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MOLECULAR RECOGNITION OF MUC1 TUMOR-ASSOCIATED CARBOHYDRATE ANTIGENS BY HUMAN MACROPHAGE GALACTOSE-TYPE LECTIN

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Glycans play a fundamental role in a variety of biological processes. Glycan-mediated interactions are also present in diverse disease mechanisms namely in the immune system.[1] MUC1 shows a tandem repeating protein domain of 20 amino acids (HGVT*S*APDT*RPAPGS*T*APPA) with five possible O-glycosylation sites. In normal tissue, MUC1 is extensively O-glycosylated with a α-O-GalNAc-unit directly linked to the hydroxyl group of serine (Ser) or threonine (Thr).[2] In cancer cells MUC1 expression is overexpressed and the glycans are severely truncated. Hence, MUC1 tumor-associated carbohydrate antigens (TACAs) as Tn (αGalpNAc(1-O-Ser/Thr), T (αGalp(1-3)-αGalpNAc(1-O-Ser/Thr)), which may also be sialylated such as ST (αNeu5Ac(2-3)-βGal(1-3)-αGalpNAc(1-O-Ser/Thr) and STn (αNeu5Ac(2-6)-αGalNAc(1-O-Ser/Thr)), are now exposed to the immune system, boosting the design of glycan-based cancer vaccines and new tools for cancer diagnosis.[3] The human macrophage galactose C-type lectin (MGL), present in dendritic cells (DCs) and macrophages, binds both Tn-motifs of tumor cells and T cells via the mucin-type glycoproteins.[4] We recently reported the binding modes of Gal/GalNAc and the structural elements of the molecular recognition process of Tn-antigen by MGL.[5] However, the precise chemical epitopes of MGL towards MUC1 glycoproteins are still poorly characterized. Therefore, we extended molecular recognition of MUC1 TACAs by MGL to MUC1 Tn-antigens at the distinct peptide regions, as well as, to a more complex library of MUC1 TACAs including the core-2 and T-antigen and the distinct sialylated forms of Tn and T. Herein, we will report new structural insights into MGL recognition event with potential application on development of novel anticancer vaccines or molecular probes for cancer diagnosis. [1]. Avci, F. Y.; Kasper, D. L.. Annu. Rev. Immunol. 2010, 28, 1, 107–130. [2] Hanisch, F-G.; Müller, S.; Glycobiology 2000, 10, 439–449. [3] Gaidzik N.; Westerlind U.; Kunz, H. Chem. Soc. Rev. 2013, 42, 4421-4442. [4] Van Vliet S. J.; Gringhuis S. I., Geijtenbeek T. B. H.; Van Kooyk, Y. Nat. Immunol. 2006, 7, 1200–1208. [5] Marcelo F., Garcia-Martin F., Matsushita T., Sardinha J., Coelho H., Oude-Vrielink A., Koller C., André S., Cabrita E. J., Gabius H.-J., Nishimura S.-I., Jiménez-Barbero J., Cañada F. J. Chem. Eur. J. 2014, 20, 16147-16155. VIP Paper Acknowledgments: Helena Coelho thanks to FCT-Portugal for the project EXPL/QEQ-MED/0799/2012, TOLLerant H2020-MSCETN-642157 European Project and to UCIBIO funding UID/Multi/04378/2013 co-financed by the ERDF under the PT2020 Partnership Agreement (POCI-01-0145-FEDER-0077. The NMR spectrometers are part of the National NMR Network (RNRMN) and are funded by FCT-Portugal (RECI/BBB-BQB/0230/2012).