Hemorrhagic Virus: towards binding inhibition

Macrophage type lectin-galactose ligands: chemical synthesis

João Manuel de Barros[a]*, Filipa Marcelo[b], Amélia P. Rauter[a]

[a] *Centro de Química e Bioquímica, Faculdade de Ciências, Universidade de Lisboa, Ed C8, Piso 5, Campo Grande, 1749-016 Lisboa, Portugal*

[b] *Unidade UCIBIO, Departamento de Química, Faculdade de Ciências e Tecnologias, Universidade Nova de Lisboa, Quinta da Torre, 2829 -516 Caparica, Portugal*

**jmvbarros@fc.ul.pt*

CQB Centro Química e Bioquímica

Ciências ULisboa

Introduction

Filoviruses, like Marburg and Ebola viruses, cause hemorrhagic diseases in humans and non-human primates with high rate of mortality.

The macrophage galactose C-type lectin (MGL) binds to Ebola or Marburg virus glycoprotein (GP). The interaction occurs via the GalNAc residue directly linked to Ser/Thr side chains on the GP of the virus and promotes viral infectivity *in vitro*, by enhancing viral attachment to cellular entry receptors [1]. Furthermore, MGL is present on cells known to be major targets of filoviruses (i.e., macrophages and dendritic cells), suggesting a role for this receptor in viral replication *in vivo*. In this context, the interactions of Gal (I), GalNAc (II), with tumor-associated MUC1 glycopeptides and MGL have been disclosed (Figures 1 and 2) [2].

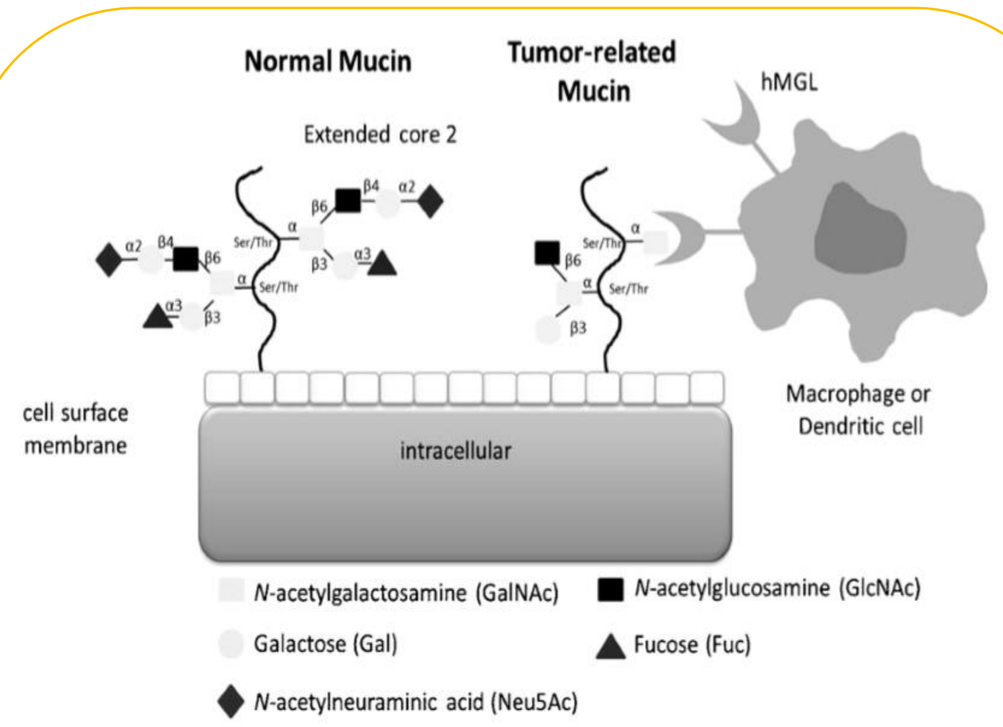


Figure 1. Interaction of MUC1 structures expressed on tumor cells with MGL, which specifically binds to MUC1-Tn on the cancer cell surface. In contrast, MUC1 in normal epithelial cells, carrying elongated and branched *O*-glycans, is much less reactive [2].

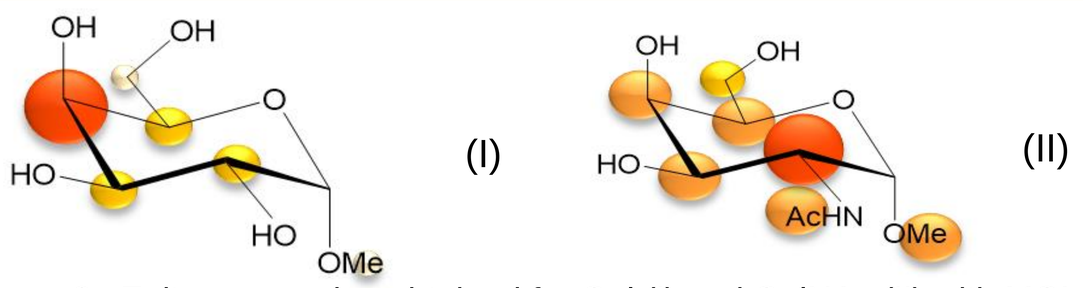
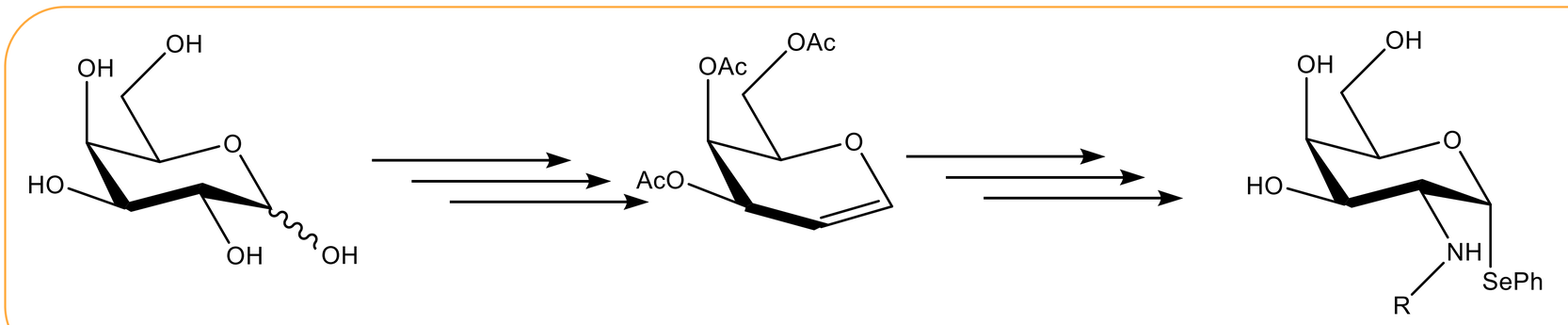


Figure 2. Epitope mapping obtained for Gal (I) and GalNAc (II) with MGL [2].

Within this project we are synthetizing mimetics of GalNAc (Scheme 1), which has better affinity for MGL than Gal. The first mimetics are phenylselenyl galactosides bearing imide functionality at position 2, expecting a higher binding affinity towards MGL receptor than GalNAc itself, therefore competing to the interaction between the MGL and the GP of Ebola or Marburg filovirus. The synthetic strategy is outlined in Scheme 1 starting from D-galactose, leading to phenylselenyl 2-deoxy-2-*N*-acylgalactosides.



Scheme 1. Synthetic strategy for the first GalNAc mimetics.

NMR spectroscopy has demonstrated its suitability to provide structural and dynamics information, at an atomic level, of carbohydrate-protein complexes [3]. The interaction of GalNAc mimetics and MGL lectin receptor will be monitored by NMR binding studies in combination with molecular modelling simulations, to clarify the key interacting features of the new molecules. NMR data of the new glycomimetics, including affinity data, will be compared with those of natural GalNAc ligand. A library of GalNAc mimetics with optimized structural features will be generated aiming to maximal binding affinity. NMR interaction studies with tumor-associated MUC1 glycopeptides complete the research.

Acknowledgments

FCT Fundação para a Ciência e a Tecnologia
MINISTÉRIO DA CIÊNCIA, TECNOLOGIA E ENSINO SUPERIOR

This work is supported by Fundação para a Ciência e a Tecnologia (FCT), Portugal (Project UID/MULTI/00612/2013)

References

[1] Takada, A., Fujioka, K., Tsuiji, M., Morikawa, A., Higashi, N., Ebihara, H., Kobasa, D., Feldmann, H., Irimura, T., Kawaoka, Y., (2004) Human Macrophage C-Type Lectin Specific for Galactose and N-Acetylgalactosamine Promotes Filovirus Entry, J. Virology, 78, 2943-2947;

[2] 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., (2014) Delineating binding modes of Gal/GalNAc and structural elements of the molecular recognition of tumor-associated mucin glycopeptides by the human macrophage galactose-type lectin, Chem. Eur. J. 20, 16147-16155. VIP Paper.

[3] Fernández-Alonso M. C., Díaz D., Berbis M. A., Marcelo F., Jiménez-Barbero J., (2012) Protein-carbohydrate interactions. From molecular recognition to drug design. Curr. Protein Pept. Sci., 13, 816-830.