Synthetic and Systems Biotechnology xxx (2017) 1–17

Contents lists available at ScienceDirect

Synthetic and Systems Biotechnology

journal homepage: http://www.keaipublishing.com/en/journals/synthetic-and-systems-biotechnology/

Review Article

Simple glycolipids of microbes: Chemistry, biological activity and metabolic engineering

Ahmad Mohammad Abdel-Mawgoud, Gregory Stephanopoulos*

Department of Chemical Engineering, Massachusetts Institute of Technology, 77 Massachusetts Ave., Cambridge, MA 02139, USA

ARTICLE INFO

Article history:
Received 2 October 2017
Received in revised form
14 November 2017
Accepted 4 December 2017

Keywords:
Biosurfactant
Glycolipids biosynthesis
Glycosyl/acyl transferases
Glycosides
Physiological roles
Lipid biotechnology

ABSTRACT

Glycosylated lipids (GLs) are added-value lipid derivatives of great potential. Besides their interesting surface activities that qualify many of them to act as excellent ecological detergents, they have diverse biological activities with promising biomedical and cosmeceutical applications. Glycolipids, especially those of microbial origin, have interesting antimicrobial, anticancer, antiparasitic as well as immunomodulatory activities. Nonetheless, GLs are hardly accessing the market because of their high cost of production. We believe that experience of metabolic engineering (ME) of microbial lipids for biofuel production can now be harnessed towards a successful synthesis of microbial GLs for biomedical and other applications. This review presents chemical groups of bacterial and fungal GLs, their biological activities, their general biosynthetic pathways and an insight on ME strategies for their production.

Contents

1. Introduction

Lipid biotechnology research has focused to date on developing sustainable alternatives to depleting fossil fuels. One strategy was plant-derived fuel, biodiesel [1]. A main drawback of this approach

* Corresponding author.
E-mail address: gregstep@mit.edu (G. Stephanopoulos).
Peer review under responsibility of KeAi Communications Co., Ltd.

https://doi.org/10.1016/j.synbio.2017.12.001

Please cite this article in press as: Abdel-Mawgoud AM, Stephanopoulos G, Simple glycolipids of microbes: Chemistry, biological activity and metabolic engineering, Synthetic and Systems Biotechnology (2017), https://doi.org/10.1016/j.synbio.2017.12.001

is that oil and land allocated for biodiesel production compete with those allocated for human food consumption. Moreover, replacement of natural vegetations with plants used for biodiesel production generates long-term environmental concerns. Another strategy is to use lipids originating from microbes, called "single cell oil" (SCO) as substrates for biodiesel production. We believe that accumulating knowledge and developed biomolecular tools obtained from lipid engineering of oleogenic microbes can now be harnessed for the microbial production of lipid derivatives of added-value.

Glycosylation of organic molecules, including lipids, usually leads to derivatives of new and/or better physicochemical properties and biological activities [2,3] that reflect in higher market prices. Metabolic engineering of lipid derivatives has previously investigated polyunsaturated fatty acids [4] and fatty acid derivatives that are used as substrates for oleochemical industries, e.g. heterologous production of ricinoleic acids by *Y. lipolytica* [5]. Other added-value lipid derivatives of commercial interest include wax esters, polyhydroxyalkanoates (bioplastics), hydroxylated fatty acids, carotenoids, polyenic polymers [6] and glycolipids.

This review focuses on simple glycolipids (SGLs) as an important family of glycolipids (GLs) class. The importance of SGLs stems from the fact that this family of GLs comprises a wide range of bioactive molecules with potential biomedical, pharmaceutical and cosmetic applications [7,8]. Nonetheless, many simple GLs are limited commercially because of their still low yield and high cost of production, particularly of high purity simple GLs aimed for biopharmaceutical purposes.

We present the chemical groups of simple GLs, their microbial producers and their biological activities. Then, we describe the key biosynthetic enzymes and metabolic precursors involved in biosynthesis of simple GLs. Finally, we discuss metabolic engineering strategies for simple GLs production in native and heterologous hosts.

2. Definition and classification of simple glycolipids

The term glycolipids (GLs), in general, encompasses a wide diversity of structurally heterogeneous biological compounds that are produced by microbes, plants, animals and humans [9]. As their names suggest, they are composed of glycosyl and lipid moieties. The IUPAC uses the term GLs to broadly designate any compound containing one or more monosaccharide residues bound by glycosidic linkage to a hydrophobic moiety [10]. Our definition of GLs is even broader to include glycoside and non-glycoside GLs in which the sugar and lipid residues are linked together via glycosidic (e.g. *O*- or *N*-glycosidic linkages) and non-glycosidic linkages (e.g. ester or amide linkages), respectively (Fig. 1). The glycosyl residue can be mono-, di-, oligo or polysaccharides (e.g. glucose, cellobiose or glycan, respectively), alcohol sugars/polyols (like mannitol, erythritol or arabinol, etc.), amino sugars (like desosamine, etc) or sugar acids (like glucuronic acids). The lipid residue of GLs ranges from fatty acids, fatty alcohols, fatty amino alcohols, polyketides, sterols, hopanoids and carotenoids with different substitutions, chain lengths, saturation levels, branching and di-/oligo-/polymerizations.

Numerous classifications exist for GLs [10], the most convenient of which is their classification into simple and complex GLs [11–13] (Fig. 1). Simple GLs (SGLs), sometimes called saccharolipids [14], are two-component (glycosyl and lipid moieties) GLs in which the glycosyl and lipid moieties are directly linked to each other. Complex glycolipids (CGLs) are, however, structurally more heterogeneous, as they contain, in addition to the glycosyl and lipid moieties, other residues like glycerol (glycoglycerolipids), peptide (glycopeptidolipids), acylated-sphingosine (glycosphingolipids), or other residues (Fig. 1). Polysaccharide-containing GLs, although containing no residues other than glycosyl and lipid moieties, are classified under complex glycolipids because of the complex nature of their polysaccharide residues; however, oligosaccharide-containing GLs are classified as simple GLs [13] (Fig. 1). Simple glycolipids addressed in this review are those of natural microbial origin, therefore, SGLs of synthetic or other biological origins are not mentioned.

3. Surfactant properties of simple glycolipids

Simple glycolipids (SGLs) are amphiphilic molecules as they comprise both the hydrophilic glycosyl and the lipophilic lipid residues. This amphiphilic nature confers surfactant activity to most GLs; those of which with pronounced surfactant activity are called biosurfactant. Compared to petroleum-derived (e.g. alkylbenzene sulfonates) or plant-based (e.g. alkyl polyglycosides) synthetic surfactants [15], microbially-produced SGL biosurfactants are mostly of higher surface activity, higher emulsifying power, lower critical micelle concentrations, higher biodegradability (compared to petroleum-derived surfactants), lower ecotoxicity [16] and lower protein denaturing potency [17–19]. The advanced properties of microbial SGLs are suggested to be attributed to a peculiar mosaic distribution of regions of polarity over the GL molecule, as well as to their branched or sometimes circular structures compared to synthetic surfactants [18]. Moreover, most SGLs are naturally produced as complex mixtures of congeners or homologues that vary in the number of glycosyl units and extent of their acylation, the number of conjugate lipid chains, their lengths, the extent of unsaturations and substitutions; these factors together contribute to their unique surfactant properties and behaviors [18].

Although the unique surface properties of some SGLs qualified some of them to be marketed as ecological surfactants [20,21], yet, their competitiveness in the detergent market is limited because of their higher prices compared to alkyl polyglycosides synthetic surfactants which are at least 50% less expensive. For example, the estimated cost of large-scale production of the SGLs: sophorolipid and rhamnolipid biosurfactants, are about US$ 2.5–3/Kg [21,22] and US$ 5–20/Kg [23], respectively, compared to US$ 1–3/Kg for the synthetic alkyl polyglycoside surfactants [23].

Aside from their surface activities, nearly all natural SGLs have interesting biological activities, as described later, that let them occupy market niches not approachable by synthetic surfactants [24]. Noteworthy, the biological activities of SGLs are thought to stem from their surface activities [25].

4. Chemical groups and origins of microbial simple glycolipids

Microbially produced SGLs are classified in chemical groups based on their chemical structures so that every group comprises SGLs members sharing unique glycosyl and/or lipid moieties for SGLs produced by bacteria (Table 1) and fungi (Table 2). In this classification, some SGLs congeners are classified in separate groups when they originate from different microbial origins and vice versa. Under each SGL group, exhaustive list of its members, together with their chemical names, their microbial producers as well as their taxonomic phyla is mentioned (Tables 1 and 2). Furthermore, the confirmed chemical structures of representative or prototypic members of each SGL group are presented (Fig. 3).

Based on our survey of microorganisms producing SGLs, we found that 50% of all known microbial SGLs are produced by microbes belonging to the phylum *Actinobacteria* (Fig. 2). Second in rank to *Actinobacteria*, comes phylum *Proteobacteria* followed by

Please cite this article in press as: Abdel-Mawgoud AM, Stephanopoulos G, Simple glycolipids of microbes: Chemistry, biological activity and metabolic engineering, Synthetic and Systems Biotechnology (2017), https://doi.org/10.1016/j.synbio.2017.12.001