Editorial

Fucosyltransferase 8 as a driver of melanoma metastasis: a new target for melanoma therapy?

Chi-Huey Wong, Tsui-Ling Hsu

The Genomics Research Center, Academia Sinica, Taipei, Taiwan

Correspondence to: Chi-Huey Wong. The Genomics Research Center, Academia Sinica, 128 Academia Road, Section 2, Nankang District, Taipei, Taiwan. Email: chwong@gate.sinica.edu.tw.

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Protein glycosylation is a complex post-translational modification process, often affecting protein folding and function, but it has not been well understood due to the lack of effective tools for the study of this process. Most of glycolipids and glycoproteins are found on the surface of cells and their glycosylation states influence intercellular recognition events, including, for example, bacterial and viral infection, differentiation and development, cancer metastasis *et al.* However, the relationship between aberrant glycosylation and disease progression, especially in cancer, has not been well defined at the molecular level until the most recent advances in glycoscience research, including the methods developed for glycan synthesis, structural analysis and functional study, that have enabled the identification of aberrant glycosylation related to diseases (1,2). However, most of the studies still focus on the analysis of glycoconjugates from cell lines and mouse models, and there is little information about the study of aberrant glycosylation in clinical samples.

The article by Agrawal *et al.* (3) reported a systems biology study of glycomic changes and corresponding enzymes associated with melanoma metastasis in patient samples. Despite recent improvement of therapies, including the use of immune checkpoint inhibitors to target PD-1, metastatic melanoma remains mostly an incurable disease. So identification of new targets for development of new therapeutics against metastatic melanoma becomes an important task. Agrawal *et al.* (3) first utilized a microarray of 102 lectins and antibody probes to examine the glycomic profiles of formalin-fixed paraffin-embedded patient-matched primary and metastatic tissues from 17 patients and 34 samples to identify the differences between normal and disease tissues. It was found that metastatic tumors showed higher levels of multi-antennary N-glycans with terminal N-acetyllactosamines repeats (recognized by the lectins DSA and WGA), α-2,6-sialic acid (recognized by the lectins SNA and TJA-I) and core fucose (recognized by PSA and LcH) and lower levels of α-1,2-fucose structures (recognized by UEA-I, TJA-II, and SNA-II) than the primary samples. These results were further corrected with glycogene data and showed that the metastatic melanomas displayed higher expression levels of N-glycan branching enzymes (MGAT2, MGAT4A), polylactosamine extension enzyme B3GNT2, sialyltransferases ST6GAL1 and ST6GAL2, and the core fucosyltransferase FUT8 than primary tissues and lower levels of enzymes responsible for α-1,2-fucosylation (FUT1 and FUT2). The authors further studied the effect of corresponding glycans by silencing the corresponding glycogenes in two human melanoma cell lines (SkMel147 and WM3211) and showed that FUT8 knockdown suppressed the invasion capacity of melanoma cells but knockdown of FUT1 or FUT2 had the opposite effect. The higher mRNA levels for FUT8 and lower mRNA levels for FUT1 and FUT2 were also found in metastatic melanoma tissues. Immunohistochemistry (IHC) analysis of the primary and disease tissues further

confirmed higher FUT8 expression in perinuclear granular staining. In addition, FUT8 knockdown had no effect on cell proliferation but attenuated the invasion ability by ~60%, and using a xenograft model of metastasis, FUT8 knockdown inhibited the metastatic potential of 113/6-4L (4L) cells carrying a luciferase reporter as demonstrated by the reduced luminescence in both lung and lymph nodes. It was further revealed that FUT8 silencing impairs the growth of established metastasis in mice injected with 4L melanoma cells stably transduced with lentiviral particles carrying a doxycycline (DOX)-inducible shRNA targeting FUT8 and a luciferase reporter vector expressing GFP. The finding that FUT8 knockdown had no effect on cell proliferation *in vitro* is interesting as two studies reported previously showed a significant inhibition of proliferation in non-small cell lung cancer (4) and hepatocellular carcinoma (5).

The results reported by Agrawal *et al*. support FUT8 inhibition as a viable therapeutic strategy against melanoma. The authors continued the study to identify a list of transcription factors that upregulate FUT8 using both in silico analysis and those shown to bind the FUT8 promoter using the ChIP Enrichment Analysis database. Of the transcription factors identified, TGIF2 was found to exhibit a 5-fold reduction of *in vitro* invasion when the 4L melanoma cells were transfected with siTGIF2; and its binding to FUT8 promoter was also found to correlate with FUT8 expression. So, TGIF2 was suggested to be a key regulator of FUT8 transcriptional induction in melanoma metastasis. Finally, to identify the core-fucosylated glycoproteins as regulators of invasion and metastasis, the authors performed the proteomic analysis of core-fucosylated membrane proteins extracted and enriched by LcH lectin chromatography from three melanoma cell lines, followed by mass spectrometric analysis and filtering of contaminant proteins. As a result, 114 proteins were found common to all three cell lines. Further analysis of these proteins, neural cell adhesion molecule L1 (L1CAM) was identified to be a possible mediator of the pro-invasion effects of FUT8, because it was known to regulate cell attachment, invasion and migration in several cancers and thus may promote melanoma progression. The authors then showed that FUT8 overexpression increased cell invasion 5-fold in a poorly invasive cell line and silencing of L1CAM strongly reduced the pro-invasive effects of FUT8 overexpression. In addition, overexpression of FUT8 was found to protect L1CAM from cleavage by a protease, which was thought to be plasmin. In a related study, core fucosylation was also negatively regulated by N-acetylglucosaminyltransferases (GnTs), especially GnT V-modified multi-antennary N-glycans (6), and by alkynyl fucose probes or fluorinated fucose (7).

Overall, for the first time, this study revealed the role of FUT8 in melanoma metastasis, and identified L1CAM as the main target of FUT8 catalyzed core fucosylation to promote metastatic outgrowth. Cleavage or silencing of L1CAM was found to impair its function as promoter of metastasis. Though core-fucosylation is a common protein glycosylation reaction and its activity is elevated in ovarian and liver cancers and related to EGFR dimerization, TGF-β activation, HGF and EGF signaling, and proliferation of non-small cell lung cancer (4) and hepatocellular carcinoma (5), the role of FUT8 in metastatic melanoma reported by Agrawal *et al.* provided a new understanding of core fucosylation in the progression of this incurable disease and a new strategy for drug discovery. Since FUT8 may be required for the core fucosylation of both normal and disease-associated proteins, a major challenge is to develop a selective or specific inhibitor of FUT8-catalyzed fucosylation of L1CAM or TGIF2-mediated FUT8 upregulation, and validate these proteins as targets for the development of new therapies against metastatic melanoma.

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Footnote

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