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Databases and ontologies

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The Xeno-glycomics database (XDB): a relational database of qualitative and quantitative pig glycome repertoire

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ABSTRACT

Summary: In recent years, the improvement of mass spectrometry-based glycomics techniques (i.e. highly sensitive, quantitative and high-throughput analytical tools) has enabled us to obtain a large dataset of glycans. Here we present a database named Xeno-glycomics database (XDB) that contains cell- or tissue-specific pig glycomes analyzed with mass spectrometry-based techniques, including a comprehensive pig glycan information on chemical structures, mass values, types and relative quantities. It was designed as a user-friendly web-based interface that allows users to query the database according to pig tissue/cell types or glycan masses. This database will contribute in providing qualitative and quantitative information on glycomes characterized from various pig cells/organs in xenotransplantation and might eventually provide new targets in the α1,3-galactosyltransferase gene-knock out pigs era.

Availability: The database can be accessed on the web at http://bioinformatics.snu.ac.kr/xdb.

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Supplementary information: Supplementary data are available at *Bioinformatics* online.

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1 INTRODUCTION

Cell surface carbohydrates can act as ligand molecules for diverse biological processes such as cell–cell interaction, signal transduction, metastasis and so forth (Ohtsubo and Marth, 2006; Rudd *et al*., 2001). Especially in pig-to-human xenotransplantation, the interaction between terminal α-Gal (Galα1-3Gal-R) antigens onzz pig tissues or cells' surfaces and circulating natural human antibodies lead to hyper acute immune rejection (Oriol *et al*., 1993). Despite the development of α1,3-galactosyltransferase gene-knock out pigs, unidentified non-Gal antigens remain as possible factors triggering delayed xenograft rejection (Ezzelarab *et al*., 2005). Thus, the comprehensive identification of α-Gal and non-Gal carbohydrate antigens from pig tissues and cells is essential for successful xenotransplantation.

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During the past decades, several databases have been developed to assist the assignment, annotation and interpretation of glycan and glycoconjugates datasets (Campbell, *et al*., 2011; Campbell *et al*., 2008; Cooper *et al*., 2003; Kameyama *et al*., 2005; Raman *et al*., 2006; von der Lieth *et al*., 2011). However, none of them systematically classify and update the pig glycans according to the specific pig tissues and cells. Qualitative and quantitative information on the glycan antigens, which play an important role in immune rejection, is also lacking.

Here, we have built up a relational database [Xeno-glycomics database (XDB)] from specific pathogen-free Chicago Medical School miniature pig (Setcavage and Kim, 1976) glycan profiles, which have been qualitatively and quantitatively characterized by various mass spectrometry-based techniques (Supplementary Data). It includes *N*-glycomes from pig kidney (Kim *et al*., 2008, 2006), endothelial cells, islets (Kim *et al*., 2009a), corneal endothelial cells, keratocytes (Kim *et al*., 2009b), heart and glycosphingolipid-derived glycans from pig endothelial cells and islets (Kim *et al*., 2009c). The *O*-glycomes from pig kidney, endothelial cells (Park *et al*., 2013) and heart (accepted) are also included. This specialized pig glycome database will offer a new insight into pig-to-human xenotransplantation as well as into many different areas of biological and biomedical research.

2 METHOD

XDB is based on open-source technology, developed in jruby 1.7.0 and trinidad1.4.4 Tomcat 7.0.37 and tested on Debian. The database was used in SQLite version 3.0 as a data storage program. The HTML-based web interface has been tested using Safari 6 and Chrome 22. The updated version of web browsers is recommended for the usage of the XDB.

3 RESULTS AND DISCUSSION

Two major query options are implemented in XDB, namely, 'pig tissue/cell specific glycans' and 'mass spectrometry-based glycan searching' (Fig. 1, Supplementary Data). The 'pig tissue/cell specific glycans' option allows the retrieval of glycans derived from a specific pig tissue/cell. Users can obtain the full lists of glycans by clicking a specific pig organ or cell icon. It is also possible to set parameters including glycan epitope (Kawasaki *et al*., 2006). On the other hand, the 'mass spectrometry-based glycan searching' is a way to look for a specific glycan information from

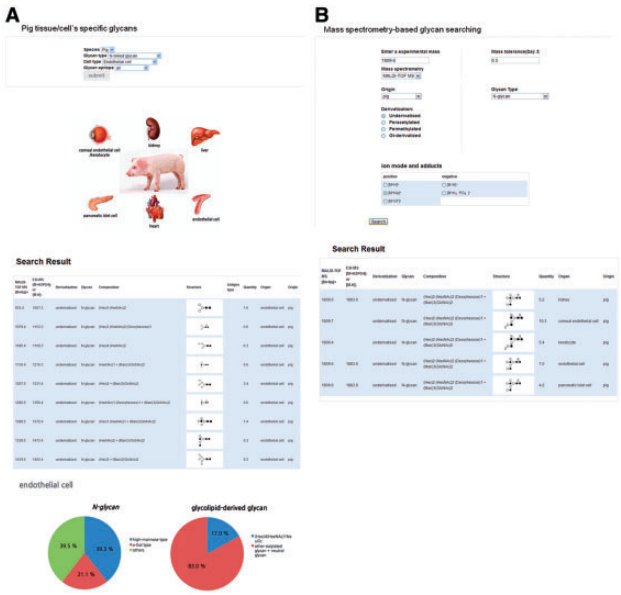

Fig. 1. The query and result pages of (**A**) 'pig tissue/cell' specific glycans and (**B**) 'mass spectrometry-based glycan searching' in XDB

a mass-to-charge ratio (m/z). If the users input the experimental mass value (m/z), the program enables the users to gather the possible glycan structures and organs. In addition, the XDB allows users to set a mass tolerance that can be specified in Daltons ± of the measured value to avert no search result found because of instrumental variations. The users can also narrow down the list of the glycans by specifying several factors. It includes the followings: mass spectrometry instrument, glycan derivatization method, glycan type, ion mode, ion adducts and origin, but it will be updated continuously.

The search result from XDB contains mass value (m/z), derivatization, glycan type, structure, antigen, quantity and origin. The mass value is an experimental value of the corresponding glycan mass (mono-isotopic) analyzed using matrix-assisted laser desorption/ionization time-of-flight mass spectrometry or electrospray ionization mass spectrometry. The derivatization indicates the chemical derivatization for glycan analysis using mass spectrometry. All the glycans in the XDB are classified into three types: *N*-linked glycans (at the side chain of Asn), *O*-linked glycans (at the Ser/Thr residues) in glycoproteins and glycosphingolipid-derived glycans. Especially, the α-galactosylatedglycans are labeled with 'α-Gal antigen' in the column of 'Antigen type'. The chemical structures were drawn with Oxford glycan nomenclature (Harvey *et al.*, 2009). The relative quantity of glycans, which was measured by NP-HPLC or quantitative MS analysis, was incorporated in the result table as well. Additionally, pie graphs represent the relative quantities of each type of glycans (e.g. high-mannose glycans, α-Gal glycans, sialylatedglycans and so on).

Although many of the well-established glycan databases offer the detailed glycan structures, it is difficult to solely collect the pig glycans according to the specific organ or cell, which is a promising candidate for xenotransplantation. Therefore, we have built a unique and specialized database to provide reliable information on glycans, which are derived from tissues and cells of pigs. Moreover, it contains both qualitative and quantitative information on xenoantigenic glycans, which play an important role in immune-rejection response. Taken together, this database is potentially promising and facilitates xenotransplantation research as well as basic carbohydrate research. The XDB will allow users to use hyperlink the human glycan database with CFG, which contains glycan profiles in human cells and tissues for pig-to-human xenotransplantation research. In the near future, this XDB will be updated with a list of glycans from α1,3- galactosyltransferase gene-knock out pig samples as well.

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