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HPV and CSC in HNSCC cisplatin resistance

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1. ABSTRACT

Cisplatin (DNA intercalator), a standard chemotherapy drug often used to treat head and neck squamous cellular carcinoma (HNSCC) has very low response rates in recurrent disease of HNSCC, this is a major clinical problem today. However, a valuable window to look in to the underlying molecular aspects of a favorable and unfavorable cisplatin response is offered by a distinct disease entity in HNSCC – HPV+ OPSCC. It responds far more favorably to cisplatin than non-HPV driven HNSCC. Another intriguing aspect of head and neck cancer biology is the emergence of the CD44+ cancer stem cell - the tumor initiating population that in all likelihood is the root cause of therapeutic resistance. The critical question is, are there any differences between the CD44+ CSC population of an HPV+ OPSCC and a non-HPV HNSCC? In this regard, the inverse relation between EGFR levels and HPV status in OPSCC may be a common thread that connects the better response rates of HPV+ OPSCC with the contribution of CD44+ stem cells of HNSCC to chemoresistance.

2. INTRODUCTION

Based on the histology, head and neck cancers are usually squamous cell carcinomas, the majority of which arise from the mucosa of the upper aerodigestive tract. This malignancy is sixth on the list of common cancers worldwide, the majority of patients diagnosed with HNSCC have advanced locoregional disease, and the five year survival rate is less than 40% in this group. Patients with HNSCC are treated with multi-modality therapy, which includes surgery, radiation with or without chemotherapy, along with targeted therapies. Most patients who succumb have loco-regional relapse rather than distant metastases (1-2). Cisplatin is a DNA intercalator, used as a major chemotherapy drug to treat HNSCC (3, 4). Cisplatin (cis-Diammineplatinum (II) dichloride) or CDDP, targets rapidly dividing cells, by either passively or actively diffusing into the cell to interact with the DNA.(5-10) It mostly binds with the guanine residues, leading to multiple inter and intra strand crosslinks, ultimately resulting in apoptosis.(11-13) Of significance is the very low percentage response (20-30%) to cisplatin that is seen in recurrent disease. (3, 4).

Cisplatin resistance offered by head and neck cancers is a major clinical problem that is being studied both from the basic research and the clinical research standpoint. While, the bench-top research is focused on molecular pathways that lead to cellular cisplatin resistance, clinical research is looking towards newer drug combinations, drug delivery routes, and prognostic indicators to better manage cisplatin resistance. Recently the direction of basic research includes studying cancer stem cells and their role in cisplatin resistance, a relatively new perspective as far as head and neck cancers are concerned.

On the clinical side, researchers have highlighted a rise in HPV associated head and neck cancers. This subgroup is largely oropharyngeal carcinoma (OPSCC). The growing OPSCC patient population is mainly composed of non-drinkers and non-smokers; the basic risk factors for developing other HNSCC. (14, 15) Most interestingly, HPV+ OPSCC patients respond much better than the HPV- HNSCC patients to cisplatin treatment (16-18).

At present, basic researchers have yet to firmly obtain evidence to implicate the cancer stem cells of HNSCC in cisplatin resistance. Similarly, clinicians have yet to fully explain the reason underlying the relatively better response rates of HPV+ OPSCC to cisplatin. In the future, these two rather distinct avenues of research in HNSCC may converge to yield a greater in-depth understanding of HNSCC cisplatin resistance. The following review is an attempt to connect these observations. We will first evaluate HPV and cancer stem cells under the purview of cisplatin response and then present a possible overarching molecular pathway to link the two to cisplatin resistance/sensitivity.

3. INFLUENCE OF HPV IN THE CHEMO RESPONSE OF OPSCC

There are more than one hundred different types of HPVs currently cataloged. (16, 17) The majority of these HPV types are not high risk, i.e. they do not cause malignant lesions. In head and neck cancers, it is the squamous cell carcinoma of the oropharyngeal region (OPSCC) that has the highest burden of HPV, mostly HPV16 and HPV18. (18) On following the incidence rates of various forms of head and neck cancers, it is the incidence of oropharyngeal squamous cellular carcinoma that is seen to be rising significantly and not Laryngeal Carcinoma. In the USA, the trend of higher incidence of OPSCC amongst many ethnic groups clearly started from 1998 and since then it has risen, as indicated by the SEER data available on the NCI website (See Figure 1A and 1B).

The major risk factors for acquiring HPV related OPSCC is now understood to be a consequence of orogenital sex and increased number of partners (19-22). The mechanism and the route by which HPV infects and causes malignant lesions are well understood in cervical carcinoma. HPV infects the basal layers of the squamous tissue, where progenitor cells are largely present. The cells of the basal layers are mitotically active and are a perfect site for lysogenic viruses like HPV to infect and integrate its DNA to the host cellular genome (23-26).

Upon infection, HPV perturbs the normal division of the basal cells by two key genes, namely E6 and E7. The HPV E6 gene marks p53 for degradation and thereby allows deregulated proliferation. E6 also targets telomerase activation via c-myc to lead to cellular immortality. Meanwhile, the HPV E7 gene inactivates pRb pathway to result in an unregulated proliferation. These precise functions of the E6 and E7 genes of HPV trigger the onset of an HPV driven OPSCC (25, 26).

A number of retrospective clinical studies have tried analyzing the puzzling, favorable survival rates associated with HPV driven OPSCC and they have always highlighted the significance of HPV as a prognostic indicator in OPSCC. Apart from Nodal status, T-stage, and Smoking (>10 packs per year), HPV status has been included as an independent prognostic indicator of survival in OPSCC patients. (29) As a result, over the last fifteen years, HPV+ OPSCC has been well studied, and its marked clinical and molecular differences from the non-HPV driven HNSCC (See Table 1) have been well documented in order to make it a distinct disease entity (27, 28).

However, the unanswered question is why HPV+ OPSCC has a relatively better prognosis when treated with chemoradiation compared to non-HPV HNSCC (18, 19 & 27). At the onset of non-HPV driven HNSCC, the tissue succumbs to constant genetic insults through exposure of tobacco and alcohol. This creates an area of genetically unstable cells, i.e. 'field cancerization.' In the case of HPV+ HNSCC, while the E6 and E7 genes immortalize infected cells, they do not create an area of genetically unstable cells. Since, the malignant transformation in HPV driven HNSCC is not dependent on random genome wide mutations that progressively selects for more aggressive and malignant cells, the level of genomic instability is much less in the case of HPV+ HNSCC as compared to non-HPV driven HNSCC. This could contribute towards the better prognosis. (28, 48) Also, the immune system of the host could recognize HPV infected cells and thereby eliminate them leading to a better prognosis. The one major drawback to this argument is that antibody production against the highly expressed p16 in HPV+ HNSCC is not significantly high. (45,46). While these represent the different viewpoints in the research community, it is also noteworthy that the HPV+ HNSCC tumors often have EGFR-lo status, and these cancers tend to respond much better than EGFR-hi HNSCC tumors. This indicates that reduced EGFR expression levels could also be a plausible reason for a favorable outcome during treatment. (31, 32)

4. INFLUENCE OF HNSCC CANCER STEM CELLS IN CHEMO RESPONSE

According to the cancer stem cell hypothesis, CSCs are believed to be resistant

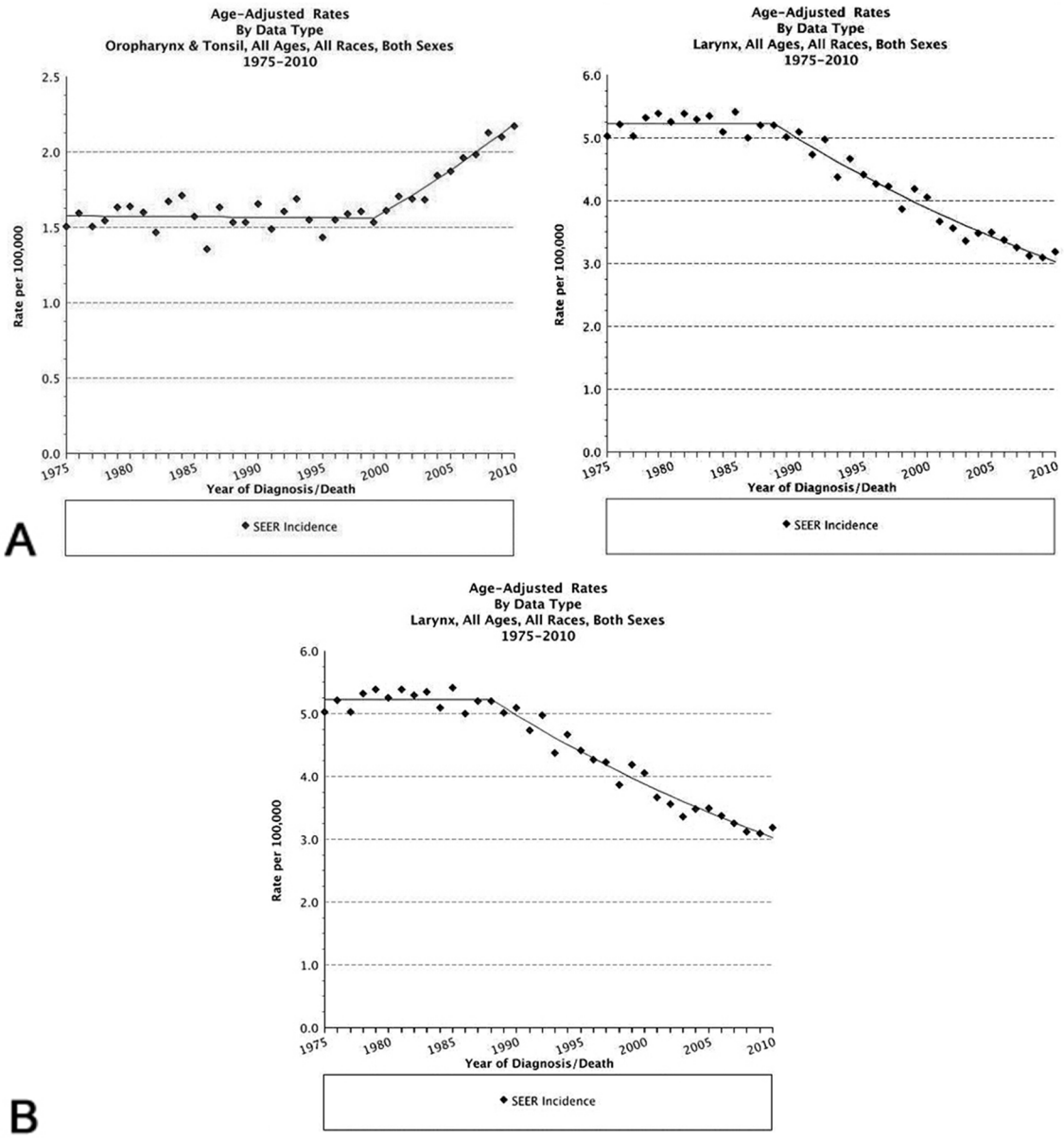

Figure 1. A. Cancer sites include invasive cases only unless otherwise noted. Rates are per 100,000 and age-adjusted to the 2000 US Std Population (19 age groups- Census P25-1130). Regression lines are calculated using the joinpoint Regression Program Version 4.0.3., April 2013, National Cancer Institute. Incidence source: SEER9 areas (San Francisco, Connecticut, Detroit, Hawaii, Iowa, New Mexico, Seattle, Utah and Atlanta). B. Cancer sites include invasive cases only unless otherwise noted. Rates are per 100,000 and age-adjusted to the 2000 US Std Population (19 age groups- Census P25-1130). Regression lines are calculated using the joinpoint Regression Program Version 4.0.3., April 2013, National Cancer Institute. Incidence source: SEER9 areas (San Francisco, Connecticut, Detroit, Hawaii, Iowa, New Mexico, Seattle, Utah and Atlanta)

to conventional therapeutic strategies like chemotherapy. (33) Although, this model strongly holds true for hematological cancers, there is evidence to suggest that some solid tumors may not have these same characteristics (34). It is important to consider the studies in HNSCC that directly or indirectly address the usefulness of markers that select specifically for a population of cells in a

Table 1. Key clinical and molecular differences between HPV^+ and non-HPV HNSCC

	HPV^+ HNSCC	Non- HPV HNSCC
Clinical differences	Favorable response to chemoradiation	Unfavorable response to chemoradiation
	Detected mostly in young adults	Detected mostly in older adults
	Detected late and usually Nodal positive	Not so
	Highly undifferentiated tumors	Not so
	Lower risk of second primary	Higher risk of second primary
	Overall loco-regional survival is higher	Overall loco-regional survival is much lower
Cellular and molecular differences	Genome is less unstable	Genome is highly unstable
	p53 wild-type but degraded by E6	p53 mutant
	p16 highly expressed	p16 not as highly expressed
	Tumor cells can suffer from hypoxia and undergo apoptosis	Not so

tumor that have cancer stem-like properties, which may possess the necessary molecular phenotype to resist conventional chemotherapy. The following figure (Figure 2) helps lay the basic ground work of cellular signaling circuits that interlink various CSC markers and their corresponding signaling cascades relevant to HNSCC. CSC markers such as, CD44, ALDH, c-Met and EGFR, all appear to be heavily interconnected via PI3K/AKT axis. This axis connects downstream effectors such as BMI-1, Nanog, Oct4 and XIAP that in turn switch on genes that help evade apoptosis, promote survival, and proliferation leading to chemoresistance.

CD44, a major CSC marker in HNSCC, is a transmembrane receptor for the ligand hyaluronan. (35, 36) Hyaluronan is a glycosaminoglycan that collaborates to form the extracellular matrix. There is now evidence that HA-CD44 interaction leads to the association of CD44 with EGFR. This interaction leads to the phosphorylation of EGFR resulting in the deployment of ERK 1 and ERK 2 which can potentially trigger cell growth, cellular migration and resistance genes against chemotherapy drugs like cisplatin, methotrexate, adriamycin etc. It also suggests that HA-CD44 interaction can employ EGFR and activate it without the need of an EGF molecule binding to it. (35) It provides a strong rationale to design drugs that inhibit HA-CD44 interaction and club it with anti-EGFR tyrosine kinase therapy to achieve much higher levels of sensitivity to chemotherapy. The key point here is the cells that find this alternate mechanism for chemotherapeutic resistance also express CD44 receptor.

The above mentioned workings of the CD44 expressing cells can be furthered characterized by additional findings of an action by HA-CD44 to phosphorylate and activate PLC-1, which in turn helps stimulate the formation of IP3. IP3 interacts with its cytosolic receptor to mobilize Ca2+ reserves in the cell, which can have a cytoprotectant effect, thereby developing resistance to cisplatin. (36) Again, this highlights the importance of CD44 expression in resistance to chemotherapy and the fact that CSCs (CD44+ cells) are the one's capable of protecting themselves under adverse conditions such as exposure to chemotherapy agents.

In another study, HNSCC cells that co-express CD44v3 and another CSC marker, ALDH1, were found to overexpress Oct4, Sox2, and Nanog, the three molecules that are associated with higher histological grades and poorer clinical survival in head and neck cancer. (37) Since these three molecules are intimately involved in self-renewal, proliferation, and differentiation, CD44v3-high ALDH1- hi cells are believed to be capable of seeding new tumor growth. A recent study indicated that CD44+ c-Met+ cells of HNSCC represent the population of cells that are spared from cisplatin treatment *in vivo*. It was also further confirmed that these CD44+ c-Met+ cells that were spared were capable of forming a secondary tumor as well. (40) These experiments imply that the characteristics of self-renewal, tumorgenicity, and cisplatin resistance are conferred upon CD44+ c-Met+ cells. Although, the molecular mechanism that permits c-Met+ cells to resist cisplatin treatment isn't clearly elucidated, this study does state that the BMI-1 gene was up

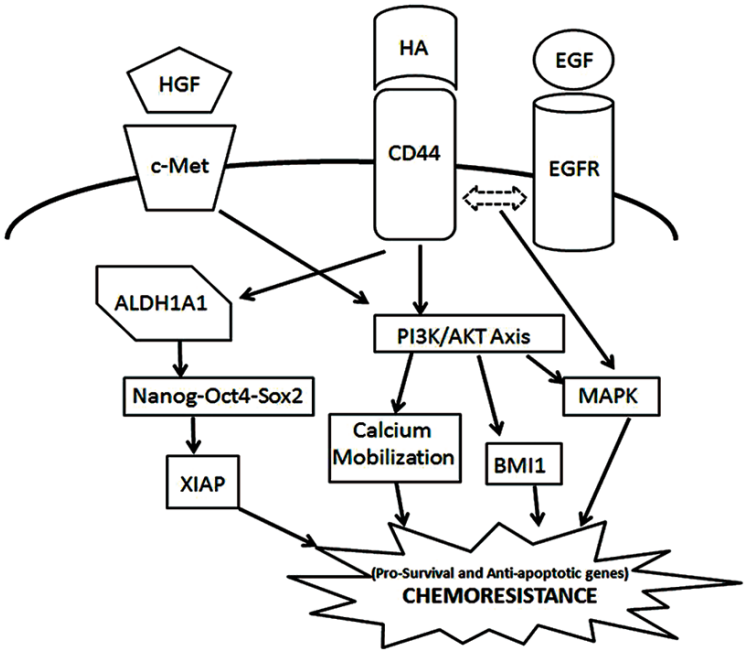

Figure 2. The Big picture – Pathways of Chemoresistance in CSCs of HNSCC. HA –Hyaluronan, HGF – Hepatocyte growth factor, EGF- Epidermal growth factor, ALDH1 – Aldehyde dehydrogenase 1, BMI1- B lymphoma Mo-MLV insertion region 1 homolog, XiAP- X-linked inhibitor of apoptosis protein , Nanog-Oct4-SOX2- Stemness related transcription factors, PI3K/AKT - Phosphatidylinositide 3-kinases/ Protein Kinase B (PKB) (MAPK- Mitogen activated kinase, Ca2+ - Calcium, c-Met- Hepatocyte growth factor receptor, EGFR - Epidermal growth factor receptor, CD44- Cluster differentiation 44, let-7a –Let-7 miRNA.

regulated in these cells. Reports also suggest that BMI-1 is highly enriched in CSCs and abnormal BMI-1 expression is detected in multiple CSC populations. (41) These observations bolster the hypothesis that the self-renewing and highly tumorigenic populations of HNSCC tumor cells are marked by CD44 and subsets of the CD44 population are the culprits in chemotherapeutic resistance.

5. BRIDGING THE TWO SCENARIOS: CSCS AND HPV IN HNSCC CHEMO RESPONSE

A key aspect of the cancer stem cell hypothesis is that CSCs originate from progenitor cells that have the capability to self-renew. In normal development, EGFR is employed to promote self-renewal and proliferation of adult stem cells. EGFR becomes tightly regulated or inactivated as they differentiate into progenitor cells. In cancer however, it is possible that certain mutations would cause EGFR to remain constitutively active even in the differentiated cells, resulting in maintenance or acquisition of self-renewal properties. (50, 51) We also know that the route HPV takes to infect and cause malignant lesions are at the basal layers of the squamous tissue, where progenitor cells are largely present.(27, 28) CSC marker combinations of CD44+EGFR-hi, CD44+ALDH1-hi and CD44+C-Met+ in HNSCC have shown the capability to offer resistance to chemotherapy (See Figure 2). The major converging point may be EGFR and its downstream activity. In HPV+ OPSCC, the EGFR dependent downstream pathways are less active, as compared to non-HPV HNSCC. (31-33) EGFR activity is essential for maintaining cancer stem-like state in HNSCC, and its interaction with CD44 (CD44v3 or one of the other variants) seems crucial for chemoresistance (35, 50, 51). The absent association of CD44 with EGFR, in the cancer stem cell compartment of the HPV+ tumors and the possible non-activation of its downstream signaling via ERK1 and ERK2, could be a strong molecular determinant in the relatively better response to chemotherapy seen in HPV+ OPSCC as compared to HPV-HNSCC (51).

Right now, a few factors that try to explain the relatively better prognosis of an HPV related OPSCC over non-HPV related HNSCC

are the fact that, HPV+ OPSCC patients have fewer co-morbidities i.e. they are much younger, are more than likely to be non-smokers, and have much smaller primaries, which improves overall prognosis for this cohort of head and neck cancer patients. (53, 54). Also, another crucial molecular factor possibly contributing to improved survival is that p53 and pRb are rendered dormant but not silenced via E6 and E7 genes. There is evidence that indicates that continued exposure to chemotherapy agents can down-regulate E6 and E7 genes which can in turn switch on the dormant p53 and pRb pathways. In Non-HPV HNSCC however, p53 and pRb are rendered inactive by loss of heterozygosity, point mutations, and promoter methylation, resulting in permanent loss of these crucial tumor suppressor pathways, conferring a progressively chemotherapy resistant phenotype to the tobacco-induced tumor. (47, 54) The immune system of the host could recognize HPV infected cells due to their increased expression of p16 and thereby eliminate them leading to a better prognosis.(45, 46) Although, these factors contribute towards a better prognosis in HPV related OPSCC, it doesn't completely add up and nor has it settled the debate of this phenomenon of better prognosis. Here, we feel that the cancer stem cell purview of HPV related OPSCC and its EGFR low status, along with the above mentioned factors give a holistic picture of the relatively better prognosis seen in HPV related OPSCC with conventional chemotherapy.

This knowledge about EGFR and its effect on CD44-Hyaluronan interaction will need much greater focus, as it holds the key to not only reveal the biology beneath the greater sensitivity of HPV+ OPSCC to chemotherapy but also shows the way to target the root of all resistance, the cancer stem cell compartment.

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