CRITICAL RESEARCH PERIODICAL

FUT8: AN EMERGING DRIVER OF METASTASIS

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ABSTRACT

This critical research periodical is mainly based on critical review of research article titled "A Systems Biology Approach Identifies FUT8 as a Driver of Melanoma Metastasis" published in Cancer Cell by Agrawal et al[1]. Glycosylation is the distinct cell and microenvironment relatedmechanism establishing glycosidic linkages with major nutrients by the action of various enzymes. Meezan et al. described aberrant glycosylation in cancer in 1969 and since then it has been recognized that process of glycosylation is altered during cancer cell transformation and its progression[2]. The above mentioned research article is also part of continuation of this concept in which Agrawal et al. documented the role of glycosyl transferase FUT8 as a facilitator of metastasis in melanoma. This facilitation opens new avenues for scientists to develop novel therapies making core fucosylation as a target for metastatic tumors.

Keywords: FUT8; Metastasis; Glycosylation; Melanoma.

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STATE OF THE FIELD

Globally, melanoma is considered a lethal skin cancer due its poor prognosis and increased affinity to metastasis. Earlier these authors reported[3]

•The aberrant glycosylation as promoter of cancer cell invasion and immunosuppression.

•Up-regulation of miR-30b/d. This upregulation was observed by analyzing GALNT7 and GALNT1, inducers of O-linked glycan biosynthesis in metastatic signatures

In addition, previous studies[4,5] revealed that

•Melanoma metastasis can be influenced by altered fucosylation.

•The main role is played by the transcription factor ATF2 that overpower metastasis by modifying a-1, 2 fucosylation.

In light of above context, the process of glycosylation can be designated as fundamental mechanisms for regulating melanoma progression. It further facilitates aberrant glycosylation as driver of metastasis in melanoma. These findings open the avenues for future research on glycosylation in clinical samples rather the cell lines.

AIM OF THE PAPER

However, glycosylation has been considered in melanoma but all these studies were planned on animal models and cancer cell lines. None of the study was designed in clinical settings. Hence, the applicability of such findings to melanoma patients for cancer progression is still lacking. So authors used technique of lectin microarray and planned a clinical cohort to study the association between melanoma progression and altered glycosylation. This aim is part of research on an important enabling hallmark of invasion and metastasis but many recent studies cited aberrant glycosylation as a 'hallmark of cancer'. Literature evidently discussed glycosylation as a distinctive feature that is causally related with the attainment of all capabilities to be designated as a hallmark[6,7].

BRIEF SUMMARY OF THE RESULTS

Agrawal et al. accomplished a comprehensive glycome analysis of melanoma patients and established anassociation of N-glycans with alpha-1,6 core fucosylation hence translating this association to its affinity towards metastasis. Melanoma samples revealed substantial alterations in glycosyltransferase transcription, in terms of amplification and reduction of expression of enzymes. Among them, a-1,2 fucosylation (FUT1, FUT2) was showing decreased expression while amplification was shown by polylactosamine extension enzyme (B3GNT2), N-glycan branching enzymes (MGAT2, MGAT4A) and sialyltransferases (ST6GAL1, ST6GAL2). This study publicized increased manifes-

tation of fucosyltransferase FUT8 in metastatic melanoma than non-metastatic tumors, enlightening the improved manifestation of alpha-1,6 core fucosylation. TGIF2 (Tumor Growth Factor β-induced factor homeobox 2) was made responsible for regulation of gene expression of FUT8. The System based strategies used by authors substantially appreciated the contribution of glycome, glycoproteomeand its variants during disease advancement and cancer therapeutics. These methodologies will nurture the basis of development of innovative strategies in cancer therapy. One such potential strategy would be the glyosylation variations studies of L1CAM by directing FUT8 (fucosyltransferase) in metastatic melanoma.

MAJOR CONTRIBUTIONS

In author's view, major contribution of this paper to science is to establish the role of fucosyltransferase FUT8 as therapeutic target for metastases. The main strength of the paper is use of avant-garde contemporary methodologies. Accompanying this, establishing the contributory role of FUT8, strengthening core fucosylation as a precariousmediator in alteration of cancer cells to a new host environment and ascertaining specific target proteins whose aberrant core fucosylation converse belligerent conduct to melanoma cells were described. Additionally, these approaches are unique in a sense that clinical samples (Tissue Melanoma samples) were used rather than mouse models or cell lines which lead to the authenticity of FUT8 as driver of metastasis.

FUTURE RESEARCH QUESTIONS

1. As glycans and glycoconjugates intercede in several stages of tumor progression, the cellular biosynthetic machinery tangled in glycan biosynthesis and modification establishes a promising target for cancer treatment. Future focus should be on the definition of specific glycosylation inhibitors that can target a pro-metastatic biological function or impede with the modulation of the immune response.
2. Fucosylation is one of the most common modifications involving oligosaccharides on glycoproteins or glycolipids. Increased levels of fucosylation have been reported in a number of pathological conditions, including inflammation and cancer. As a next step, levels of cellular fucosylation by lectin blot can be determined in other cancers like Pancreatic and inflammatory breast cancer.
3. Exceedingly metastatic melanoma cell lines condensed their invasive aptitude without stirring proliferation by FUT8 silencing. This is in divergence to findings in both non-small cell lung and hepatocellular carcinoma where FUT8 silencing was expressing anti-proliferative behavior. Silencing FUT8 abridged spreading of melanoma cells to the lungs and repressed the growth of pre-seeded metastases in liver, brain, and kidney, suggestive of that core fucosylation may be obligatory for the alterations that disseminated cancer cells endure to survive in "foreign" tissues. However, FUT8 silencing did not influence the growth of primary melanoma. So FUT 8 silencing effects can be observed in other tissue samples of metastatic cancers.

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CONFLICT OF INTEREST

Authors declare no conflict of interest.

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