	ND
IL10	Worse: advanced stages, increased metastasis, recurrence, shorter survival *Favourable: stage 1 NSCLC*	Resistance: chemotherapy in TC, GC, CRC, NSCLC, Mel	Improve effectiveness of chemotherapy in GBM	In Phase II evaluation, AS101 Improves effectiveness of chemotherapy in NSCLC

In pivotal clinical trials, trastuzumab (Herceptin), a monoclonal anti-HER2 antibody, shows activity in HER2-positive metastatic breast cancer as single agent (61, 62) and in combination therapy with multiple standard chemotherapy regimens, e.g., anthyracycline plus cyclophosphomide, paclitaxel (63). The activity of trastuzumab is associated with the HER2 expression status. Trastuzumab is currently being evaluated as adjuvant therapy in patients with primary breast cancer (64-66). These studies have established the therapeutic value of trastuzumab and indirectly the HER2-targeting approach in breast cancer. The situation in other cancer types is less promising. In spite of strong preclinical data (67, 68), trastuzumab fails to show activity either as monotherapy or in combination with standard chemotherapy such as cisplatin plus gemcitabine or docetaxel in patients with HER2-positive advanced non-small cell lung cancer or prostate cancer (69-71). This failure is presumably, at least partly, due to compensation by coexpression of EGFR1 (72, 73).

EGFR modulators, including tyeosine kinase inhibitors (TKIs) (i.e., gefitnib or Iressa, erlotinib or Tarceva) and monoclonal antibody (cetuximab or Erbitux), are well tolerated in patients. These agents show activity in patients with advanced chemotherapy-refractory squamous cell head and neck cancer, non-small cell lung cancer, pancreatic cancer and colorectal cancer, either as monotherapy (e.g., gefitinib as third line treatment of non-small cell lung cancer patients) or in combination with standard chemotherapy (e.g., cetuximab in combination with irinotecan in irinothecan-refractory colorectal cancer patients) (28, 74-80). However, in large randomized phase III trials, all three modulators failed to show superior response rate and survival in chemotherapy-naïve, advanced non-small cell lung cancer (gefitnib and erlotinib) or colorectal cancer (cetuximab) compared to standard chemotherapy (28, 74-76, 79, 81, 82).

Unlike the association between HER2 expression and responsiveness to trastuzumab in breast cancer, patient response to EGFR modulators are not correlated with the EGFR expression. Two recent studies have identified mutations in the tyrosine kinase domain of EGFR in a subset of non-small cell lung cancer patients (less than 10% in American patients and ~30% in Japanese patients) as potential prognostic indicator of patient response. These mutations result in enhanced intensity and duration of EGFR activation by EGF and the corresponding survival signals as well as enhanced sensitivity to EGFR inhibition by gefitnib (83-85).

There are several interesting aspects to the profiles of clinical activities of the various HER2 and EGFR modulators. First, the finding that the EGFG/HER2-targeting approach results in therapeutic benefits in several major tumour types suggests an common role of EGFR in chemosensitivity/chemoresistance of solid tumours. Second, the success in chemotherapy-refractory patients together with the failure in chemotherapy-naïve patients suggests an role of EGFR in the clinically acquired resistance to platinum-, irinotecan-, and taxane-based therapy. The selective benefits of EGFR modulators in the second/third-line setting are also consistent with a scenario of selection of subclones carrying mutated EGFR receptors. Third, the failure of EGFR modulators as first-line treatment in lung and colorectal cancer, together with the opposite effects of trastuzumab in breast and lung cancer patients, suggest the presence of redundant, compensatory survival signalling from other HER2/EGFR family members or other growth factors.

2.1.2 Fibroblast growth factors and their receptors

FGFs constitute a large family of 22 growth factors with molecular weights ranging from 17 to 34 kDa. FGFs are expressed in most, if not all, tissues. FGF1 and/or FGF2 (also called acidic and/or basic FGFs) are involved in the development and function of numerous organ systems, induce cell proliferation, migration, survival, and angiogenesis, and stimulate wound healing and repair, under *in vivo* and *in vivo* conditions (86-90).

FGF2 has been extensively studied. The FGF2 gene encodes several different isoforms. The low molecular weight (18kD) isoform is present in extracellular compartment and the high molecular weight (22 and 24 KD) isoforms are localized in intracellular compartment. The following discussion focuses on the extracellular FGF2. Multiple studies

have implicated FGF2 in chemoresistance, whereas the role of FGF1 was demonstrated recently by our laboratory (26).

The binding of FGFs to FGF receptors (FGFRs) in the presence of heparan sulfate proteoglycans results in FGFR dimerization. The FGFR family includes four members and, through various possibilities of alternative splicing, potentially consists of up to 100 isoforms (91). FGFR1, FGFR2, and FGFR3 are widely expressed in adult human tissues whereas the distribution of FGFR4 is more limited. The 7 major FGFR isoforms have different ligand-binding specificity, which is determined by the alternative splicing in Ig domain III (87, 92, 93). Activation of FGFRs results in activation of different signalling pathways leading to gene transcription and diverse responses (88, 94, 95). The signal transduction pathways of FGF2, including Ras-Raf-MEK-MAP kinase, PLC-DAG-PKC, and PLC-PI3K-Akt pathways; are implicated in cell survival (96-107).

Depending on cell types and growth conditions, FGF2 can cause mitogenesis or inhibit cell growth (108-110) and can either induce resistance or sensitization to cytotoxic insults (111) under *in vitro* conditions. On one hand, addition of exogenous FGF2 or over-expression of FGF2 confers resistance to chemotherapy (etoposide, cisplatin, fludarabine, doxorubicin, methotrexate, hydroxyurea, 5-fluorouracil, paclitaxel, N-(phosphonacetyl)-L-aspartic acid) in solid tumour cells (i.e., small lung cancer, prostate, bladder), chronic lymphocytic leukaemia cells, and fibroblasts (111-113). On the other hand, exogenous FGF2 or FGF2 overexpression enhances the sensitivity of breast, prostate, ovarian and pancreatic tumour cells and fibroblasts to chemotherapeutic agents (i.e., cisplatin, etoposide, 5-fluorouracil, doxorubicin, carboplatin, and docetaxel), and to oxidative stress (111).

Consistent with the dual roles of FGF2 in chemoresistance and chemosensitization, FGF2 also shows opposite effects in prognosis of cancer patients. Some studies reported association between high FGF2 expression and higher tumour apoptotic indices or improved overall and disease free survival and association between lower FGF2 levels and increased tumour size or higher tumour stage in breast cancer (114-118), ovarian cancer (119) and pediatric high-grade gliomas (120). Conversely, other studies reported associations between increased local FGF2 expression and shorter survival in nodal-negative breast cancer (121), and between elevated systemic and/or local tissue FGF2 levels and worse prognosis and shorter survival in leukaemia and lymphoma (122, 123), in solid tumours including non-small and small cell lung cancer (124-127), colorectal cancer (128), renal cell carcinoma (129), advanced carcinoma of head and neck (130), gastric cancer (131, 132), non-Hodgkin's lymphoma (133, 134), oesophageal carcinomas (135), thyroid carcinomas (136), malignant solitary fibrous tumour (137), mesothelioma (138), and Wilms' tumour (139). In pancreatic cancer, there is no relationship between FGF2 level and postoperative recurrence and survival, but increased FGF receptor expression is associated with shorter survival (140). A similar observation in non-small cell lung cancer patients has been reported (141). Mutation in the transmembrane domain of FGFR4 is associated with shorter disease-free survival in breast cancer (121, 142), colorectal cancer (142) and high-grade soft tissue sarcoma (143). Constitutively active FGFR3 mutation has been found in bladder and cervix carcinomas (144). Furthermore, elevated serum FGF2 levels are associated with poor response to chemotherapy in small cell lung cancer (145), suggesting a direct contribution of FGF2 to resistance.

The mechanisms of FGF2-conferred survival appear to be context-dependent, differ in different cells and differ in response to different stress signals. The FGF2-induced chemoresistance in small cell lung cancer cells is mediated through activation of the MAP kinase pathway resulting in upregulation of anti-apoptotic proteins Bcl-2, Bcl-XL and IAPs (146, 147), and the resistance in fibroblasts is mediated through MDM2 induction and the subsequent inhibition of p53 pathways (148). The mechanism of chemosensitization in breast tumour cells is presumably due to Bcl-2 down-regulation (111, 149, 150).

In addition to inducing resistance in tumour cells, FGF2 also protects endothelial cell against radiation- or chemotherapy-induced cell death, which in turn results in chemoresistance.

Alternatively, FGF2 may regulate the expression and signalling of other environmental survival factors (151-153). For example, in multiple myeloma, FGF2 secreted by tumour cells stimulates IL6 secretion from stromal cells, and IL6 in turn stimulates tumour cells to secrete more FGF2 (151). As discussed below, IL6, similar to FGF2, also protects tumour cells from cytotoxicity conferred by chemotherapy.

The reasons of the dual effects of FGF2 on chemosensitivity or chemoresistance are not clear. As FGF2 functions are regulated by multiple environmental factors, e.g. heparan sulfate proteoglycans (154-157), cell-matrix adhesion (158), cell-cell interaction (159-161), it is tempting to postulate that the switch between induction of resistance or sensitization is governed by intersecting microenvironmental factors..

The earlier studies on FGF2-induced chemoresistance used exogenous FGF2 concentrations that far exceed the concentrations in patient plasma and urine samples (10-50 vs <1 ng/ml) (26, 111) , thus raising questions on the clinical relevance of this mechanism. Our laboratory recently demonstrated that a second FGF, i.e., FGF1, amplified the FGF2 effect such that combinations of FGF1 and FGF2, at clinically relevant concentrations, induce up to 10-fold resistance to several anticancer drugs (26). We further showed that monoclonal FGF antibodies and/or a non-specific inhibitor of FGF1 and FGF2, suramin, reversed the FGF-induced resistance and significantly improved the sensitivity of human xenograft tumours to multiple chemotherapeutic agents, i.e., paclitaxel, 5-fluorouracil, doxorubicin and irinotecan (26, 162, 163), under *in vitro* and *in vivo* conditions. The suramin chemosensitization was broad spectrum and applied to colorectal, renal cell, breast, pancreatic, and bladder cancer (164-167), and was attained at dosing regimens yielding low, FGF-inhibitory but non-toxic suramin concentrations. These encouraging preclinical results have motivated several phase I/II clinical trials using non-toxic suramin regimens in lung, breast and kidney cancers. The first phase II trial in non-small cell lung cancer has been completed and the results suggest therapeutic efficacy using FGF-inhibitory suramin regimens (168).

2.1.3 Insulin-like growth factors and their receptors.

The insulin-like growth factor (IGF) family consists of two extracellular ligands, IGF-1 and IGF-2. The two membrane IGF receptors are IGF1R and IGF2R. Binding of IGF1 and IGF2 to IGF1R initiates the signalling cascades. Six circulating IGF binding proteins (IGFBP1-6) compete with IGF1R for binding with IGFs. IGF2R is responsible for the hydrolysis of the IGF/IGFBP1-6 complex, thereby making IGFs available for binding to IGF1R (169, 170).

The IGF signalling system regulates cell proliferation, apoptosis and differentiation and thereby plays critical roles in the development and physiological growth control of most if not all tissues. Aberrant activation of the IGF system contributes to carcinogenesis, tumour progression and metastasis in experimental tumour models (169-172). In patients, elevated activation of the IGF system, resulting from either increased serum IGF level or decreased IGFBP level, is associated with increased risk of breast, colon, prostate and lung cancers (169, 173-178). Similarly, the overall IGF system activity, represented either by increased expression of IGF and/or IGF1R or decreased levels of IGFBPs and/or IGF2R, is associated with poor prognosis and/or shorter disease- free interval or overall survival time in patients with ovarian cancer (179, 180), colorectal cancer (181, 182), head and neck cancer (183), non-small cell lung cancer (184), multiple myeloma (185), breast cancer (172, 186-190) and pulmonary adenocarcinoma (191).

Interestingly, an inverse association between the activation level of the IGF system and the prognosis or survival of breast cancer patients was not observed in patients undergoing surgical intervention (188, 189), but was observed in patients receiving chemotherapy or radiotherapy (187, 190). This suggests that the poor prognosis associated with the high IGF system activity is not due to enhanced tumour progression but rather due to resistance to chemotherapy and/or radiotherapy.

In tumour cells, activation of IGF1R stimulates cell proliferation and, through activation of MAPKs and PI3K/AKT pathways, also inhibits apoptosis induced by stress conditions such as treatments with

cytotoxic drugs or radiation, or deprivation of growth factors and/or nutrients (192-196). These two effects result in tumour cell resistance to multiple anticancer drugs, including doxorubicin, cisplatin, 5-fluorouracil, camptothecin, mitomycin C, actinomycin D, lovastatin, Cox-2 inhibitors, and to cytokines, e.g., tumour necrosis factor and interferon-γ (192, 193, 197-208).

Approaches to target the IGF signaling system have been evaluated in *in vitro* and *in vivo* preclinical tumour models (209, 210). IGF1R shows a high degree of similarity to insulin receptor (up to 70% homology). This, together with the wide distribution and broad physiological functions in normal tissues of these receptors, raise the concern of host toxicity. Hence, approaches targeting the IGF1R-specific gene sequences, including antisense RNA, ribozymes, triplex and small interfering RNA, are favored over the more conventional approaches using small molecule tyrosine kinase inhibitors and monoclonal antibodies. Antisenses against IGF1R, either by vector-expressed or chemical synthesized oligonucleotides, effectively (a) downregulate IGF1R and consequently inhibit survival in cultured cells, (b) through inhibition of tumourigenicity and metastasis, exert *in vivo* antitumour activity in multiple tumour types, and (c) enhance the cytotoxicity of several drugs in cultured Ewing's sarcoma, bladder cancer and prostate cancer cells (209, 210). These studies further yielded the unexpected finding that IGF1R reduction stimulates the host immune response, which in turn enhances the antitumour efficacy of the IGF system targeting approach. This finding has resulted in a pilot clinical trial in patients with malignant astrocytomas, where autologous glioma cells are collected, treated ex vivo with IGF1R antisense oligodeoxynucleotide, and then placed in small diffusion chambers that are reimplanted in patients (210-212).

2.1.4 Hepatocyte growth factor/scatter factor and receptor.

Hepatocyte growth factor/scatter factor, HGF/SF, and its specific receptor c-Met are involved in tumourigenesis and tumour progression (213-217). HGF/SF are predominantly expressed by mesenchymal cells. Although the HGF/c-Met system in tumours is primarily activated through endocrine or paracrine mechanisms (217, 218), autocrine activation has also been reported in *in vitro* and *in vivo* tumour models (219-222). For example, HGF/SF is predominantly expressed in tumour but not stromal cells present in non-small cell lung tumours (222).

Elevated serum and tissue HGF levels and aberrant *c-met* expression (constitutively active mutation and overexpression) are found in multiple tumours including the most common and most malignant types such as breast cancer, non-small cell lung cancer, multiple myeloma and pancreatic cancer (223-229).

In nearly all tumour types, enhanced activation of the HGF/c-Met system in patients is associated with resistance to radiotherapy and chemotherapy, and with worse prognosis and shorter survival (228-236). It is noted, however, that HGF exhibits cytotoxicity and enhances apoptosis induced by paclitaxel and cisplatin in ovarian carcinoma cell lines (237).

In experimental models, exogenous HGF protects human cancer cells (i.e., breast, leiomyosarcoma, gastric, prostate, glioblastoma and rhabdomyosarcoma) as well as endothelial cells from cell death induced by ion radiation or cytoxtoxic drugs including doxorubicin, cisplatin, etoposide, camptothecin, paclitaxel and tumour necrosis factor (238-248). The protective effects are derived from its anti-apoptotic (238-240, 242, 243 ,245 ,247) and/or enhanced DNA repair function (246, 248).

Several specific small molecular inhibitors of the HGF/SF/c-Met system or the biological agonist NK4 (HGF N-terminal four Kringle domain variant), which is a proteolytic cleavage product of HGF that competitively inhibits the binding of HGF to its receptor (249), have shown antitumour activity as single agents, in *in vitro* and *in vivo* preclinical models. Whether these agents enhance the activity of the conventional cytotoxic agents is not known.

2.2 Cytokines

Cytokines, a large family of immune modulator proteins, have been used to activate the immune system in cancer biotherapy or immunotherapy. A

recent review discusses the roles of cytokines in tumour pathogenesis and immunotherapy (250). Among the cytokines, transforming growth factor-β (TGFβ) and Th2 interleukins, secreted by T helper cells and tumour cells, contribute to tumour progression and protect tumour cells from cytotoxic chemotherapy, as follows.

2.2.1 Transforming growth factor-β

TGFβ is a pleiotropic growth factor and regulates multiple cellular functions including proliferation, adhesion, migration, and differentiation (251-257). TGFβ also induces the expression of matrix metalloproteinases, matrix components and adhesion molecules. These various effects together enable the remodelling of the microenvironment to provide for the appropriate physiological functions (251-257).

There are two types of TGFβ receptors, Type 1 and Type II. These receptors are widely distributed and expressed in normal and tumour cells. Members of the TGFβ family of proteins (TGFβ1 through TGFβ3 in mammalian species) bind to specific TGFβ receptors, followed by heterodimerization of the lignad-bound Type I and Type II receptors, and activation of the corresponding serine/threonine kinases (258). The activated receptors initiate multiple intracellular signaling cascades; the best characterized of which is the Smads-mediated signaling and transcriptional regulation pathway (258-260). TGFβ also activates TAK1 (TGFβ-activated kinase 1) (261) and small G-proteins (i.e., Ras, RhoA and RhoB), resulting in the activation of different MAPKs pathways, including ERK, p38 and JNK (262-268). In addition, TGFβ inhibits the phosphatase 2A-mediated activation of p70S6K, which is a ribosomal protein that regulates protein synthesis (269, 270). TGFβ also activates the PI3k/AKT survival pathways after a lag time; the delayed nature of this effect suggests the involvement of other mediating factors (271, 272).

TGFβ exhibits both tumour suppressing and tumour promoting functions (257, 273-275). TGFβ suppresses early stage carcinogenesis by inhibiting the growth of neoplastic cells of epithelial lineage. The tumour promoting function is largely through its suppression of host immune responses, stimulation of angiogenesis and promotion of tumour cell invasion and metastasis.

TGFβ overproduction is observed in most common tumour types, including prostate (276-285), breast (286-291), lung (292-300), hepatic (301-303), colorectal (304), gastric (305, 306) and brain cancer (307), and is associated with increased pathological stages, metastasis and/or poor prognosis. In most cases, TGFβ overproduction is associated with loss of responsiveness of tumour cells to TGFβ mediated growth inhibition, through alterations in various steps of the TGFβ signalling cascade, i.e., downregulation of TGFβ receptors, mutation of Smad, and upregulation of c-myc (282, 283, 285, 294, 296, 298, 308-314).

Pretreatment serum TGFβ level is a predictor of the outcome of radiation therapy in cervical cancer; higher levels are associated with worse locoregional control and shorter survival (315). However, pretreatment serum TGFβ level is not associated with acute radiation morbidity (315). These data indicate the selective effect of TGFβ on the radiosensitivity of tumour cells and not normal tissues.

Teicher and colleagues have conducted a series of elegant studies demonstrating the role of TGFβ in chemoresistance (20, 316-328). These investigators established an *in vivo* acquired drug resistance mouse mammary tumour model by repeated administration of alkylating agents to tumour-bearing mice (20). The key findings are as follows. First, the resistance phenotype was lost in monolayer cultures of the disaggregated tumour cells, indicating the involvement of environmental factors (20). Second, the implantation of the resistant tumour on one side of a mouse reduced the sensitivity of bone marrow cells and of the sensitive parent tumour implanted in the opposite side of the same host, indicating the present of circulating soluble resistance factors (20, 324, 326-328). Third, tumour morphological studies demonstrated the more fibrous nature, increased blood vessel density and increased metastatic potential of the resistant tumours, as compared to the parent, chemosensitive tumours (20, 324, 326-328). Based on these morphological changes that are typical of TGFβ functions, the investigators evaluated and established the role of TGFβ in chemoresistance.

First, mice bearing the resistant subclone showed higher pretreatment serum and intratumoural TGFβ levels compared to mice bearing the chemosensitive parent tumour (319, 321, 323). Second, blocking TGFβ by neutralizing antibodies (323) or the natural inhibitor decorin (319, 321) sensitizes the resistant tumours to chemotherapy. Third, over-expressing TGFβ by transfection in the parent chemosensitive cells resulted in chemoresistant tumours *in vivo* (319). This chemoresistance development was accompanied by several other changes observed in the acquired resistance tumour model developed by repeated challenges with chemotherapy, including elevation of serum TGFβ level and resistance of bone marrow cells. Furthermore, the chemoresistance due to TGFβ transfection was reversed by decorin (319). Finally, serum and intratumoural TGFβ levels are enhanced by chemotherapy, suggesting TGFβ as a mediator of chemoresistance acquired after therapy (316, 318). Similar findings have been reported in other tumour models including prostate, liver and gastric cancers, thus indicating the broad-spectrum nature of the TGFβ induced drug resistance (318, 320, 322).

In spite of the abundant evidence suggesting an important role of TGFβ in the chemoresistance observed in tumour-bearing animals, exogenous TGFβ does not induce resistance in monolayer cultures. The differences of TGFβ effects under *in vitro* and *in vivo* conditions suggest the involvement of additional factors present in tumour microenvironment. For example, in hepatocellular carcinoma cells, TGFβ promotes survival pathways including PI3K/AKT and FAK, an effect that is dependent on integrin-mediated adhesion and is most likely due to activation of integrin-linked kinase (329). In addition, TGFβ, together with growth factor signalling (IGF, EGF), through activation of receptor tyrosine kinases and Ras, stimulate epithelial-to-mesenchymal transition (i.e., squamous carcinoma to spindle carcinoma)(257). Furthermore, both direct and indirect effects of TGFβ, including host immune suppression, increased vascular endothelial growth factor (VEGF) production, remodelling of extracellular matrix and modulation of cell-cell adhesion molecule expression and signalling, contribute to angiogenesis in tumours. These various findings suggest the *in vivo* TGFβ-mediated chemoresistance as a result of the effects of complex networking between TGFβ and other environmental factors on the different compartments in a solid tumour, i.e., tumour cells, stroma, and blood vessel, as well as the host immune system.

Due to the critical roles of TGFβ in tumour progression and resistance to chemo- and radiotherapy, TGFβ and the associated signalling pathways are attractive cancer therapy targets. However, the fact that TGFβ also suppresses early stage tumour development and promotes carcinogenesis introduces the uncertainty that inhibition of TGFβ may lead to undesirable outcome. A better understanding and differentiation of the molecular mechanisms of these various TGFβ effects may provide more specific targeting approaches to blocking its tumour promoting and chemoresistance functions while retaining its tumour suppressive function. Furthermore, inhibitors of TGFβ signaling may have promise as enhancers of chemotherapy or radiotherapy, as suggested by tumor model studies where inhibition of TGFβ by neutrilization antibodies or the natural inhibitor decorin enhanced the efficacy of chemotherapy.

2.2.2 Interleukins

Various cytokines including interleukins (IL) are secreted by two types of T helper cells, i.e., types 1 and 2 or Th1 and Th2. Th1 cells express IL2, interferons and tumour necrosis factor β and mediate cellular immune response. Th2 cells express IL4, 5, 6, 10, 13 and mediate humoral immune response (330). In tumour-bearing animals, TGFβ shifts the balance between Th1 and Th2 responses toward Th2 response by inducing the overproduction of IL10, which initiates Th2 functions and inhibits Th1 functions.

Overproduction of Th2 cytokines and/or aberrant activation of the signalling pathways of Th2 cytokines have been found in patients with multiple types of advanced cancer, and in most cases are indicators for poor prognosis or short survival. For example, elevated serum IL6 level is observed in advanced metastatic prostate cancer, hormone-refractory metastatic breast cancer, glioblastoma multiforme, and renal cell carcinoma, and is

predictive of poor prognosis and shorter survival in these patients following chemotherapy and/or immunotherapy (331-338). Elevated serum IL10 levels, in some cases accompanied by elevated IL6 and/or IL8 levels, have been found in patients with gastric and colon cancer, aggressive Hodgkin's lymphoma, metastatic melanoma, advanced non-small cell lung cancer, hepatocellular carcinoma, and are associated with recurrence and/or shorter survival following therapy (339-354). On the other hand, a lack of IL10 expression in the tumour tissue of stage 1 non-small cell lung cancer patients is associated with a poor prognosis and shorter survival, suggesting a tumour suppressive function of IL10 in early stage disease (355). These biphasic effects of IL10 mirror the biphasic effects of TGFβ on tumour progression, and raise the interesting question whether the TGFβ effects are mediated through Th2 cytokines.

IL4 is overexpressed in thyroid cancers and high IL4 levels are associated with the resistance of thyroid cancer to chemotherapy (356). However, IL4 level is not associated with cancer progression, response to chemotherapy or immunotherapy, or prognosis in other tumour types. In fact, IL4 shows antitumour activity in breast and renal cell carcinoma. In the Japanese population, IL4 levels are no effects whereas genetic polymorphisms of IL4 receptor α gene result in heightened IL4 signalling and Th2 immunity and are associated with higher incidence and poor prognosis in renal cell carcinoma (330).

Since Th1-meidated immunity is the major antitumour immunity mechanism under *in vivo* conditions, Th2-mediated immunity, by suppressing Th1 immunity, results in tumour promotion and/or resistance. However, multiple lines of evidence support the notion that Th2 cytokines, including IL4, IL6, and IL10, confer survival advantage to tumour cells directly. Primary cultures of disaggregated thyroid cancer cells from patients produce IL4 and IL10 and cause the over-expression of anti-apoptotic proteins Bcl-2 and Bcl-XL and thereby confer resistance to cytotoxic chemotherapy (356). These findings are in agreement with the clinical observation that high level of Bcl-2 and Bcl-XL in thyroid tumours is associated with high resistance to chemotherapy (356). Likewise, murine B16 melanoma cells and primary cultures of human stomach adenocarcinoma and glioblastoma multiforme produce high levels of IL10, which protects tumour cells from cytotoxic chemotherapy (357). The IL10-induced chemoresistance was observed under *in vitro* and *in vivo* conditions, and is mediated by STAT3-dependent upregulation of anti-apoptotic Bcl-2 family proteins (357). Similarly, autocrine or paracrine activation of IL6 signalling induces multidrug resistance in breast, prostate, pancreatic, cervical and oesophageal carcinoma cells. IL-6 induced resistance is mediated by activation of STAT3, MAPK and/or PI3K/AKT pathways, through upregulation of anti-apoptotic Mcl1 and Bcl-2 family proteins, mdr1 drug transporter and/or detoxification enzyme glutathione transferase.

IL6 and IL10 have been investigated as potential therapeutic targets. Blocking IL10 actions using an inhibitor AS101, an immunomodulator, inhibits STAT3 activation, downregulates anti-apoptotic Bcl-2 family protein and sensitizes aggressive human glioblastoma multiforme to paclitaxel treatment under *in vitro* and *in vivo* conditions in preclinical models. The chemosensitization effect of AS101 was achieved at nontoxic drug levels (357). A subsequent phase II trial using AS101 in combination with chemotherapy in unresectable or metastatic non-small cell lung cancer patients shows higher response rate and lower toxicity, partially validating the concept of using IL10 inhibition as a chemosensitizer in patients (358).

Inhibition of IL6 or IL6 receptor using blocking antibodies sensitizes renal carcinoma and prostate cancer cells to anti-tumour drugs, e.g., etoposide, cisplatin and mitomycin C (359, 360). Sant7, a modified high affinity analog of IL6 that binds to IL6R without initiating downstream signaling, inhibits multiple myeloma and prostate cancer cell growth and sensitizes tumour cell to cytotoxic drugs (361, 362).

3. CELL ADHESION MOLECULES

Extensive studies have demonstrated the critical roles of cell adhesion to extracellular matrix and tumour/stromal cell interaction in tumourigenesis

and tumour progression (160, 363-374). The two major categories of adhesion/interaction molecules are (a) integrins which are the major mediators of cell-matrix adhesion, and (b) cadherins, selectins and members of the immunoglobulin superfamily cell adhesion molecules (CAM-Ig), which mainly mediate cell-cell interaction. Multiple lines of evidence support important roles for these compounds in mediating chemoresistance of solid tumours, as follows.

First, the expression levels of adhesion molecules, including ICAM1(375-383), CD44 (384-386), NCAM (387-390), LFA-3 (383), E-cadherin (391, 392), P-cadherin (393), integrin β1(394, 395), are correlated with poor prognosis, resistance to chemotherapy and radiotherapy, and shorter survival in multiple types of solid tumours and leukaemia, suggesting a potential role of cell adhesion mediated clinical drug resistance.

Second, conventional cytotoxic chemotherapy upregulates the expression of adhesion molecules in solid tumours, suggesting alteration in cell adhesion as a response to chemotherapy. A comparison of the gene expression profiles in three lung cancer patients using the cDNA array technique shows significant increases in adhesion molecules, including matrix metalloproteinases, integrins, endonexin, collagens and FGFR3, in post-chemotherapy lung cancer tissues compared to normal lung tissues from other donors (396). Similarly, patients with Barrett's-associated adenocarcinoma showed significantly elevated E-cadherin expression following chemotherapy or radiotherapy compared to patients who did not receive therapy (397). Higher E-cadherin levels are also associated with a shorter survival in patients receiving chemotherapy or radiotherapy, but this association was not observed in patients that did not receive therapy (397), demonstrating direct contribution of this responsive induction of E-cadherin to chemoresistance. The role of adhesion in chemoresistance was further demonstrated in series of studies on small cell lung xenograft tumours, the adhesion-dependent chemoresistance mimic the *in vivo* resistance in patients and involves altered extracellular matrix and cell adhesion molecules expression, constitutive activation of MAPK and AKT pathways and modulation of apoptosis molecules (398, 399).

Third, preclinical studies have demonstrated that specific cell adhesion to either extracellular matrix or neighbouring stromal/cancer cell causes drug resistance in different experimental models. Altered expression of extracellular matrix components e.g., collagen IV and membrane integrins, is associated with acquired resistance in tumour cells398, 400, 401. Adhesion to protein or non-protein extracellular matrix components, e.g., fibronectin, collagens, tenacin, laminin and hyaluronan, protects multiple types of tumour cells against apoptosis induced by cytotoxic drugs or radiation (399, 402-412). The protective action of the extracellular matrix (ECM) is mediated by integrin activation and signalling; several recent reviews summarize the integrins promoting drug resistance (e.g., integrin α4β1, α5β1) and the corresponding experimental systems (408-411). Activation of these integrins leads to activation of the downstream PI3K/AKT, MAPK and PLCγ pathways, resistance by inhibiting cell death through regulation of apoptosis regulatory proteins (e.g., Bcl-XL and Bad), decreased cell proliferation through upregulation of the CDK inhibitor p27 protein, and decreased DNA damage by downregulation of DNA topisomerase II (408).

Fourth, tumour-stromal contact and cell-cell contact (e.g., when tumour cells are cultured as multi-cellular spheroids) alter tumour cell sensitivity to cytotoxic treatment (410-414). For the former, the contact between myeloma cells and bone marrow stroma *in vitro* resulted in protection of myeloma cells from the cytotoxicity of a topoisomerase II inhibitor mitoxantrone, as well as induction of yet-unknown soluble factors that mediated partial inhibition of apoptosis and accelerated tumour cell proliferation (413). E-cadherin has been identified as an important player in the cell-cell contact dependent resistance, and its inhibition by a blocking antibody reversed the drug resistance in cultured colon cancer spheroids (415). The mechanisms for the resistance mediated by cell-cell contact are not known, but could be due to direct or indirect mechanisms.

4. HYPOXIA

Dysregulated tumour growth and progression cause imbalance between oxygen supply and consumption. These, together with structural and functional dysfunction of intratumoural vasculature, induce higher level of hypoxia in solid tumours. The phenomenon and the mechanisms of hypoxia-induced tumour cell resistance to radiation were discovered more than 70 years ago (416, 417). Since then, the availability and application of quantitative polarographic oxygen electrode technique (pO2 histograph) and other techniques using antibodies for detecting hypoxic markers have enabled detailed studies on the characteristics, development, and clinical relevance of hypoxia in human tumours (418, 419).

Hypoxia is observed in almost all types of human solid tumours, with substantial inter- and intra-tumour heterogeneity (420). Hypoxia contributes to tumour progression and invasion, and affects the prognosis in patients with various types of solid tumours (419, 420). The extensive studies on uterine cervix and head and neck tumours have shown that hypoxia in patient tumours is independent of tumour size, stages/grade and pathological types (419, 420). However, a high level of hypoxia is correlated with the tumour grade in other tumours, e.g., brain tumour(421). Hypoxia is associated with worse prognosis in non-small cell lung (422-424), brain (421, 425-427), and head and neck cancer (419), presumably due to enhanced malignancy and resistance to radiotherapy or chemotherapy.

Hypoxia directly or indirectly affects tumour sensitivity to radiation or chemotherapy drugs through chemical, biological and/or micro-evolutional mechanisms (418-420, 428), as follows.

Chemically, oxygen is required for enhancing the radiation-induced DNA damage and thereby enhancing cell kill. Hence, hypoxia causes resistance to radiotherapy. Typically, a 2.5-3 folds higher radiation is required to kill cells under fully hypoxia condition compared to aerobic conditions (428).

Hypoxia induces multiple biological responses simultaneously, through transcriptional and post-transcriptional mechanisms. Hypoxia-induced factor-1 (HIF1), mainly acts as a transcription factor, is the key element mediating the downstream transcriptional response in mammalian cells (418, 429-433). HIF1 is a heterodimer of the oxygen-regulated HIF1a and the constitutively expressed HIF1b. In the presence of oxygen and iron cofactors, proline hydroxylase hydroxylates HIF1a, resulting in its ubiqutin-mediated proteosome degradation initiated by the binding to VHL (von Hippel-Lindau tumour suppressor). This process, which serves to control the HIF1 level, is inhibited by hypoxia. Other oxygen sensing system may also be involved in HIF1 induction. Increases in HIF1 levels enable binding of HIF1 to hypoxia-response-elements in target genes and thereby regulates the transcription of these genes. Hypoxia also activates common stress-responsive transcription factors, e.g., p53, NFkb (434), AP-1 (Jun and c-fos heterodimer)(435, 436). Furthermore, APE-1/Ref1, a widely expressed dual-function protein, is activated under hypoxia and, through post-translational modifications, regulates transcriptional factors, leading to proteomic changes and subsequent biological responses to hypoxia and reoxygenation (435, 437-440).

The oxygenation status affects tumour cell sensitivity, under *in vitro* and *in vivo* conditions, to DNA-active agents. The mechanisms include decreasing the free radical generation (e.g., belomycin, etoposide), by causing acidosis which decreases the activity of the weakly basic drugs (e.g., vinblastin, doxorubicin, bleomycin), by causing elevated levels of glutathione which competes for alkylation of DNA or proteins, e.g., melphalan, cyclophosphamide, 1-nitrosourea (BCNU), or indirectly by complex biological consequences (see below). Besides inducing these drug-specific resistance mechanisms, hypoxia also causes resistance through broad-based mechanisms, as follows.

First, hypoxia induces G0/G1 phase cell cycle arrest through HIF-1 dependent upregulation of cyclin dependent kinase inhibitors p27/Kip1 and p21/Cip1 in tumour cells and fibroblasts (441-446). Downregulation of cyclin D, cyclin E and upregulation of 15/ink4a may also be involved in hypoxia-induced G0/G1 arrest. Because most chemotherapeutic drugs preferentially kill active dividing cells and/or target tumour cells at specific

cell cycle stages, slow down of cell proliferation by hypoxia protects tumour cells from drug toxicity. Furthermore, p27/kip1 protects tumour cells from hypoxia, nutrition depletion-induced cell death, and confers survival benefits in the presence of cyototoxic drugs.

Second, hypoxia modulates the expression and the balance of pro- and anti-apoptotic proteins. Chronic/severe hypoxia causes cell death mainly via mitochondria permeation-mediated apoptotic and necrotic pathways. Hypoxia induces the expression of the pro-apoptotic protein NIP3 and its homologue NIX, in a wide range of cell lines, an effect that requires HIF1 (447, 448). The expression of NIP3 is found in the perinecrotic region in human tumours (447, 449); its induction causes cells to undergo caspase-independent necrosis-like cell death while its inhibition by antisense RNA abolishes hypoxia-induced cell death (450-452). This data suggest that NIP3, and possibly NIX as well, mediate hypoxia-induced necrosis. However, hypoxia, through both HIF1-dependent and HIF1-independent pathways, also transcriptionally and/or post-transcriptionally upregulates the anti-apoptotic proteins Bcl-2, Bcl-XL and IAP family members (453), and downregulates the pro-apoptotic proteins Bid, Bad and Bax (454), and thereby protects tumour cells from hypoxia-induced cell death.

Third, the expression of ATP-binding cassette drug efflux protein P-glycoprotein (455, 456) is upregulated in human tumour and endothelia cells under hypoxic conditions, probably as a part of adaptative reactions to hypoxia (see also below). The induction requires prolonged chronic hypoxia, is dependent on HIF1, and is rapidly reversed by reoxygenation (456-458). Similarly, breast cancer resistance protein (BCRP or ABCG2) is upregulated by hypoxia *via* an HIF-dependent mechanism, and thereby protects tumour cells from hypoxia-induced cell death (459). These drug efflux transporters, by decreasing the intracellular drug accumulation, confer drug resistance (4-6, 460-463).

Fourth, hypoxia reorganizes and modulates the intra-tumour microenvironment, by upregulating vascular endothelial growth factor (464-468) and its receptors (469-471), FGF1 and/or FGF2 (468, 472), HGF/c-Met system (473, 474), IGFII (475, 476), IGFBP1 (477, 478), TGFβ1 and 3 (479), TGFα /EGFR system (480), IL1(481-483), IL6 (484-486) and IL8 (487-490). Many of these signalling pathways confer survival advantage to tumour cells as discussed in earlier sections.

Fifth, tumour cells, unlike normal cells, can survive and even benefit from hypoxic conditions through genetic and epigenetic adaptive changes. As a persistent stress, hypoxia selects for cells more adaptive to adverse conditions, and causes cross-resistance to therapy. Hypoxia and the associated acidosis, as well as nutrient deprivation, diminish DNA repair and cause genetic instability, accelerating the long-term micro-evolutionary process. The frequency of mutation and chromosome alteration increases 5-folds in tumour cells grown as solid tumours in mice or under hypoxic culture conditions, as compared to the same cells grown as monolayer cultures under aerobic conditions (491). Hypoxia induces genetic instability by downregulating the expression of the Mlh1 gene, a key component in DNA mismatch repair system (MMR), and thereby causes a deficiency in the MMR functionality (492), which in turn (a) increases genomic mutations and facilitates the selection of more aggressive and resistant tumours cells, and (b) activates adaptive responses to low oxygen level and/or nutrient depletion, including altered oxygen transport, iron metabolism, glycolysis and pH regulation and promoting angiogenesis. These changes affect the activity or delivery of chemotherapeutics and initiate micro-environmental remodeling by modulating the expression of growth factors, cytokines, matrix metalloproteinases, adhesion molecules and extracellular matrix components, resulting in enhanced invasiveness, metastasis and drug resistance. Hypoxia also accelerates the selection of transformed epithelial cells that are apoptosis-deficient (493, 494).

Therapeutic approaches targeting hypoxia, either through HIF1 blocking or use hypoxia activated prodrug, have been developed (418, 428). Among them, tirapazamine, a prodrug preferentially activated under hypoxic condition, has been evaluated clinically; its ability to improve the activity chemotherapy in advanced non-small cell lung and breast cancer patients has been demonstrated in randomized trials (495, 496).

5. INTERACTION BETWEEN TUMOUR- AND MICROENVIRONMENT-DERIVED FACTORS

Interactions between tumour- and microenvironment-derived factors affect chemosensitivity or chemoresistance in two ways. First, these factors can modulate each other and act cooperatively on several levels, e.g., regulation of expression of factors to induce environmental remodelling, cooperative activation between adhesion molecules and receptor tyrosine kinases, and cross-talk between downstream signalling pathways. In addition to the examples discussed in the above sections, growth factors or cytokines can activate changes in adhesion molecules, and cell-cell or cell-matrix adhesion can promote expression of survival-conferring soluble factors. Interactions between adhesion molecules (e.g., integrins, cadherins and adhesion molecules) and receptor tyrosine kinases on the cell membrane regulate the downstream signalling pathways and cell survival in multiple experimental models. In addition, N-cadherin, which is upregulated to replace E-cadherin during tumour progression in solid tumours, a phenomenon called cadherin switch, is able to activate or augment the signalling of the FGF system. Simultaneous upregulation of adhesion molecules and FGFR3 in tumour tissues obtained from advanced lung cancer patients after chemotherapy further suggests a common response of tumour- and microenvironment-derived factors to cytotoxic insults. Individual factors may also have direct and indirect effects on multiple levels. For example, in addition to triggering the protective mechanisms on hypoxic cells, hypoxia initiates environment change by regulating the expression of certain growth factors, matrix components and adhesion molecules, and thereby protects hypoxic tumour cells as well as the neighbouring non-hypoxic cells from stress. These various interactions often confer survival advantages to tumour cells.

Second, there is a high degree of redundancy between the intracellular signalling pathways activated by receptors and adhesion molecules. Cross-talk between these pathways regulates the intensity and duration of the activation and plays critical role in signalling differentiation. An example is the redundant intracellular signalling pathways of integrins and growth factors. The effects of redundant signalling are two fold. On one hand, the activation of one factor can compensate for the blocking of the activation of the second factor, e.g., the EGF-mediated protection is attenuated when cells are adherent to extracellular matrix components. Furthermore, the redundant provides for a more reliable protection, and, hence, it is more difficult to overcome the survival advantage by blocking only a single target.

6. CONCLUSIONS AND PERSPECTIVES

The recent advances of cancer biology and genetics provide unprecedented opportunities for innovative therapeutic paradigms. Abundant preclinical and clinical evidence indicates tumour resistance to therapy, either intrinsic or acquired, is determined by three major groups of tumour microenvironmental factors, i.e., soluble factors, adhesion molecules and hypoxia. The implications of the complex interplay between these factors and their redundant signalling pathways are two-fold. First, they highlight the importance of using appropriate experimental models. For example, the tumour-stromal interaction is not addressed by the monolayer culture system that is widely used in the experimental therapeutics field. Future successes in therapy development depend on establishing experimental models that can capture the various components of the tumour microenvironment that contribute to the protection of tumour cells against chemotherapy or radiotherapy. The availability of such models is also critical to the elucidation of the survival mechanisms conferred by environmental factors. Experimental systems and techniques, such as, 3-dimensional cultures, tumour-stromal cell co-cultures, and orthotropic tumours, especially the surgical orthotropic implantation of tumour cells from individual patients, include microenvironment compartments, and are more likely to yield clinically relevant information. Second, it is reasonable to postulate that approaches aiming at a single target

are not likely to yield significant and durable therapeutic successes. A logical approach is to aim at multiple targets, simultaneously eliminating the survival benefits conferred by multiple factors, present in either tumour and/or stromal compartments. Additional challenges include the chemotherapy-induced microenvironment remodelling, the kinetics of signalling initiated by tumour- and environment-derived factors and the interaction of these signalling pathways resulting in chemoresistance.

ACKNOWLEDGEMENT

The authors thank Dr. M.G. Wientjes for his critical review and input. This work was supported in part by research grants R37CA49816, R01CA77091, R01CA78577, R21CA91547 and R01CA93871 from the National Cancer Institute, NIH, DHHS.

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