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Current Status of Fucanomics and Galactanomics in Drug Discovery and Glycomics

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Abstract

Although many biomedical applications for sulfated fucans and galactans have been discovered over the past two decades, only in inflammation, hemostasis, and vascular biology and their mechanisms of actions have been satisfactorily elucidated to a real contribution in drug development. Moreover, advanced structure-function relationships have been achieved only for the anticoagulant and antithrombotic activities, in which glycans of well-defined structures have been assayed. Here, the current status, and the remaining challenges of fucanomics and galactanomics in drug discovery and in glycomics are presented.

Keywords: Angiogenesis; Cancer; Hemostasis; Inflammation; Sulfated galactans; Sulfated fucans

Introduction

Sulfated fucans (SFs), including the well-known brown algal fucoidans, and sulfated galactans (SGs), including the widely studied red algal carrageenans and agarans, are relatively young classes of glycans under study in glycomics. They can be found in algae (SFs are exclusively from brown algae whereas SGs can be found either in green or red algae) and invertebrates such as sea-cucumber and sea-urchins. The increasing interest on these types of glycans over the last twenty years has occurred mostly because of their potential biomedical properties [1-3]. This was also accompanied by the natural technological evolution in glycomics or its sub-projects [4,5]. Some SFs and SGs, essentially those from invertebrates and red algae, exhibit a very rare pattern of well-defined chemical structures (Table 1), which has been also a reason to the growing interest of studies on these glycans. This structural regularity not only makes easier characterization works, but also leads to accurate structure-function correlations [1,2]. The range of therapeutic actions of SFs and SGs is impressively broad. They include benefits in inflammation, nociception, hemostasis, vascular biology, oncology, oxidative-stress, and virus infections [3].

Mechanisms of Actions

Despite the several clinical systems in which SFs and SGs have been reported to be active, trustworthy explanations about the molecular mechanisms of action have been proposed only for inflammation, hemostasis, vascular biology, and cancer [3]. In their anti-inflammatory actions, SFs and SGs are capable to interact specifically with P- and L-selectins (curiously, not E-selectins) [6] and very likely with chemokines that express heparin-binding motifs [3]. These inhibitory interactions abrogate the trafficking, activation, and the resultant infiltration process of leukocytes to the sites of inflammation. Furthermore, the specificity of interactions with just certain types of selectins collaborates towards selectivity in action of these drug candidates.

In anticoagulation and antithrombosis, certain SFs and SGs can interact directly with the serpins, antithrombin and heparin cofactor II, as well as with pro-coagulant and pro-thrombotic proteases, like thrombin and factor xa [7]. These molecular interactions lead to the inhibition of the proteases either through a template-modulated mechanism or through an allosteric-modulated mechanism in ratios over one order of magnitude when compared to the physiological condition without the exogenous glycan [3,8].

The anti-angiogenic effect of the SFs and SGs is the main route for their anticancer properties, although some of these glycans have shown the ability to additionally reduce *in vitro* the cell-adhesion capacity of certain highly metastatic cancer cell lines [9]. However, no molecular mechanisms underlying this latter effect have been proposed so far. The mechanisms involved in antitumor angiogenesis reside mainly in the inhibition of the basic fibroblast growth factor, and vascular endothelial growth factor, either through direct interactions with them, or with their receptors [6]. The inhibition process of these pro-angiogenic factors disturbs the appropriate balance that feeds the cell differentiation required to supply the neovascularization.

The Contribution of the Well-defined Structures

Although some attempts to establish a minimal structure-function relationship in the above-mentioned clinical actions have been made [6,9] structural determinants of SFs and SGs have been accurately proposed only for their anticoagulant and antithrombotic properties [1-3]. This is a consequence of two factors. Firstly, hemostasis and vascular biology are the most studied and explored clinical systems for these molecules. This happens because of the pressing need of alternative agents to heparin, together with the elevated demand of new therapeutics due to the high incidence of thromboembolic diseases worldwide. Secondly, up-to-now the SFs and SGs of well-defined structures (Table 1) have been assayed only in these clinical systems. From these studies, the mechanistic influences of sulfation patterns monosaccharide types and conformational preferences have been pointed out [10,11]. Consequently, advanced structure-function relationships have been proposed [1,2]. These achievements comprise really breakthroughs towards drug development in fucanomics and galactanomics, since they provide the structural requirements of SFs and SGs necessary to reach certain levels of clinical effectiveness [2].

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Species (Class)	Structure
Ludwigothuria grisea (Holothurioidea)	$[\rightarrow 3)$-α-L-Fucp-2,4di(OSO_3^-)-$(1\rightarrow 3)$-α-L-Fuc*p*-$(1\rightarrow 3)$-α-L-Fuc*p*-2(OSO_3^-)-$(1\rightarrow 3)$-α-L-Fuc*p*-2(OSO_3^-)-$(1\rightarrow]_n$
Strongylocentrotus purpuratus I (Echinoidea)	80% $[\rightarrow 3)$-α-L-Fuc*p*-2,4di(OSO_3^-)-$(1\rightarrow]_n$ and 20% $[\rightarrow 3)$-α-L-Fuc*p*-2(OSO_3^-)-$(1\rightarrow]_n$
Strongylocentrotus purpuratus II (Echinoidea)	$[\rightarrow 3)$-α-L-Fuc*p*-2,4di(OSO_3^-)-$(1\rightarrow 3)$-α-L-Fuc*p*-4(OSO_3^-)-$(1\rightarrow 3)$-α-L-Fuc*p*-4(OSO_3^-)-$(1\rightarrow]_n$
Strongylocentrotus franciscanus (Echinoidea)	[3)-α-L-Fuc*p*-2(OSO_3^-)-$(1\rightarrow]_n$
Strongylocentrotus droebachiensis (Echinoidea)	$[\rightarrow 4)$-α-L-Fuc*p*-2(OSO_3^-)-$(1\rightarrow]_n$
Strongylocentrotus pallidus (Echinoidea)	$[\rightarrow 3)$-α-L-Fuc*p*-2(OSO_3^-)-$(1\rightarrow 3)$-α-L-Fuc*p*-2(OSO_3^-)-$(1\rightarrow 3)$-α-L-Fuc*p*-$(1\rightarrow 3)$-α-L-Fuc*p*-$(1\rightarrow]_n$
Lytechinus variegatus (Echinoidea)	$[\rightarrow 3)$-α-L-Fuc*p*-2(OSO_3^-)-$(1\rightarrow 3)$-α-L-Fuc*p*-2(OSO_3^-)-$(1\rightarrow 3)$-α-L-Fuc*p*-4(OSO_3^-)-$(1\rightarrow 3)$-α-L-Fuc*p*-2,4di(OSO_3^-)-$(1\rightarrow]_n$
Arbacia lixula (Echinoidea)	$[\rightarrow 4)$-α-L-Fucp-2(OSO_3^-)-$(1\rightarrow 4)$-α-L-Fucp-2(OSO_3^-)-$(1\rightarrow 4)$-α-L-Fucp-$(1\rightarrow 4)$-α-L-Fucp-$(1\rightarrow]_n$
Echinometra lucunter (Echinoidea)	$[\rightarrow 3)$-α-L-Galp-2(OSO_3^-)-$(1\rightarrow]_n$
Glyptosidaris crenularis (Echinoidea)	$[\rightarrow 3)$-β-D-Galp-2(OSO_3^-)-$(1\rightarrow 3)$-β-D-Galp-$(1\rightarrow]_n$
Botryocladia occidentalis (Rodophyta)	$[\rightarrow 3)$-β-D-Galp-2R_1-4R_2-$(1\rightarrow 4)$-α-L-Galp-2R_3-3R_4-$(1\rightarrow]_n$, where $R_{1\text{-}4}$ = OSO_3^- or OH, R_1 and R_2 = OSO_3^- in ~66%, and ~33%, respectively.
Gelidium crinale (Rodophyta)	$[\rightarrow 3)$-β-D-Galp-2R_1-4R_2-$(1\rightarrow 4)$-α-L-Galp-2R_3-3R_4-$(1\rightarrow]_n$, where $R_{1\text{-}4}$ = OSO_3^- or OH, R_1 and R_2 = OSO_3^- in ~60%, and ~15%, respectively.
Styela plicata (Ascidiacea)	$\{\rightarrow 4)$-α-L-Galp-2$[\rightarrow 1)$-α-L-Galp]-3(OSO_3^-)-$(1\rightarrow\}_n$
Hedmania monus (Ascidiacea)	$[\rightarrow 4)$-α-L-Galp-3(OSO_3^-)-$(1\rightarrow]_n$

Table 1: Few illustrative examples of oligosaccharide repetitive units of the structurally well-defined SFs and SGs. These polysaccharides are extracted from sea urchins (Echinoidea), sea cucmber (Holothuroidea), red algae (Rodophyta), and ascidians, also known as tunicates (Ascidiacea).

With respect to the activities in inflammation, angiogenesis, and cancer, the brown algal SFs have been the mostly used molecular models in attempt to establish some structure-function correlations. The lack of a clear and regular structural pattern in these algal molecules is the main reason that impairs some advanced propositions for these clinical systems. However, notation of species with the highest levels of action has been made [6,12]. The minimal explanation regarding structure-function relationship of these algal glycans was the influence of sulfation content in their anti-angiogenic properties [6,12]. However, conclusions about the contribution of sulfation degrees in biological responses of sulfated polysaccharides may be considered still simple. In addition, the mechanisms in which SFs and SGs exhibit their capacity to inhibit cell-adhesion in metastatic tumor cells are yet poorly understood [9]. Hence, the contribution of fucanomics and galactanomics in inflammation, angiogenesis, and in the fight against cancer are still very limited.

Suggestive Discussing Topics in Future Scientific Events

The Division of Blood Diseases and resources of the National Heart, Lung, and Blood Institute (NHLBI) convened a working group of scientific investigators on February 25-26, 2008, in Bethesda, MD. The primary objective of this group was the identification of new scientific opportunities, and priorities emerging from the recent explosion of technological and biological advances in the glycoscience [13]. The establishment of this group was made in order to manage the new approaches that have been arising with the advent of glycomics. It is also mentioned therein, that the emerging glycomics knowledge are the current foundations for the developments of novel diagnostic and therapeutic strategies based on recent discovers regarding structures and functions of glycans. The working group met at the request of the NHLBI to discuss the importance of glycans, with the specific emphasis on their roles in hemostasis, inflammation, and vascular biology [14]. These clinical areas are exactly the biomedical specialties of fucanomics and galactanomics. Therefore, through this report we want to express the importance in considering fucanomics and galactanomics as future topics of discussion in the next glyco-events. This is promptly demanded to establish future collaborative networks on the upcoming scientific endeavors involving SFs and SGs, and to push glycomics forward in what concerns glycans of biomedical properties.

Remaining Challenges

Within the discovery of new types of structures and potential pharmacological actions of SFs and SGs, numerous opportunities and challenges have appeared in fucanomics and galactanomics. Among many, here we enlist the top five approaches. First, the deposition of the structures recently characterized (Table 1) in an internationally public carbohydrate databank. This task is very relevant in order to share these structures with other groups, and to help the development of future scientific projects, such as conformational studies based on computational dynamics.

Second, as consequence of the structural studies concerning the conformational preferences of SFs and SGs, information about the binding properties with proteins related to their biomedical actions would ultimately lead to an advanced comprehension of the therapeutic systems. Third, the use of the SFs and SGs of well-defined chemical structures (Table 1) can result in accurate structure-function relationships. This has been proved for the studies of their anticoagulant and antithrombotic properties [1]. Conversely, the other clinical properties, especially those where the molecular mechanisms have been uncovered, the use of these regular molecules are of promising diagnostic of the glycosidic structural requirements needed to reach suitable biomedical responses. Fourth, information about the biosynthesis of these glycans is virtually unknown. Studies in this area may represent a totally new avenue of research in glycobiology. The annotation of the related glycosyl transferases and sulfotranferases would help the understandings about the metabolisms of these relatively new polysaccharides.

The studies of biosynthesis would consequently approach the fifth task that would be the phylogenetic concerns between SFs and SGs. Hypothesis about the evolutionary relationships between the organisms that express these glycans could be raised from these endeavors. The correlation with the well known biosynthetic pathways of the glycosaminoglycans would enhance the impact of such approach through an improved understanding about the metabolisms of sulfated polysaccharides in ancient organisms. Moreover, the resultant knowledge would help to build in the future engineered glycans enriched with the adequate structural features required to enhance their therapeutic effects. The results from all these tasks would lead to a reliable conjunction of data to make SFs and SGs competent candidates for future clinical trials.

References

1. PominVH, Mourão PA (2008) Structure, biology, evolution, and medical importance of sulfated fucans and galactans. Glycobiology 18: 1016-1027.

2. Pomin VH (2009) Review: An overview about the structure-function relationship of marine sulfated homopolysaccharides with regular chemical structures. Biopolymers 91: 601-609.

3. Pomin VH (2012) Fucanomics and galactanomics: Marine distribution, Medicinal impact, Conceptions, and Challenges. Mar Drugs 10: 793-811.

4. Hart GW, Copeland RJ (2010) Glycomics hits the big time. Cell 143: 672-676.

5. Cohen M, Varki A (2010) The sialome--far more than the sum of its parts. OMICS 14: 455-464.

6. Cumashi A, Ushakova NA, Preobrazhenskaya ME, D'Incecco A, Piccoli A, et al. (2007) A comparative study of the anti-inflammatory, anticoagulant, antiangiogenic, and antiadhesive activities of nine different fucoidans from brown seaweeds. Glycobiology 17: 541-552.

7. Mourão PA, Paulo AS (2004) Use of sulfated fucans as anticoagulant and antithrombotic agents: Future perspectives. Current Pharmaceutical Design 10: 967-981.

8. Pereira MS, Melo FR, Mourão PA (2002) Is there a correlation between structure and anticoagulant action of sulfated galactans and sulfated fucans? Glycobiology 12: 573-580.

9. Croci DO, Cumashi A, Ushakova NA, Preobrazhenskaya ME, Piccoli A, et al. (2011) Fucans, but not fucomannoglucuronans, determine the biological activities of sulfated polysaccharides from *Laminaria saccharina* brown seaweed. Plos One 6: e17283.

10. Pereira MS, Vilela-Silva ACES, Valente AP, Mourão PA (2002) A 2-sulfated, 3-linked α-L-galactan is an anticoagulant polysaccharide. Carbohydrate Research 337: 2231-2238.

11. Becker CF, Guimarães JA, Mourão PA, Verli H (2007) Conformation of sulfated galactan and sulfated fucan in aqueous solutions: Implications to their anticoagulant activities. J Mol Graph Model 26: 391-399.

12. Koyanagi S, Tanigawa N, Nakagawa H, Soeda S, Shimeno H (2003) Oversulfation of fucoidan enhances its anti-angiogenic and antitumor activities. Biochemical Pharmacology 65: 173-179.

13. Pomin VH (2012) Fucanomics and galactanomics: current status in drug discovery, mechanisms of action and role of the well-defined structures. Biochim Biophys Acta 1820: 1971-1979.

14. Varki AP, Baum LG, Bellis SL, Cummings RD, Esko JD, et al. (2008) Working group report: The roles of glycans in hemostasis, inflammation and vascular biology. Glycobiology 18: 747–749.