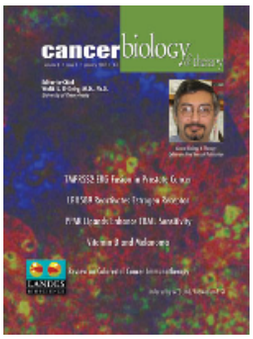

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Commentary

The Role of CD44 in HNSCC

Aaron D. Nelson[1]

Jennifer R. Grandis[1,2,*]

[1]Department of Otolaryngology and [2]Department of Pharmacology, University of Pittsburgh; Pittsburgh, Pennsylvania USA

*Correspondence to: Jennifer R. Grandis; Department of Otolaryngology and Department of Pharmacology, University of Pittsburgh; Pittsburgh, Pennsylvania 15213 USA; Tel.: 412.647.5280; Fax: 412.383.5409; Email: grandisjr@upmc.edu

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KEY WORDS

CD44, HNSCC, EGFR, isoform, cancer stem cell

Commentary to:

Characterization of CD44v3 Containing Isoforms in Head and Neck Cancer

E.P. Reategui, A. Antúnez de Mayolo, P.M. Das, F.C. Astor, R. Singal, K.L. Hamilton, W.J. Goodwin, K.L. Carraway and E.J. Franzmann

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Understanding the underlying molecular mechanisms that lead to tumorigenesis and tumor recurrence is paramount to developing targeted strategies for treatment of cancers. Head and neck squamous cell carcinoma (HNSCC) is commonly treated using multifaceted approaches including surgical resection in combination with radiation and chemotherapy. Unfortunately, these current treatments have a 50% success rate.[1] Grandis et al.[2] reported that HNSCC tumors overexpressed EGFR, suggesting that specific targeting of EGFR may lead to reduced tumor cell survival and subsequent tumor volume reduction. Administration of a monoclonal antibody targeting EGFR in conjunction with radiotherapy increased the rate of HNSCC patient survival; however tumor recurrence still remains an issue.[3] Therefore, it appears that better targets for therapeutic intervention are needed in HNSCC.

Significant advances have been made toward understanding the role that extracellular matrix proteins play in creating a microniche in which cancer cells are able to thrive. Extracellular proteins have been isolated and examined in vitro for their tumor promoting capabilities. Hyaluronan, which interacts with CD44 cell surface receptors, has previously been shown to increase CD44 cleavage and induce subsequent cell proliferation and motility.[4-6] Interestingly, CD44, in the presence of hyaluronan, interacts with EGFR, leading to increased activation of EGFR-dependent downstream signaling cascades.[7] These results suggest a role for CD44 in tumorigenesis and tumor recurrence.

The CD44 gene contains 10 exons which can be alternatively spliced to form virtually hundreds of different protein isoforms. These alternatively spliced proteins display different properties when compared with one another. For example, the novel CD44 splice variant CD44v6 has previously been shown to stimulate proliferation by sustaining MAP kinase levels.[8] Of the potentially hundreds of CD44 protein isoforms, very few have been studied extensively in human malignancies.

Perhaps the most widely studied CD44 isoform is CD44v6. This isoform has been linked to increased proliferation by sustained activation of MAP kinase[8] as well as inducing a Ras-mediated positive regulatory splicing loop, leading to continual CD44v6 splicing and subsequent sustained downstream Ras signaling.[9] One major caveat of these studies is that all results were obtained through in vitro analysis. Therefore, it is important that future studies include evaluation of human tumor samples to elucidate the importance of the microenvironment including the extracellular matrix which influences cell signaling dramatically.

In the study presented by Reategui et al. in this issue of *Cancer Biology &Therapy*, the authors demonstrate that CD44v3, a novel CD44 isoform previously unknown to be expressed in HNSCC, is present in both fresh HNSCC tumors as well as established HNSCC cell lines. This CD44 variant contains a growth factor binding site, thus making it a possible modulator of RTK activation and an attractive candidate target for future investigations and therapies. The study evaluates the expression of CD44v3 by RNA extraction and subsequent RT-PCR analysis. Comparisons of normal tumor margins, normal tissue, and tumor tissue demonstrated expression of CD44v3. One concern, as the authors state, is that the particular primers used in the study may not have specifically amplified CD44v3, but may have also amplified CD44v2-v3. Further studies are necessary to eliminate this possibility. Reategui et al. examined the proliferation kinetics and migratory behavior of CD44v3 transfected cells and found moderate increases in cell migration but not change in cell proliferation. EGFR has been implicated in chemotaxis and induction of cellular migration in HNSCC.[10] Therefore, further studies characterizing changes in EGFR expression status in the presence of CD44v3 overexpression are essential to our understanding of the role of CD44v3 in HNSCC.

CD44 has been shown to be expressed in a wide variety of malignancies and recently has been implicated as a marker of tumor-initiating cells.[11] The isolation of unique side

populations of cells by their ability to efflux Hoechst vital dye has ignited a new field of cancer stem cell biology. Multiple studies have now shown that this unique side population can be isolated from a variety of tumors, including breast, prostate, and glioblastoma among others.[11-13] Recently, a tail population was identified in HNSCC.[14] Chen et al. suggested that EGFR regulated this tail population observed by cellular efflux of Hoechst dye. Because CD44 may modulate EGFR, it remains to be determined whether specific isoforms of CD44 (i.e., CD44v3) plays a specific role in tumor initiation and activation of a cancer stem cell phenotype. A common theory in cancer stem cell biology is that of the stem cell hierarchy. Essentially, one cancer stem cell sits atop this hierarchy and is therefore capable of producing those cells commonly observed in tumors. Demonstration of this hierarchy has remained difficult in cancer biology perhaps due to abnormal alterations in the genetic makeup of the cancer cells. As an interesting note, CD44v3 is also expressed in those tumors capable of producing a unique side population of cells. Further defining the characteristics of these side populations in light of CD44 isoforms and receptor tyrosine kinases (RTKs) will be essential to better understanding what role this side population plays and whether a cellular hierarchy is modulated by these factors.

It remains unknown how critical CD44 and the specificity of isoform expression are to regular maintenance of the cell. For example, is it possible that different CD44 isoforms can substitute for one another? RNAi approaches to this problem in HNSCC may provide information that unique CD44 isoforms play a critical role in normal cellular function and that these roles cannot be substituted with other CD44 isoforms. In the study by Reteagui et al., the finding that CD44v3 is expressed in both HNSCC tumors as well as in HNSCC cell lines suggests that further analysis can be carried out using in vitro systems.

References

1. Goodwin WJ Jr.. Salvage surgery for patients with recurrent squamous cell carcinoma of the upper aerodigestive tract: when do the ends justify the means? Laryngoscope 2000; 110:1-18.
2. Grandis JR, Zeng Q, Drenning SD, Tweardy DJ. Normalization of EGFR mRNA levels following restoration of wild-type p53 in a head and neck squamous cell carcinoma cell line. Int J Oncol 1998; 13:375-8.
3. Bonner JA, Harari PM, Giralt J, Azarnia N, Shin DM, Cohen RB, Jones CU, Sur R, Raben D, Jassem J, Ove R, Kies MS, Baselga J, Youssoufian H, Amellal N, Rowinsky EK, Ang KK. Radiotherapy plus cetuximab for squamous-cell carcinoma of the head and neck. N Engl J Med 2006; 354:567-78.
4. Aruffo A, Stamenkovic I, Melnick M, Underhill CB, Seed B. CD44 is the principal cell surface receptor for hyaluronate. Cell 1990; 61:1303-13.
5. Itano N, Atsumi F, Sawai T, Yamada Y, Miyaishi O, Senga T, Hamaguchi M, Kimata K. Abnormal accumulation of hyaluronan matrix diminishes contact inhibition of cell growth and promotes cell migration. PNAS 2002; 99:3609-14.
6. Sugahara KN, Hirata T, Hayasaka H, Stern R, Murai T, Miyasaka M. Tumor cells enhance their own CD44 cleavage and motility by generating hyaluronan fragments. J Biol Chem 2006; 281:5861-8.
7. Wang SJ and Bourguignon LYW. Hyalurnona and the interaction between CD44 and epidermal growth factor receptor in oncogenic signaling and chemotherapy resistance in head and neck cancer. Arch Otolaryngol Head Neck Surg 2006; 132:771-8.
8. Marhaba R, Bourouba M, Zöller M. CD44v6 promotes proliferation by persisting activation of MAP kinases. Cellular Signaling 2005; 17:961-73.
9. Cheng C, Yaffe MB, Sharp PA. A positive feedback loop couples Ras activation and CD44 alternative splicing. Genes Dev 2006; 20:1715-20.
10. Huang SM, Li J, Harari PM. Molecular inhibition of angiogenesis and metastatic potential in human squamous cell carcinomas after epidermal growth factor receptor blockade. Mol Cancer Ther 2002; 1:507-14.
11. Patrawala L, Calhoun T, Schneider-Broussard R, Li H, Bhatia B, Tang S, Reilly JG, Chandra D, Zhou J, Claypool K, Coghlan L, Tang DG. Highly purified CD44+ prostate cancer cells from xenograft human tumors are enriched in tumorigenic and metastatic progenitor cells. Oncogene 2006; 25:1696-708.
12. Hirschmann-Jax C, Foster AE, Wulf GG, Nuchtern JG, Jax TW, Gobel U, Goodell MA, Brenner MK. A distinct "side population" of cells with high drug efflux capacity in human tumor cells. PNAS 2004; 101:14228-33.
13. Patrawala L, Calhoun T, Schneider-Broussard R, Zhou J, Claypool K, Tang DG. Side population is enriched in tumorigenic, stem-like cancer cells, whereas ABCG2+ and ABCG2- cancer cells are similarly tumorigenic. Cancer Res 2005; 65:6207-19.
14. Chen JS, Pardo FS, Wang-Rodriguez J, Chu TS, Lopez JP, Aguilera J, Altuna X, Weisman RA, Ongkeko WM. EGFR regulates the side population in head and neck squamous cell carcinoma. Laryngoscope 2006; 116:401-6.