THE DIVERSITY AND FUNCTIONALITY OF THE CANCER GLYCOME: MOLECULAR MECHANISMS AND CLINICAL IMPLICATIONS

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Alterations of glycosylation in the tumour and its microenvironment are common molecular alterations with major biological implications for disease progression [1]. Cancer is a heterogeneous and complex disease that requires the understanding of the different components underlying the biology of the tumour. Alterations of glycosylation, such as the overexpression of sialylated glycans are common molecular features during carcinogenesis with major biological implications during cancer progression [1]. This presentation will report on the basis of alterations of glycosylation that occur in gastric cancer (GC). Recent results applying glycomic and glycoproteomic strategies have provided key information regarding the alterations of glycosylation occurring in cancer cells and their impact the activation of oncogenic receptors tyrosine kinase (RTK) in tumour samples, such as EGFR and HER2 (ErbB2) [2,3]. We demonstrate that ErbB2 is modified with both α2,6- and α2,3-sialylated glycan structures in GC. Glycomic and glycoproteomic of ErbB2's ectodomain disclosed a site-specific glycosylation profile in GC cells, in which the sialyltransferase ST6Gal1 specifically targets ErbB2 N-glycosylation sites occurring within the receptor's binding domain of the therapeutic antibody used in the clinics [2]. Abrogation of ST6Gal1 reshaped the cellular and ErbB2-specific glycosylation, expanded the cellular half-life of the ErbB2 receptor, and sensitized ErbB2-dependent GC cells to therapeutic antibody-induced cytotoxicity through the stabilization of ErbB dimers at the cell membrane, and the decreased activation of both ErbB2 and EGFR RTKs [2]. These results highlight the functional aspects of sialylated glycoforms occurring in cancer and supports their potential application of glycans as biomarkers for patient stratification [1,3,4,5]. Recent advances in cancer patient-derived organoids and their glycosylation will also be presented as models for cancer targeted therapies.

References:

1. S. Mereiter et al., *Cancer Cell.* **2019**, 36(1), 6-16.
2. Duarte, HO. et al. *Oncogene.* **2021**, 40(21), 3719-3733.
3. Rodrigues JG, et al. *Cell Oncol.* **2021**, 44(4), 835-850.
4. Martins ÁM, et al., *Advanced Science*. **2023**, 10(24), e2300588.
5. Poças J, et al., *Proc Natl Acad Sci U S A*. **2023**, 120(20), e2214853120.