Directed evolution of glycosyltransferase for the artificial biosynthesis of natural product glycosides

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Over one fifth natural product drugs (including protein biopharmaceuticals), cosmetics, and nutraceuticals have a diverse set of sugars in their structures. These glycosylations dramatically influence the physicochemical and pharmacological properties of these compounds. Glycosyltransferases (GTs) offer very attractive approaches to the biosynthesis of complex glycosylated natural products. However, the limited number of available GTs, together with their instability and strict substrate specificity, have severely hampered the broad application of these enzymes. In the past few years, we have used directed evolution as a tool to tailor the GTs with desired substrate specificity and higher catalytic activity. Here I will introduce some of our efforts in 1) the semi-rational design of a glucosyltransferase UGT51 from *S. cerevisiae* to repurposing its promiscuous activity towards the biosynthesis of rare ginsenoside Rh2; and 2) the directed evolution of an α1,3-fucosyltransferase using a single-cell ultrahigh-throughput screening method. I will also discuss the development of new tools for the high-throughput screening method for GTs and the mechanistic insight we found during the evolution of these enzymes.

Brief Biography

Dr. Guangyu Yang received his Ph.D. in Biochemistry and Molecular Biology at Jilin University, China in 2009 with Prof. Yan Feng. He studied in Dr. Stephen Withers' lab at University of British Columbia, Canada firstly as a visiting student (2007-2008) and later as a postdoc (2012-2013). He joined Shanghai Jiao Tong University at 2009 as a Lecture, and then was promoted to an Associate Professor in 2013 and a full Professor in 2018. His research activity mainly focuses on the analysis the catalytic mechanism of enzymes, enzyme molecular evolution, and the design of artificial enzymatic cascades. He has 35 articles published in prestigious journals including *Science advances*, *Nature Communications, Angewandte Chemie International Edition, Journal of the American Chemical Society, and Journal of Biological Chemistry*, etc.

Education:
1999- 2003 BS in Biological Science, Jilin University, China
2003- 2009 Ph.D in Molecular Biology and Biochemistry, Jilin University, China (Supervisor: Prof. Yan Feng)
2007-2007 Visiting student, Seoul National University, (Supervisor: Prof. Young Je Yoo)
2007- 2008 Jointly educated Ph.D student, University of British Columbia, (Supervisor: Prof. Stephen G. Withers)

Professional Career:
2012-2013 Postdoc fellow, University of British Columbia, (Supervisor: Prof. Stephen G. Withers)
2009-2012 Lecturer, School of Life Sciences and Biotechnology, Shanghai Jiao Tong University

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Research Interests:
1. structure-function relationship of enzymes
2. directed evolution of enzymes
3. in vitro synthetic biology

Selected publications

1) Yumeng Tan, Yong Zhang, Yunbin Han, Hao Liu, Haifeng Chen, Fuqiang Ma, Stephen G Withers, Yan Feng, Guangyu Yang. Directed evolution of an α1,3-fucosyltransferase using a single-cell ultrahigh-throughput screening method. ***Science Advances***, **accepted**
2) Fuqiang Ma[#], Meng Ting Chung[#], Yuan Yao, Robert Nidet, Lap Man Lee, Allen P. Liu, Yan Feng, Katsuo Kurabayashi*, **Guang-Yu Yang***. Efficient molecular evolution to generate enantioselective enzymes using a dual-channel microfluidic droplet screening platform. ***Nature Communications***, 2018, 9:1030. (#equal contribution)
3) Zhuang Y[#], **Yang GY**[#], Chen X, Liu Q, Zhang X, Deng Z, Feng Y. Biosynthesis of plant-derived ginsenoside Rh2 in yeast via repurposing a key promiscuous microbial enzyme. ***Metabolic Engineering***. 2017, 42:25-32. (#equal contribution)
4) Han YB, Chen LQ, Li Z, Tan YM, Feng Y, **Yang GY***. Structural insights into the broad substrate specificity of a novel Endo-glycoceramidase I belonging to a new subfamily of GH5 glycosidase. ***J Biol Chem***. 2017, 292(12):4789-4800.
5) Fuqiang Ma, Michael Fischer, Yunbin Han, Stephen G. Withers, Yan Feng, **Guang-Yu Yang*.** Substrate engineering enabling fluorescence droplet entrapment for IVC-FACS-based ultrahigh-throughput screening. ***Analytical Chemisty***, 2016, 88, 8587−8595
6) FT Huang, YB Han, Y Feng, **GY Yang***. A facile method for controlling the reaction equilibrium of sphingolipid ceramide N-deacylase for lyso-glycosphingolipid production. ***Journal of lipid research***. 2015, 56(9):1836-1842.
7) **Guang-Yu Yang,** Caishun Li, Michael Fischer, Christopher W. Cairo, Yan Feng, Stephen G. Withers. A FRET Probe for Cell-Based Imaging of Ganglioside-Processing Enzyme Activity and High-Throughput Screening. ***Angewandte Chemie International Edition.*** 2015, 54(18):5389-5393