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Molecular Mechanisms Involving Therapeutic Resistance in Head and Neck Squamous Cell Carcinoma (HNSCC) – Roles of Hypoxic Microenvironment and Cancer Stem Cell

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1. Introduction

Locally advanced diseases accounting for most HNSCC have a poor prognosis. The main reason for this is that corresponding symptoms of HNSCC are not always obvious or ignored by patients at early stage, which is mostly reflected by the fact that more than 2/3 HNSCC patients present with stage III/IV disease (AL-Sarraf, 1987; Argiris, 2008). Patients characterized with advanced HNSCC are subjected to worse prognosis than those with confined disease, exhibiting 5-year survival of 10-40%, cure rate of 30% and median survival time of 6-10 months (Argiris, 2008; Vokes et al, 1993; Cohen et al, 2004). Our recent study in a large series (X. Li et al, 2009) demonstrated that overall survival rates of patients with distant metastases in clinic were 56.8% at 1 year, 9.1% at 3 years, and 6.8% at 5 years, respectively. In addition, traditional treatment related morbidities could negatively influence quality life of patients, which involves loss of speech, permamant tracheostomy or gastrostomy dependence, dysphagia and other systematic side effects. Therefore, it is necessary to seek novel strategies to cure advanced HNSCC aiming at organ preservation, prevention of metastases as well as second malignancies and improvement in quality of life.

2. Necessities for adjuvant therapies in HNSCC

Surgical ablation plays a major role in the management of locoregional diseases of HNSCC. At early stage of HNSCC, current novel surgical alternatives, such as laser surgery, can achieve curable effects for 5-year survival rate of 80% even without prominent functional detriments. However, many tumors in the advanced stage are inoperable either due to the invasion of some major structures by tumor or due to the unfavorable general conditions of patients. Moreover, even with very skillful surgeons, some tumors remain after surgical resection, leading to postoperative recurrence if additional complimentary treatment is not carried out. In tumors with regional lymph node metastasis, extracapsular nodal spread always implicates poor prognosis even after a comprehensive neck dissection. For these conditions, adjuvant therapies such as radiotherapy, chemotherapy and chemoratiation are

due to undertake to increase the chance of cure or to prolong duration of survival of advanced cases.

2.1 Traditional adjuvant therapies improve outcome of advanced HNSCC

The participation of radiotherapy improved effects of surgery alone. In 2008, *Cancer* journal (Lavaf et al, 2008) reported a large-scale analysis with regard to effects of combined surgery and radiotherapy on survival of patients with lymph node-positive HNSCC patients. In 8795 patients meeting the inclusion criteria, 54.9% of 3-year overall survival and 43.2% of 5-year overall survival for adjuvant therapy could be gotten compared with 44.4% and 33.4% for surgery alone. More recently, a new analysis with large series (Shrime, 2010) reported that postoperative radiotherapy improved 5-year overall survival rate in patients with $T_{1-2}N_1$ oral squamous carcinoma (41.4% for surgery alone vs. 54.2% for surgery plus radiotherapy). Although statistically significant, slight improvement in survival has to indicate the limitation of single radiotherapy addition, which appeals the need of chemotherapy in the management of advanced HNSCC. In 2009, the journal of *The Lancet Oncology* published a 10-year follow-up report of a trial for chemoradiotherapy for locally advanced head and neck cancer conducted by The UK Head and Neck (UKHAN) cancer group (Tobias et al, 2009). In this follow-up analysis, patients who did not undergo previous surgery benefited from scheduled simultaneous addition of chemicals to radiotherapy, exhibiting 4-7 years in the median overall survival. However, the median overall survival of patients undergoing surgery was still higher without substantial benefit from chemotherapy alone. Furthermore, sequent toxicity reactions, such as mucositis and xerostomia, are due to occur. All these findings suggest that the effects of traditional chemicals in treating the HNSCC are limited due to their unspecific hallmarks.

2.2 Limitations of traditional adjuvant chemoradiation therapies

As is known, HNSCC depend on many intrinsic or extrinsic factors to protect against traditional chemotherapeutic agents, such as cisplatin and 5- fluorouracil. As evidenced by clinical observations, HNSCC possesses a decreased sensitivity and increased resistance to chemo- and radiotherapy, giving rise to a poor tumor control efficacy of these treatment modalities. This situation is mostly reflected by the fact that many HNSCCs (including primary and recurrent carcinomas) have less or no response to the adopted treatment regimens in the course of chemotherapy and/or radiotherapy. For this reason, some tumors regenerate or relapse following a short- or long-term paracmasis during which time the tumor bulk contracts or even disappears visually in response to therapy. Therefore, chemo- and radiotherapeutic resistance and post-treatment relapse has been always a puzzling problem that needs to be solved urgently.

3. Role of hypoxia in therapeutic resistance in HNSCC

The mechanisms underlying resistance to chemo- and/or radiotherapy by HNSCC are very complicated. Among various factors that are associated with therapeutic resistance in HNSCC, hypoxic microenvironment resulting from hypoxia in local cancer lesions is thought to be important one. It has been demonstrated that, most solid tumors have a lower pressure of oxygen (PO_2) compared with normal tissues from which they originate. Hypoxia occurs due to rapid proliferation of cells and/or insufficient supplies of blood. The latter

attributes to poor drugs delivery, leading to a common cause of chemoresistance. In addition, activated intrinsic pathways within tumor cells contribute to comprehensive radio- and chemo-resistance under hypoxic condition. In this section, we will focus on these intrinsic responses underlying resistance under hypoxia.

3.1 The general responses to hypoxia in tumor cells

General responses of tumor cells under hypoxia include translation inhibition, paradoxical translation and genetic instability. ATP defect caused by hypoxia invokes global translation inhibition for maintaining energy homeostasis. However, paradoxically, tumor cells activate some factors which are always unexpressed under normal conditions for adaptation to hypoxic stress. These proteins act as mediators of PH and metabolism, as well as function to propagate therapeutic resistance. In the long run, hypoxia-induced reactive oxygen species (ROS) and/or defective DNA repair induce mutagenesis of tumor cells to confer selection of heterogeneous population with hypoxia tolerance (see Fig. 1).

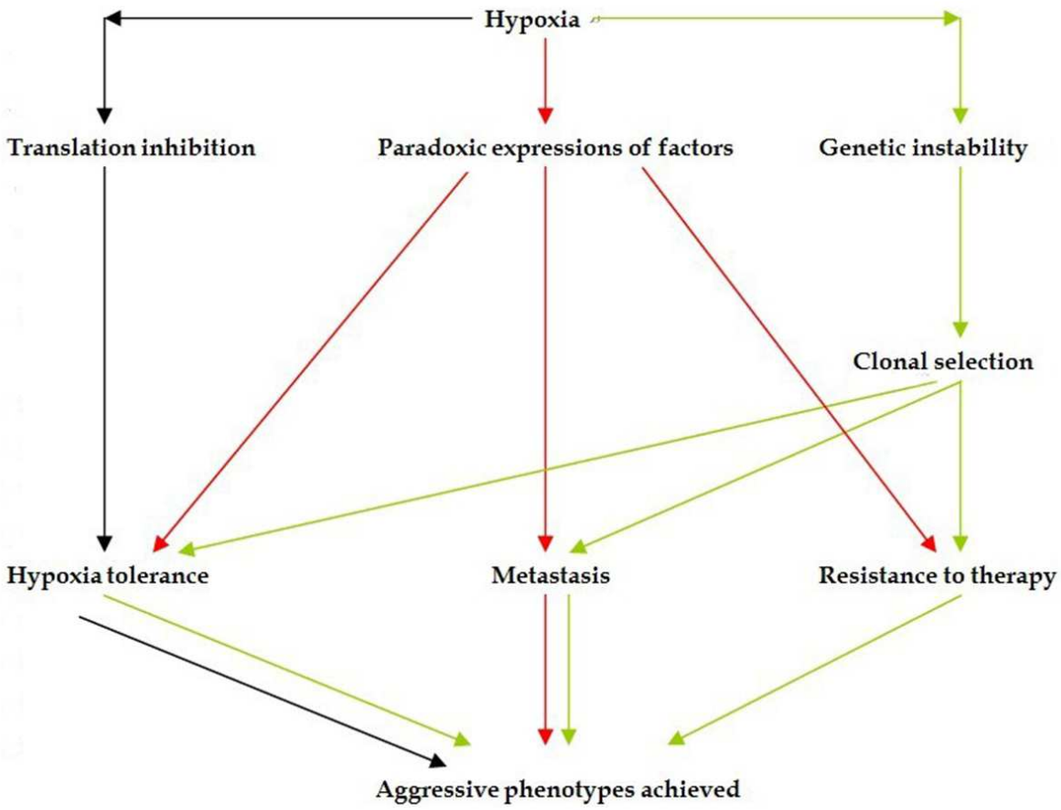


Fig. 1. General responses to hypoxia of tumor. Hypoxic tumor cells inhibit translation via mTOR pathways as well as UPR for energy homeostasis. Meanwhile paradoxically, they express some factors, such as HIF-1α and GRP78, to degrade nonfunctioning protein, regulate PH and counter apoptosis. These factors also act as resistance to therapy and metastasis. Hypoxia induced mutagenesis select clonal subset characterized with aggressive phenotypes, which confer more malignant biological behaviors including therapeutic resistance.

3.2 Hypoxia-related translation inhibition

3.2.1 The mammalian target of rapamycin (mTOR) pathways

Protein synthesis is processed as a result of energy-consumption. To date, emerging data have evidenced that inhibition of translation is an important category of cellular hypoxic tolerance, and the process occurs during the initial step of translation. The initiation of translation involves two components, the eukaryotic initiation factor 4F (eIF4F) as well as 43S preinitiation complex. The former consists of the cap binding protein eIF4E, a scaffolding protein eIF4G and an ATP-dependent helicase eIF4A (RNA helicase activity), among which eIF4E and eIF4G mostly participate in the regulation of initiation of translation. Under nutrient and/or oxygen repletion, mTOR phosphorylates eukaryotic initiation factor 4E binding protein 1 (4EBP1) that has a high affinity with eIF4E to low the affinity. Together with eIF4G, released eIF4E contributes to assembly of eIF4F complex that binds to the 5′m^{7}GpppN cap structure of mRNA to facilitate the recruitment of 43S preinitiation complex that includes the 40S ribosomal subunit and the ternary complex (eIF2-GTP and the methionine-loaded initiator tRNA) for the start of translation initiation. The ribosomal constituents of preinitiation complex scan though the 5′ untranslated region (5'UTR) until the AUG initiation codon is recognized. Sequently, the 60S ribosomal subunit joins to form 80S ribosome for the elongation of translation. Lots of recent reports have implicated that hypoxia can disturb the process above via hypoxic activation of the tuberous sclerosis protein 1 (TSC1)–TSC2 complex-mediated downregulation of mTOR. Thereby, corresponding expressions of translation initiation-related proteins, such as phosphorylated 4EBP1 and eIF4F, other mTOR-mediated targets and S6 protein kinases (S6K 1 and 2), all of which also function in translation, would be inactivated accordingly. In addition, hypoxia also interferes with formation of preinitiation complex to inhibit translation via PERK-mediated cascade of unfolded protein responses.

3.2.2 Unfolded protein responses (UPR)

UPR is an evolutionary conserved protective response to microenvironment stress. Because of abnormal vascular structure and aggressive cellular growth, hypoxia and glucose starvation always occur in tumor microenvironment, resulting in defective usage of energy in response to accumulation of many unfolded protein in endocytoplasmic reticulum (ER). Tumor cells must adapt to this stress though inhibiting mRNA and protein synthesis as well as degrading excessive useless protein, which is executed though activation of UPR. Glucose-regulated protein 78 (GRP78/BiP) is the core regulator in ER-stress and overexpressed in most tumor as a predictor of poor prognosis. Routinely, GRP78 binds to ER-stress sensors, IRE1α (inositol-requiring 1 alpha), PERK (double-strand RNA-activated protein kinase-like ER kinase), and ATF6 (activating transcription factor 6), to inactivate their downstream targets. Once ER-stress occurs, the role of GRP78 is shifted towards that of a chaperone. After dissociation, GRP78 handles unfolded protein to facilitate degradation and binds to Ca^{2+} to inhibit apoptosis. Importantly, the dissociation activates these integral ER membrane sensors PERK, IRE-1 and ATF6. Activated PERK phosphorylates eukaryotic initiation factor 2 subunit α (eIF2α), leading to either inhibition of global protein translational attenuation or paradoxical expression of the transcription factor 4 (ATF4) that immediately blocks eIF2α phosphorylation and sequently encodes genes upregulating stress-adaptive factors, such as GRP78 and hypoxia inducible factors (HIFs). UPR also

includes IRE-1 and ATF6 arms. Activated IRE-1 serves as an endoribonuclease to remove a 26 nucleotide intron from X-box binding protein 1 (XBP1) pre-mRNA. The resulting XBP1 protein by spliced XBP1 mRNA can activate lots of ER chaperones and enzymes to remove mis/unfolded protein and help ER-localized protein maturation as well as ER-associated degradation. Similar with XBP1, ATF6 needs cleavage for its activation. Briefly, upon UPR activation, ATF6 is transmitted from ER to Golgi apparatus where ATF6 completes its splicing process. Subsequently, cleaved ATF6 also activates target genes functioning in protein degradation and upregulation of molecular chaperones. As a matter of fact, their functions and target genes overlap one another. Overall, these sensors play a critical role in inhibition of mRNA and protein synthesis and upregulation of stress-adaptive factors. As a final step, unfolded protein is transported to cytoplasm and degraded via ubiquitin-proteasome pathway (UPP) or autophagy. To our understanding, UPR is a double-edged sword. On the one hand, PERK--eIF2a-ATF4 pathway is a dominant UPR arm offering survival advantage under hypoxia. On the other hand, once severe stress persists, UPR will induce ER-stress-relared cell death (apoptosis, autophagy associated programmed death or necrosis). To date, GADD153/CHOP induced by ATF4, has been identified as a pro-apoptosis factor that can activate cascades of caspases, mediating type I programmed cell death (known as apoptosis). It remains to be determined by what mechanisms the UPR induces autophagic death and necrosis.

3.3 Factors expressed paradoxically under hypoxia

3.3.1 HIF-1α

HIFs are core factors regulating oxygen and energy supplies of the tumor bulk, by which tumor cells adapt to hypoxia through inducing expressions of related genes to overcome such an unfavorable low-oxygen condition. HIFs are members of bHLH-PAS protein family including HIF-α and HIF-β subunit, the former of which also includes HIF-1α, HIF-2α and HIF-3α. Functionally, HIF-α (HIF-1α, HIF-2α) can be stably sustained in the hypoxic niche. In the event of cell signaling, HIF-α (HIF-1α, HIF-2α) and HIF-β can form a heterodimer that binds to promoters or enhancers of target genes. Hypoxia not only induces the expression of HIF-1α, but also activates many specific biological effects of HIF-1α gene protein, which functions either to acquire the tolerance to hypoxia or to commit the capability of invasion, metastasis and therapeutic resistance: 1) inducing expression of carbonate dehydrates (CAH) to maintain a stable cytoplasmic PH to promote the survival ability of cancer cells in response to apoptosis-inducing factors; 2) upregulating the expression of MDR gene and its product, P-gp, resulting in resistance to multiple chemotherapeutic agents; 3) mediating the overexpression and activation of DNA kinase (DNA-PK), contributing essentially to the repair of DNA double-strand breaks (DSBs); 4) acting as an upstream regulator of genes encoding vascular endothelial growth factor (VEGF) as well as some key enzymes related to glycolysis, responsible for angiogenesis and glycometabolism within tumors; 5) promoting expressions of anti-apoptosis proteins such as Survivin and XIAP to inhibit the activation of pro-apoptosis proteins Bax and caspases, rendering the tumor cells the ability to escape from apoptosis.

3.3.2 Signal transducer and activator of transcription 3 (STAT3)

STAT3 is an important factor overlapped by many intracellular signal pathways. It can be activated though Janus kinases (JAKs) or tyrosine kinase receptors such as EGFR. Upon

phosphorylation at the Tyr705 residue, p-STAT3 translocates to nucleus to bind DNA for inducing the transcription of downstream targets. Emerging reports have demonstrated that STAT3 is associated with poor prognosis in many cancers including HNSCC. STAT3 induces resistance to therapy in tumors via activation of anti-apoptosis factors, such as Bcl-2, Bcl-xl as well as Survivin and downregulation of P53. Recently, a study demonstrated that STAT3 participates in inhibition of apoptosis caused by PIs in HNSCC (C. Li et al, 2009). Under hypoxia, STAT3 can be activated by ROS (Simon et al, 1998). Selvendiran et al (Selvendiran et al, 2009) found that STAT3 can be activated by production of ROS under 1% O_2 in ovarian cancer. In their study, overexpressed STAT3 contributed to similar rate of proliferation as that under normoxia but increased drug resistance under hypoxia. Through blockage of STAT3 using RNAi technique, ovarian tumor cells with defective expression of STAT3 exhibited affected proliferation as well as increased sensitivity to traditional chemotherapeutics under hypoxia. In HNSCCs, STAT3 was also found to be constitutively activated and associated with cervical lymph node metastasis in laryngeal cancer. Silencing STAT3 gene with specific siRNA enhances the sensitivity of Hep-2 human laryngeal carcinoma cells to ionizing radiation both in vitro and in xenotransplanted mice model. (X. Li, et al, 2010a, 2010b)

3.4 Hypoxic dynamic complication in solid tumor

3.4.1 Category of hypoxia

In solid tumor, hypoxia can be categorized as chronic continuing hypoxia and cyclic hypoxia (also called intermittent hypoxia or fluctuating hypoxia) depending on distances of tumor cells from the adjacent vessels. The former is incurred from the condition that tumor cells locating far from vessels result to diffusion-limited and relatively stable delivery of oxygen. On the other hand, the latter characterized by acute hypoxia/reoxygenation is caused by status of nearby vessels that suffer from dynamic changes in blood perfusion not least as a result of the abnormal vasculature and the mechanical instability of microvessel walls caused by proliferating tumor cells and/or circulating blood cells. With regard to insufficiency in blood or oxygen supply, hypoxia is classified as mild hypoxia (PO2: 1-3%), moderate hypoxia (PO2: 0.1-1%) and severe hypoxia (PO2: 0-0.1%) ((Koumenis & Wouters, 2006). Additionally, in term of duration of persistent hypoxic condition, hypoxia is divided into acute hypoxia lasting several minutes to several hours as well as prolonged chronic hypoxia during which cells are exposed to hour-to-day intracellular low PO2. The complex nature of hypoxia and different responses to distinct hypoxia by tumor cells may explain why it is so difficult to antagonize hypoxia-induced therapeutic resistance in HNSCCs.

3.4.2 Chronic versus cyclic

In most lab experiments, there is an important difference ignored by us. That is the parameters of hypoxic condition selected by most investigators are usually simple and fairly stable. However, reoxygenation may occur during manipulation of assorted cells. To date, cyclic hypoxia has been less studied than chronic hypoxia. The setting of cyclic hypoxic condition was not consistent among various studies on cyclic hypoxia. Here we introduce the difference between the two as follows with special emphasis on the importance of cyclic hypoxia. Firstly, cyclic hypoxia confers more potential therapeutic resistance than chronic hypoxia. It has been demonstrated by many studies that increased expression of HIF-1α contributes to cyclic hypoxia-induced resistance. In addition, it has been confirmed that chronically hypoxic tumor cells are more susceptible to ionizing radiation (IR) or DNA-damaging drugs than acutely hypoxic tumor cells because of decreased homologous

recombination (HR) function, a main pathway to repair DNA double-strand breaks (DSBs) in the S and G2 phases of the cell cycle. Secondly, cyclic hypoxia induces an enhanced metastasis. It was found that mice bearing melanoma xenografts exposed to cyclic hypoxia suffered from increased incidence of pulmonary metastases (Rofstad et al, 2010). Furthermore, tumor cells treated by cyclic hypoxia up-regulates the expression of VEGF-A, the ligand of VEGFR-1 on bone marrow derived cells confirmed to form ''premetastasis niche''. Therefore, induction of VEGF-A by hypoxia may be an important promoter of metastasis. Thirdly, cyclic hypoxia enhances metabolism of Tirapazimine (TPZ), an agent with specific hypoxic cytotoxicity, by intratumoral vessels adjacent to the populated tumor cells, which attenuates the effects of TPZ (Cárdenas-Navia et al, 2007). Finally, cyclic hypoxia is pervasive. As early as 1996, Kimura's group (Kimura et al, 1996) measured microvessel red cell flux (RCF) and perivascular PO2 in xenotransplant of R3230Ac mammary carcinomas using intratumoral dorsal flap window chambers. They found that the baseline RCF and PO2 underwent a highly dynamic process, demonstrating that fluctuating hypoxia is a common phenomenon within a tumor. More recently, another group (Cárdenas-Navia et al, 2008) used phosphorescence lifetime imaging to detect fluctuation of vascular PO2 in rat fibrosarcomas, 9L gliomas and R3230 mammary adenocarcinomas transplanted in dorsal skin-fold window chambers. By short interval periodic imaging, they found O2 delivery to tumors is constantly instable. In addition, hypoxia, including acute and chronic hypoxia, causes genomic instability. Cyclic hypoxia mostly induces DNA double-strand breaks (DSBs) by generating reactive oxygen species (ROS). Chronic hypoxia causes genomic instability due to the defective HR ability. Thereby, both types of hypoxia facilitate mutagenesis leading to clonal selection with therapy-resistant, invasive and metastatic phenotype (see Fig. 2).

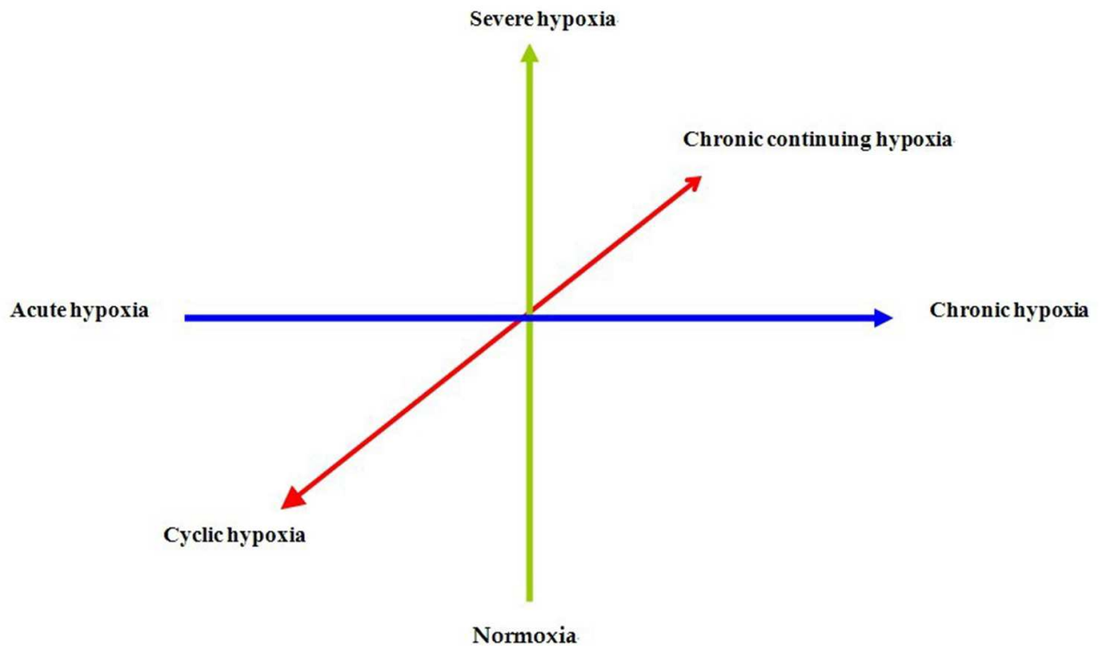


Fig. 2. Dynamic heterogeneity of hypoxia in solid tumor. Distinct hypoxia patterns exist in solid tumor. These patterns may overlap and co-exist in the same tumor bulk, which can be reflected though the 3D axis. Any point of this axis represents a combined type of hypoxia pattern in a tumor.

3.4.3 Hypoxic duration- and/or degree-related responses

The existing status of oxygen level in tumor bulk is very heterogeneous, which is reflected by detected PO_2 ranging from 0% to 100%, namely, from anoxia to normoxia. It is plausible that paradoxical activation of associated factors under hypoxia is also heterogeneous and dynamic in solid tumor, implying that focusing on one single target factor is insufficient to carry out an effective therapy. To date, although HIF-1α has been comprehensively studied under different hypoxic conditions, it is not the case in the study of short period of severe hypoxia as well as chronic moderate hypoxia. This can be partially explained by the fact that regulation of HIF-1α is actually a negative feedback loop via HIF-1α-dependent induction of prolyl hydroxylase enzymes that promote the von Hippel-Lindau (VHL) tumour suppressor protein-mediated HIF-1α degradation by ubiquitin-proteasome system under moderate hypoxia. On the contrary, the induction of prolyl hydroxylase enzymes is inhibited under severe hypoxia. Activation of eIF2α has been indicated as a transient process during severe hypoxia, which is decreased following the prolonged duration of hypoxic status. Under moderate hypoxia, eIF2α exhibits a gradually elevated activation along with elongation of hypoxic time.

4. Role of cancer stem cells (CSCs) in hypoxia-induced therapeutic resistance in HNSCC

4.1 Identification of CSCs in HNSCC

The theory of CSCs, as a milestone of cancer research, has a history of 150 years. The focus of this theory is that there exists a sub-group of tumor cells, like stem cells of normal tissues, with stem traits characterizing growth stasis and self-renewal with specific cell surface markers. This subset of cells within the tumor bulk is known as "cancer stem cells" (CSCs) or "tumor initiating cells (TICs)". Other tumor cells that are considered as progeny of CSCs would face a final differentiation followed by programmed cell death. In term of CSC theory, tumor bulk only originates from CSCs; therapeutic failures in cancer management are a result of insufficient elimination of these heterogeneous subpopulation. In addition, the subset is believed to play important roles in invasion, metastasis and therapeutic resistance in various malignancies. To date, CSCs or CSC like cells have been identified in different cancer including HNSCC. In 2007, a subpopulation of cells with characterized stemness and CD44 marker in HNSCC was first isolated and identified (Prince et al, 2007). It was also demonstrated that $CD133^+$ cells in Hep-2 human squamous laryngeal carcinoma cells have stem cell-like characters (Zhou et al., 2009). Subsequently, other investigators identified a $CD133^+$ CSC-like subset with chemoresistance in oral squamous carcinoma (Zhang et al., 2009). More recently, $CD44^+$ CSCs have also been isolated and identified from human laryngeal squamous carcinoma. All these data confirm the existence of CSCs in HNSCC, which shed light on a novel area to get further insight into the mechanisms of chemo- and radioresistance in HNSCC with respect to SCCs.

4.2 CSCs and microenvironment

4.2.1 "Seeds and soil" theory

The microenvironment of CSCs also called "niche", consists of cellular and non-cellular components surrounding CSCs (Scadden, 2006), including direct cell contacts, cell-matrix

contacts, cytokines, blood vessels, mesenchymal cells and so on. It serves to protect CSCs from differentiation and apoptosis, and keeps the status of self-renewing (Iwasaki & Suda, 2009). As a matter of fact, the significance of the niche function is far beyond these, as it affects the physiology of CSCs to a far more great extent. As early as 1889, through analysis of 735 cases of breast cancers, British assistant doctor Stephen Paget (Paget, 1989) found that breast cancer cells preferred liver to settle in rather than spleen that has vascular supply as abundant as liver. Nearly a century later, after the quiescence of the " seeds and soils ", Hart and Fidler (Hart & Fidler, 1980) injected melanoma cells into mice implanted with ovary tissue, kidney tissue and lung tissue in muscle or under the skin, and these implanted tissues had previously established vascular supplies of their own. Finally, they demonstrated that melanoma cells just metastasized to grafted ovary and kidney, suggesting that the formation of tumor is not only influenced by the characters of tumor cells but also depends on the niche. Because CSCs are a kind of cells that can self-renew in malignancy, the niche of CSC must be critical for preserving the property of self-renewal.

Recently, many studies provided evidence for the "seeds and soil" even as they further disclosed the relationship between CSC and its niche. A group attenuated the adhesion between CSCs and some components of the niche, such as hyaluronan, through interfering with CD44, thereby, inhibited the neoplasia of myeloid leukemia (Jin et al, 2006; Krause et al, 2006). Calabrese et al (Calabrese et al, 2007) found that most medulloblastoma stem cells grew by adhering to endothelial cells selectively, and these CD133+ cells could give rise to new tumors only when co-transplanted with endothelial cells. Kaplan et al (Kaplan et al, 2005) introduced a concept of "premetastatic niche", which meant the microenvironment of metastasized organs had been induced to transform into a condition better for the formation of secondary tumor. All of the findings above suggest that targeting the niche will be a very significant approach to eliminate CSCs.

4.2.2 Niche and heterogeneity

Species are selected by adaptation to environmental changes as proven by the earliest dinosaurs to today's diverse biological species. Such is Darwinian evolution, a possible explanation for survival. The development of tumors might be a process of survival of the fittest by the pressure of microenvironment.

It is known to all that cells in various types of tumors are different from each other in many aspects, such as size, appearance, antigen expression, cell membrane composition and sensitivity to different treatment modalities (Ichim & Wells, 2006; Heppner, 1984; Axelson, 2005). There are two explanatory models to the potential heterogeneity of the tumor cells, the stochastic model and the hierarchical model. Firstly, the stochastic model attributes the tumor development to the "genetic instability", through which the ones best adapting to the microenvironment are selected to obtain the advantage of proliferation (Nowell, 1976; Tysnes & Bjerkvig, 2007). This model shows that the tumor parenchyma contains many types of tumor cells with the ability to form tumors in the microenvironment (Bjerkvig, 2009). Secondly, the hierarchical model supports that the initial tumor and the metastatic tumor are both evolved from CSCs, which seems contradicting to the first model.

The two controversial models are currently interpreted by some recent investigations. Odoux et al (Odoux et al, 2008) found that a small number of CSCs subsets with the ability of self-renewal and differentiation exist in liver metastases in patients suffering from colon cancer, and this sub-group of cells are more invasive and expanding than the CSCs in the primary tumor. Surprisingly, as a considered decisive element in the evolution of tumor (Cahill et al, 2009), genetic instability was present in this subset. A recent genomics study found that aberrant stem cells significantly express the regulatory protein molecules which function to adapt to microenvironmental stimuli with respect to the gene expression profile of murine embryonic stem cell lines and its malignant counterpart, murine teratocarcinoma cell lines (Heffron, 2007). Campbell and Polyak (Campbell & Polyak, 2007) integrated the results of their research on breast cancer and a number of related reports, and ended up with that the heterogeneity of tumor cells may be due to the combination of some levels of the stochastic model and the hierarchical model. They found that the origin of breast cancer may initially be normal CD44-expression stem cells or progenitor cells, which undergo self-renewal, differentiation and mutation-driven clonal evolution motivated by the environmental changes and gene mutations, resulting in a bunch of different genotypes and diverse stages of development of tumor cells. This indicates that the hierarchical model in cancer stem cell theory is the extension of the stochastic model. Tumor tissues are evolved through genetic alterations, phenotypic changes and the impacts of micro-environment. So there may be more than one type of stem cell subsets with different characteristics in parenchyma, which exhibits different genetic or epigenetic phenotypes and ability to adapt to microenvironment, and the distinct characteristics of epithelial to mesenchymal transition (Werb & Evans, 2004). Therefore, not all CSCs have the ability to survive and metastasize, only those with the ability to adapt to the microenvironment are selected (Odoux, C et al, 2008; Lagasse, 2008) to do so.

4.2.3 Hypoxia and CSCs

As is known, CSCs are a subpopulation of tumor cells that co-exist with differentiated tumor cells in the same microenvironment, in which hypoxia serves as a necessary component for CSCs growth, self-renewal and differentiation (Keith & Simon, 2007). It has been demonstrated that HIF-1α could induce the expression of some crucial genes related with CSCs' self-renewal and multipotency, including Oct4 and Notch1. Under hypoxia, stable expression of HIF-1α in CSCs can stimulate expressions of Oct4 and Notch1, and activate the associated signaling of critical pathways, promoting specific properties of CSCs and related multipotency. In view of the mentioned above, we can introduce the concept of interaction between tumor hypoxic microenvironment and CSCs. Traditionally, the standard for evaluating the efficacy of a treatment regimen is the sizable contraction of the tumor bulk. However, most tumor relapse after a period of paracmasis, probably because traditional chemo- and radiotherapy only kill tumor cells in rapid proliferation and differentiation rather than CSCs, the latter of which with are in slow divisions and proliferation, conferring therapeutic resistance. The formation of the relapsed tumor is driven by CSCs under proper microenvironment at a certain time after the treatment regimens are completed.

4.2.4 CSC's resistance and related mechanisms

Lots of convincing data showed that CSCs subset displays powerful resistance to traditional chemo- and/or radio-therapy compared with non-CSCs of in same tumor or parent cells in

vitro. Currently, the mechanisms of CSCs-related therapeutic resistance have not been well understood. Perhaps, basic principles regarding CSC-caused therapeutic resistance can be categorized as follows.

4.2.4.1 Quiescence

Lots of cytotoxic drugs mostly kill tumor cells with rapid proliferation, which settle in cellular s-phase cycle. However, it is believed that CSCs, like normal stem cells, mostly reside in G_0/G_1 phase, which reduces efficacy of anti-cancer agents.

4.2.4.2 Overexpression of protective genes

Another cause of CSCs-related resistance is that this subset overexpresses some factors that protect CSCs from apoptosis and cytotoxicity. It has been well confirmed that CSCs express high levels of ABC drug transporters. Due to ATP hydrolysis, these proteins function to efflux drugs from tumor cells to protect against cytotoxicity. ABC superfamily includes 7 subfamilies from ABCA to ABCG (ABCB1 is P-gp). Among the superfamily, ABCG2 has been studied most extensively and is believed to be the most critical transporter of drugs. However, in clinic, targeting on ABCG2 alone has a minimal effect in the correction of chemorisistance by cancers, suggesting other ABC components also participate in chemoresistance or CSC's resistance is not determined only by ABC transporters. Liu et al (Liu et al, 2006) isolated CD133-positive tumor cells from glioblastoma and demonstrated that along with ABC transporters, these CSCs overexpressed anti-apoptotic factors, such as BCL-XL, Xiap, Survivin as well as cIAPs and DNA repair protein MGMT, which suggests that powerful repair ability combined with anti-apoptotic features may be partially responsible for CSC's resistance. Through studying CSCs from hepatocellular carcinoma (HCC), Ma et al (Ma et al, 2008) demonstrated that HCC CSCs confer chemorestistance via preferential induction of AKT/PKB and BCL-2 survival pathways. Using specific AKT1 inhibitors, survival of HCC CSCs can be abolished.

5. How to cope with the therapeutic resistance induced by hypoxia

5.1 Targeting genes related with hypoxia

Based on the mentioned above, it is evident that blockage of paradoxical activation of genes by transgenic techniques or improvement of hypoxic status in tumor microenvironment could overcome hypoxia-induced therapeutic resistance and relapse in HNSCC. Gene therapy mostly pointing to some critical target genes and associated gene products in HIF-1α, UPR and mTOR pathways and some activators and regulators of HIF-1α in alternative pathways such as EGFR and STAT3 pathways offers hope in this regard. However, transgenic techniques using either viral or non-viral vectors have limitations for application in human body. As previously described, dynamic hypoxic heterogeneity exists in solid tumors. It is difficult to determine the specificity and effectiveness of a single-gene targeted therapy to hypoxic cells in a huge tumor bulk. Therefore, there should be a long-term exploration before gene therapy can be used as an efficient method of modifying therapeutic resistance in HNSCC. It is likely that a strategy targeting multiple genes would be a potential solution to CSC-associated therapeutic resistance under the condition that hypoxic status in each individual tumor is evaluated objectively.

5.2 Targeting CSCs and hypoxic microenvironment

As stated, only CSCs can facilitate tumorigenesis and confer therapeutic resistance, which is the major cause of therapeutic failure. Therefore, successful targeting on CSCs is expected to provide a chance of cure for cancers. To date, targeting on CSCs has been faced with difficulties, because mechanisms underlying CSC-related therapeutic resistance have not been well understood. Although Notch, Oct-4, Wnt, Bmi and other stemness related factors were demonstrated to play a critical role in CSCs physiology, it is difficult to target them specifically in CSCs among the huge population of cancer cells. It is interesting to note that the clinical course of anti-ABCG-2 drugs in cancer treatment mirrors that of anti-bacterial agents in the control of infection. Based on this observation, some scholars believe that CSCs also experience evolutionary processes, and the driving force for these processes, selection stress by microenvironment, should be the target for cancer therapy. Although more CSCs markers have been identified in cancers, CSCs isolated by these markers are in minority, approximately 2-5%. However, increasing evidence has revealed that CSCs are not rare when isolated based on stem traits, which suggests that CSC markers are limited and not all CSCs express the same markers. Therefore, it is possible that CSCs are existing in separate subpopulations with distinct biological features, which are affected by their niche, and what is worse, these features are in constant change. Given that targeting CSCs is a putative approach, it would be much more important to concentrate on the manipulation of niche as the direct target in curing cancers. For example, we can resort to approaches to maintain the homeostasis of the niche by manipulating non-cellular components, especially fluctuating hypoxia. Consistent with this idea, traditional Chinese medicine (TCM) is to cure the disease by rectifying imbalance in body environment and re-establish the homeostasis of the human body, which may offer some hope in this regard. And intriguingly, lots of herbs have been identified as antioxidant compounds. Cai et al (Cai et al, 2004) have demonstrated that 112 traditional chinese medicinal plants used as anti-cancer herbs have a more powerful antioxidant activity compared with common vegetables and fruits which are considered as good natural sources of dietary antioxidants. Tang et al (Tang et al, 2004) also identified the antioxidant function of TCM extracts. These pieces of evidence implicate that TCM is a promising strategy capable of targeting on ROS-induced evolution of CSCs. Indeed, data from several reports have provided direct evidence that some herbs in TCM could target CSCs. Observations made by Jiang et al (Jiang et al, 1983) demonstrated that camptothecin and harringtonin could inhibit the clonal formation of human stem cells. Furthermore, anti-tumor and therapeutic resistance-reversing effects of some phytochemicals such as Curcumin have been confirmed and proven to be prospective, which exhibit the capability of targeting side population cells (Fong et al, 2010). More recently, high inhibitory effect on breast cancer cells was acquired by combining stealthy liposomes from vinorelbine and parthenolide (Liu et al, 2008). Taken together, chemotherapy combined with TCM may dominate anti-cancer treatment if the niche is properly manipulated to overcome the chemoresisitance of CSCs resulting from genetic instability.

5.3 Inducing UPR pro-death arms

As is known, UPR is a double-edged sword. On the one side, it can help tumor cells relieve hypoxic stress； On the other hand, UPR can induce apoptosis or autophagy-related cell

death under severe stress. Induction of UPR pro-death arms may be a promising modality to reverse hypoxia-induced resistance to traditional therapy. At this point, some agents, such as PIs, which can enhance ER overload, represent a promising perspective. PIs inhibit proteasome to reduce ERAD, which can intensify ER-stress caused by accumulation of unfolded protein. Recently, Fels et al (Fels et al, 2008) found that PIs can effectively enhance UPR responses of hypoxic tumor cells and ameliorating ER-stress can reverse PIs effects. They demonstrated that hypoxic tumor cells treated by PIs underwent apoptosis, autophagy and necrosis. Intriguingly, some groups reported that tumor cells can activate STAT3 to resist PIs therapy in HNSCC (C. Li et al, 2009). Therefore, PIs combined with STAT3 inhibition could achieve potential efficiency.

5.4 Chopping off hypoxia from the "root"

For strategies used to improve local hypoxia, some groups have tried using inhalation of Carbogen（95%O2 and 5%CO2）and hyperbaric oxygen chambers to improve local hypoxic condition within tumors, and thus therapeutic resistance, but the results are not as satisfactory. In this regard, it is necessary to modify traditional approaches and to explore a new way of oxygen delivery to rectify the intratumoral hypoxic condition. It is a common sense that vascular structure of tumor is very different from its counterpart of normal tissue, the former of which exhibits architectural distortion, higher permeability and irregular infuse, facilitating fluctuating hypoxia and providing specific target strategy. Vascular disrupting agents (VDAs) serve as a novel type of anti-cancer target agent. In contrast with angiogenesis inhibitors (AIs) that mostly prevent neoformation of vascular structure, VDAs directly block or damage existing blood vessels in tumor bulk to commit necrosis. To date, VDAs have been in phase of clinic trails, and small molecular VDAs have been mostly studied. The mechanisms of VDAs action include: 1) induce TNF-α secretion by tumor cells to cause apoptosis of endothelial cells constituting microvessels; 2) through binding to microtubule protein, VDAs facilitate disaggregation of microtubules to damage cell skeleton of vascular endothelium. VDAs have been believed to cause intratumoral necrosis, leaving the remaining periphery to be oxygenated. Therefore, combination of VDAs may cut both fluctuating and continuous hypoxia from the "boot".

Although improvement of tumor hypoxia has been achieved, imaging results are not always consistent with changes of endogenous markers of hypoxia, indicating that the improvement of intratumor hypoxia as observed by imaging does not represent the thorough rectification of intracellular hypoxic metabolisms of the cancer cells. Therefore, it is highly likely that there exist a "time gap" between improvement of intratumor hypoxia and thorough rectification of intracellular hypoxic metabolisms. Currently, length of this window phase is unclear. It is of paramount importance for hypoxic cells to gain thorough recovery of the intracellular oxygenation using this compensation time and become more susceptible to chemoratiation.

6. Future directions

Up till now, the impact of hypoxia on CSCs in HNSCC and its relation between chemo- and radiotherapeutic resistance is largely unknown. To further elucidate the causes of chemo- and radiotherapeutic resistance and post-treatment relapse in HNSCC with respect to effects

of tumor microenvironment on tumor cells, the first step is to study how hypoxic microenvironment regulates CSCs in HNSCC. Through establishment of HIF-1α knock-down cell lines (HIF-1α$^{-/-}$), the correlation between induction of HIF-1α and related gene expressions associated with self-renewal as well as multipotency of CSCs is to be observed. Meanwhile, the differential expression of these genes between CD133^{+} and CD133^{-} cells must be documented. Furthermore, the proliferative activity of CD133^{+} CSCs should be measured by culturing HIF-1α$^{+/+}$ and HIF-1α$^{-/-}$ cells under normal or hypoxic conditions, thereby to understand whether hypoxic microenvironment modulates the differentiation and proliferation of CSCs by regulation of HIF-1α in HNSCC.

The established concept of interaction between tumor hypoxic microenvironment and CSCs helps us to further understand the mechanisms behind the therapeutic resistance in HNSCC. If CSCs are taken as anti-cancer targets, the strategies by focusing on tumor microenvironment will be promising for purposely intervention of CSCs (Iwasaki & Suda, 2009). It can be inferred that CSCs are the critical element responsible for therapeutic resistance in HNSCC. Improving hypoxic conditions and regulating CSCs-related signaling pathways during chemo- and radiotherapy of HNSCC offers hope for reversion of therapeutic sensitivity in HNSCC and elimination of therapeutic resistance and relapse, aiming at improving outcomes of HNSCC.

7. References

Al-Sarraf, M. (1987). Chemotherapeutic management of head and neck cancer. Cancer and Metastasis Reviews, Vol 6, No. (3), pp. 181–98. ISSN 0167-7659

Argiris, A., Karamouzis, MV., Raben, D. & Ferris, RL. (2008). Head and neck cancer. Lancet, Vol 371, No. (9625), pp. 1695–1709. ISSN 0140-6736

Axelson, H., Fredlund, E., Ovenberger, M., Landberg, G. & Pahlman S. (2005). Hypoxia-induced dedifferentiation of tumor cells—a mechanism behind heterogeneity and aggressiveness of solid tumors. Seminars in Cell & Developmental Biology, Vol. 16 No. (4-5), pp. 554–563. ISSN 1084-9521

Bjerkvig, R., Johansson, M., Miletic, H. & Niclou, SP. (2009). Cancer stem cells and angiogenesis. Seminars in Cancer Biology, Vol. 19 No. (5), pp. 279–284. ISSN 1044-579X

Cahill, DP., Kinzler, KP., Vogelstein, B. & Lengauer, C. (1999). Genetic instability and darwinian selection in tumours. Trends in Cell Biology, Vol, 9 No. (12), pp. 57–60. ISSN 0962-8924

Cai, Y., Luo, Q., Sun, M. & Corke, H. (2004). Antioxidant activity and phenolic compounds of 112 traditional Chinese medicinal plants associated with anticancer. Life Sciences, Vol 74, No. (17), pp. 2157–2184. ISSN 0024-3205

Calabrese, C., Poppleton, H., Kocak, M., Hogg, TL., Fuller, C., Hamner, B., Oh, EY., Gaber, MW., Finklestein, D., Allen, M., Frank, A., Bayazitov, IT., Zakharenko, SS., Gajjar, A., Davidoff, A. & Gilbertson, RJ. (2007). A perivascular niche for brain tumor stem cells. Cancer Cell, Vol. 11 No. (1), pp. 69–82. ISSN 1535-6108

Campbell, LL. & Polyak, K. (2007). Breast Tumor Heterogeneity - Cancer Stem Cells or Clonal Evolution? Cell Cycle, Vol. 6 No. (19), pp. 2332–2338. ISSN 1538-4101

Cárdenas-Navia, LI., Secomb, TW., & Dewhirst, MW. (2007). Effects of fluctuating oxygenation on tirapazamine efficacy: Theoretical predictions. International Journal of Radiation Oncology Biology Physics, Vol 67, No. (2), pp. 581–586. ISSN 0360-3016

Cárdenas-Navia, LI., Mace, D., Richardson, RA., Wilson, DF., Shan, S. & Dewhirst MW. (2008). The pervasive presence of fluctuating oxygenation in tumors. Cancer Research, Vol 68, No. (14), pp. 5812–5819. ISSN 0008-5472

Cohen, EE., Lingen, MW. & Vokes, EE. (2004). The expanding role of systemic therapy in head and neck cancer. Journal of Clinical Oncology, Vol 22, No.(9), pp: 1743–1752. ISSN 0732-183X

Fels, DR., Ye, J., Segan, AT., Kridel, SJ., Spiotto, M., Olson, M., Koong, AC. & Koumenis, C. (2008). Preferential cytotoxicity of bortezomib toward hypoxic tumor cells via overactivation of endoplasmic reticulum stress pathways. Cancer Research, Vol 68, No. (22), pp. 9323–9330. ISSN 0008-5472

Fong, D., Yeh, A., Naftalovich, R., Choi, TH. & Chan, MM. (2010). Curcumin inhibits the side population (SP) phenotype of the rat C6 glioma cell line: towards targeting of cancer stem cells with phytochemicals. Cancer Letters, Vol 293, No. (1), pp. 65–72. ISSN 0304-3835

Hart, IR. & Fidler, IJ. (1980) Role of organ selectivity in the determination of metastatic patterns of B16 melanoma. Cancer Research, Vol. 40 No. (7), pp. 2281–2287. ISSN 0008-5472

Heffron, CC., Gallagher, MF., Guenther, S., Sherlock, J., Henfrey, R., Martin, C., Sheils, O. & O'Leary, JJ. (2007). Global mRNA analysis to determine a transcriptome profile of cancer stemness in a mouse model. Anticancer Research, Vol. 27 No. (3A), pp. 1319–1324. ISSN 0250-7005

Heppner, GH. (1984). Tumor heterogeneity. Cancer Reserch, Vol. 44 No. (6), pp. 2259–2265. ISSN 0008-5472

Ichim, CV. & Wells, RA. (2006). First among equals: The cancer cell hierarchy.Leukemia & Lymphoma, Vol. 47 No. (10), pp. 2017–2027. ISSN 1042-8194

Iwasaki, H. & Suda, T. (2009). Cancer stem cells and their niche. Cancer Science, Vol 100, No. (7), pp. 1166–1174. ISSN 1347-9032

Jiang, TL., Salmon, SE. & Liu, RM. (1983). Activity of camptothecin, harringtonin, cantharidin and curcumae in the human tumor stem cell assay. European Journal of Cancer & Clinical Oncology, Vol 19, No (2), pp. 263-270. ISSN 1078-8956

Jin, L., Hope, KJ., Zhai, Q., Smadja-Joffe, F. & Dick, JE. (2006). Targeting of CD44 eradicates human acute myeloid leukemic stem cells. Nature Medicine, Vol. 12 No. (10), pp. 1167–1174. ISSN 1078-8956

Kaplan, RN., Riba, RD., Zacharoulis, S., Bramley, AH., Vincent, L., Costa, C., MacDonald, DD., Jin, DK., Shido, K., Kerns, SA., Zhu, Z., Hicklin, D., Wu, Y., Port, JL., Altorki, N., Port, ER., Ruggero, D., Shmelkov, SV., Jensen, KK., Rafii, S. & Lyden, D. (2005). VEGFR1-positive haematopoietic bone marrow progenitors initiate the pre-metastatic niche. Nature, Vol. 438 No. (7069), pp. 820–827. ISSN 0028-0836

Keith, B. & Simon, MC. (2007). Hypoxia-inducible factors, stem cells, and cancer. Cell, Vol 129, No (3), pp. 465-472. ISSN 0092-8674

Kimura, H., Braun, RD., Ong, ET., Hsu, R., Secomb, TW., Papahadjopoulos, D., Hong, K. & Dewhirst, MW. (1996). Fluctuations in red cell flux in tumor microvessels can lead to transient hypoxia and reoxygenation in tumor parenchyma. Cancer Research, Vol 56, No (23), pp. 5522-5523. ISSN 0008-5472

Koumenis, C. & Wouters, BG. (2006). "Translating" tumor hypoxia: unfolded protein response (UPR)-dependent and UPR-independent pathways. Molecular Cancer Research, Vol 4, No. (7), pp. 423–436. ISSN 1541-7786

Krause, DS., Lazarides, K., von Andrian, UH. & Van Etten, RA. (2006). Requirement for CD44 in homing and engraftment of BCR-ABL-expressing leukemic stem cells. Nature Medicine, Vol. 12 No. (10), pp. 1175–1180. ISSN 1078-8956

Lagasse, E. (2008). Cancer stem cells with genetic instability: the best vehicle with the best engine for cancer. Gene Therapy, Vol. 15 No. (2), pp. 136–142. ISSN 0969-7128

Lavaf, A., Genden, EM., Cesaretti, JA., Packer, S. & Kao, J. (2008). Adjuvant radiotherapy improves overall survival for patients with lymph node-positive head and neck squamous cell carcinoma. Cancer. Vol. 112, No. (3), pp. 535–543. ISSN 0008-543X

Li, C., Zang, Y., Sen, M., Leeman-Neill, RJ., Man, DS., Grandis, JR. & Johnson, DE. (2009). Bortezomib up-regulates activated signal transducer and activator of transcription-3 and synergizes with inhibitors of signal transducer and activator of transcription-3 to promote head and neck squamous cell carcinoma cell death. Molecular Cancer Therapeutics, Vol 8, No (8), pp. 2211-2220. ISSN 1535-7163

Li, X., Di, B., Shang, Y., Zhou, Y., Cheng, J. & He, Z. (2009). Clinicopathologic risk factors for distant metastases from head and neck squamous cell carcinomas. European Journal Surgical Oncology, Vol 35, No 12, () pp. 1348-1358. ISSN 0748-7983

Li, X., Wang, H., Lu, X. & Di, B. (2010a). Stat3 blockade with shRNA enhances radiosensitivity in Hep-2 human laryngeal squamous carcinoma cells. Oncology Reports, Vol 23, No (2), pp. 345-353 ISSN 1021-335X

Li, X., Wang, H., Lu X. & Di, B. (2010b). Silencing STAT3 with short hairpin RNA enhances the radiosensitivity of xenograft human laryngeal squamous cell carcinoma in vivo. Experimental and Therapeutic Medicine, Vol 1, No (6), pp. 947-953 ISSN 1792-0981

Liu, G., Yuan, X., Zeng, Z., Tunici, P., Ng, H., Abdulkadir, IR., Lu, L., Irvin, D., Black, KL. & Yu, JS. (2006). Analysis of gene expression and chemoresistance of CD133+ cancer stem cells in glioblastoma. Molecular Cancer, Vol 5, No (67), pp. ISSN 1476-4598

Liu, Y., Lu, WL., Guo, J., Du, J., Li, T., Wu, JW., Wang, GL., Wang, JC., Zhang, X. & Zhang, Q. (2008). A potential target associated with both cancer and cancer stem cells: a combination therapy for eradication of breast cancer using vinorelbine stealthy liposomes plus parthenolide stealthy liposomes. Journal of Controlled Release, Vol 129, No (1), pp. 18-25. ISSN 0168-3659

Ma, S., Lee, TK., Zheng, BJ., Chan, KW. & Guan, XY. (2008). CD133+ HCC cancer stem cells confer chemoresistance by preferential expression of the Akt/PKB survival pathway. Oncogene, Vol 27, No (12), pp. 1749-1758 ISSN 0950-9232

Nowell, PC. (1976). The clonal evolution of tumor cell populations. Science, Vol. 194 No. (4260), pp. 23–28. ISSN 0036-8075

Odoux, C., Fohrer, H., Hoppo, T., Guzik, L., Stolz, DB., Lewis, DW., Gollin, SM., Gamblin, TC., Geller, DA. & Lagasse, E. (2008). A Stochastic Model for Cancer Stem Cell Origin in Metastatic Colon Cancer. Cancer Research, Vol. 68 No. (17), pp. 6932–6941. ISSN 0008-5472

Prince, ME., Sivanandan, R., Kaczorowski, A., Wolf, GT., Kaplan, MJ., Dalerba, P., Weissman, IL., Clarke, MF. & Ailles, LE. (2007). Identification of a subpopulation of cells with cancer stem cell properties in head and neck squamous cell carcinoma. Proceedings of the National Academy of Sciences of the United States of America, Vol. 104, No. (3), pp. 973–978. ISSN 0027-8424

Paget, S. (1989). The distribution of secondary growths in cancer of the breast. Cancer and Metastasis Reviews, Vol. 8 No. (2), pp. 98–101. ISSN 0167-7659

Rofstad, EK., Gaustad, JV., Egeland, TA., Mathiesen, B. & Galappathi K. (2010). Tumors exposed to acute cyclic hypoxic stress show enhanced angiogenesis, perfusion and metastatic dissemination. International Journal of Cancer, Vol. 127, No. (7), pp. 1535–1546. ISSN 0020-7136

Scadden, DT. (2006). The stem-cell niche as an entity of action. Nature, Vol. 441 No. (7097), pp. 1075–1079. ISSN 1078-8956

Selvendiran K, Bratasz A, Kuppusamy ML, Tazi MF, Rivera BK & Kuppusamy P. (2009). Hypoxia induces chemoresistance in ovarian cancer cells by activation of signal transducer and activator of transcription 3. International Journal of Cancer, Vol. 125, No. (9), pp. 2198–2204. ISSN 0020-7136

Shrime, MG., Gullane, PJ., Dawson, L., Kim, J., Gilbert, RW., Irish JC, Brown DH & Goldstein DP. (2010). The impact of adjuvant radiotherapy on survival in T1-2N1 squamous cell carcinoma of the oral cavity. Archives of Otolaryngolgoy Head & Neck Surgery, Vol. 136, No. (3), pp. 225–228. ISSN 0886-4470

Simon, AR., Rai, U., Fanburg, BL. & Cochran, BH. (1998). Activation of the JAK-STAT pathway by reactive oxygen species. American Journal of Physiology, Vol. 275, No. (6 pt 1), pp. c1640-1652. ISSN 0002-9513

Tang, SY., Whiteman, M., Peng, ZF., Jenner, A., Yong, EL. & Halliwell, B. (2004). Characterization of antioxidant and antiglycation properties and isolation of active ingredients from traditional chinese medicines. Free Radical Biology and Medicine, Vol. 36, No. (12), pp. 1575–1587. ISSN 0891-5849

Tobias, JS., Monson, K., Gupta, N., Macdougall, H., Glaholm, J., Hutchison, I., Kadalayil, L., Hackshaw, A. & UK Head and Neck Cancer Trialists' Group. (2010). Chemoradiotherapy for locally advanced head and neck cancer: 10-year follow-up of the UK Head and Neck (UKHAN1) trial. Lancet Oncology, Vol. 11, No. (1), pp. 66–74. ISSN 1470-2045

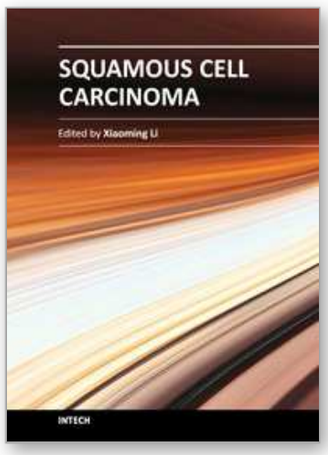
Tysnes, BB. & Bjerkvig, R. (2007). Cancer initiation and progression: involvement of stem cells and the microenvironment. Biochimica et Biophysica Acta, Vol. 1775 No. (2), pp. 283–297. ISSN 0006-3002

Vokes, EE., Weichselbaum, RR., Lippman, SM. & Hong, WK. (1993). Head and neck cancer. New England Journal of Medicine, Vol. 328, No. (3), pp: 184–94. ISSN 0028-4793

Werb, Z. & Evans, G. (2004). Oncogenes and cell proliferation: maintenance of genomic integrity, tumor stem cells, and the somatic microenvironment. Current Opinion in Genetics and Development, Vol. 14 No. (2), pp. 1–3. ISSN 0959-437X

Zhang, Q., Shi, S., Yen, Y., Brown, J., Ta, JQ. & Le, AD. (2009). A subpopulation of CD133(+) cancer stem-like cells characterized in human oral squamous cell carcinoma confer resistance to chemotherapy. Cancer Letters, Vol. 289 No. (2), pp. 151–160. ISSN 0304-3835

Zhou, L., Wei, X., Cheng, L., Tian, J. & Jiang, JJ. (2007). CD133, one of the markers of cancer stem cells in Hep-2 cell line. Laryngoscope, Vol. 117 No. (3), pp. 455–460. ISSN 0023-852X



Squamous Cell Carcinoma
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This book points to some new areas for investigation on squamous cell carcinoma (SCC). Firstly, the features and management of some specific SCC is discussed to give the readers the general principles in dealing with these uncommon and sophisticated conditions. Some new concepts in adjuvant therapy including neoadjuvant therapy and gold nanoparticle-based photo dynamic therapy are introduced. Secondly, a detailed discussion of molecular aspects of tumor invasion and progression in SCC is provided with the emphasis on the roles of some important factors. The role of tumor microenvironment in head and neck SCC is specifically discussed. Thirdly, the roles of cancer stem cells (CSC) in cancer therapy of SCC are described. Molecular mechanisms involving therapeutic resistance and new therapeutic strategies targeting CSC are discussed in detail. Finally, other aspects concerning SCC are included, which involve the assessment, genetic manipulation and its possible clinical implications for the treatment of SCC.

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