Biomaterials 132 (2017) 28–36

Contents lists available at ScienceDirect

Biomaterials

journal homepage: www.elsevier.com/locate/biomaterials

Review

Molecular imaging based on metabolic glycoengineering and bioorthogonal click chemistry

Hong Yeol Yoon [a, 1], Heebeom Koo [b, 1], Kwangmeyung Kim [a, c, *], Ick Chan Kwon [a, c, **]

[a] Center for Theragnosis, Korea Institute of Science and Technology, 39-1 Hawolgok-dong, Seongbuk-gu, Seoul, 136-791, Republic of Korea
[b] Department of Medical Lifescience, College of Medicine, The Catholic University of Korea, 222, Banpo-daero, Seocho-gu, Seoul, 06591, Republic of Korea
[c] KU-KIST Graduate School of Converging Science and Technology, Korea University, 145 Anam-ro, Seongbuk-gu, Seoul, 02841, Republic of Korea

ARTICLE INFO

Article history:
Received 11 January 2017
Received in revised form
28 March 2017
Accepted 3 April 2017
Available online 4 April 2017

Keywords:
Molecular imaging
Metabolic glycoengineering
Click chemistry
Tumor imaging
Cell tracking

ABSTRACT

Metabolic glycoengineering is a powerful technique that can introduce various chemical groups to cellular glycan by treatment of unnatural monosaccharide. Particularly, this technique has enabled many challenging trials for molecular imaging in combination with click chemistry, which provides fast and specific chemical conjugation reaction of imaging probes to metabolically-modified live cells. This review introduces recent progress in molecular imaging based on the combination of these two cutting-edge techniques. First, these techniques showed promising results in specific tumor cell imaging for cancer diagnosis and therapy. The related researches showed the surface of tumor cells could be labeled with bioorthogonal chemical groups by metabolic glycoengineering, which can be further conjugated with fluorescence dyes or nanoparticles with imaging probes by click chemistry, *in vitro* and *in vivo*. This method can be applied to heterogeneous tumor cells regardless of genetic properties of different tumor cells. Furthermore, the amount of targeting moieties on tumor cells can be freely controlled externally by treatment of unnatural monosaccharide. Second, this sequential use of metabolic glycoengineering and click chemistry is also useful in cell tracking to monitor the localization of the inoculated therapeutic cells including chondrocytes and stem cells. This therapeutic cell-labeling technique provided excellent viability of chondrocytes and stem cells during the whole process *in vitro* and *in vivo*. It can provide long-term and safe therapeutic cell imaging compared to traditional methods. These overall studies demonstrate the great potential of metabolic glycoengineering and click chemistry in live cell imaging.

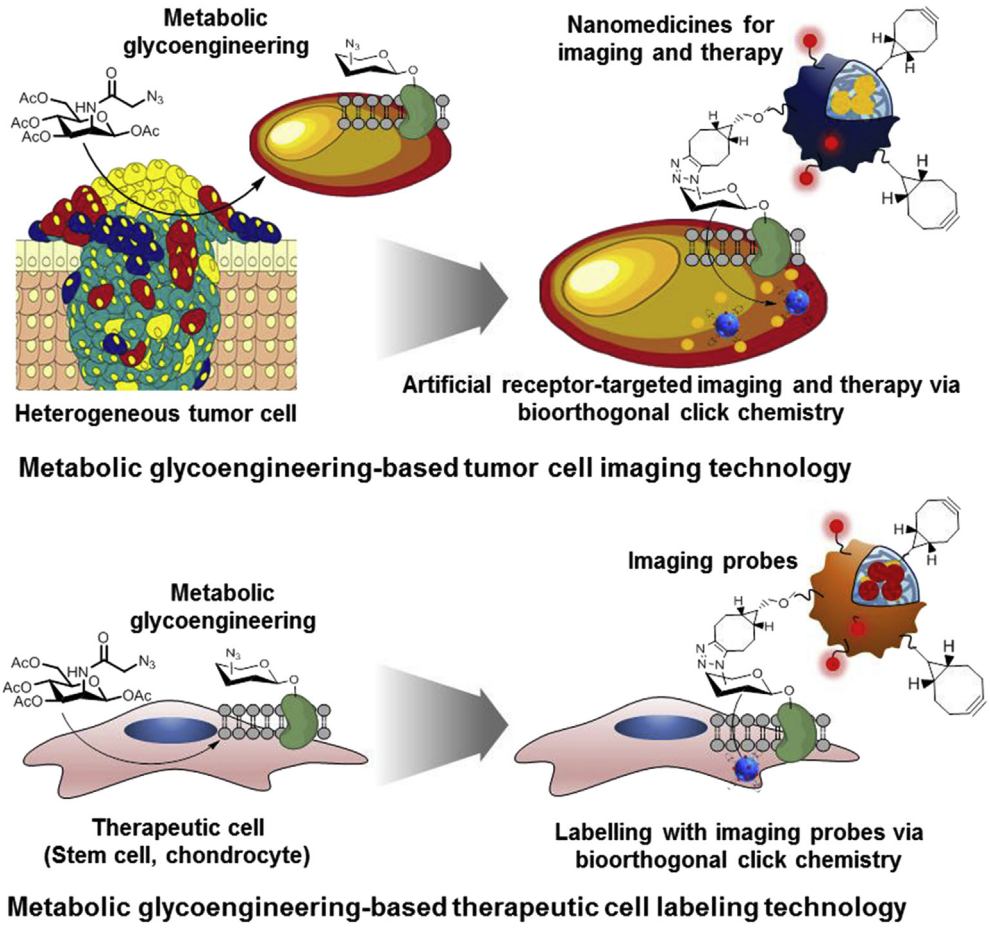
1. Introduction

Molecular imaging is a type of medical imaging that can monitor or analyze the spatiotemporal changes in body at molecular or cellular level for biological or biomedical applications [1]. Even though it is still controversial to define the exact range of molecular imaging among numerous imaging techniques and applications, molecular imaging has provided valuable information to researchers by precise imaging of the disease [2]. Particularly, researchers have paid much attention to the molecules on cell surface because proteins, glycans, and lipids on cell surface are directly related on the metabolism and function of the cells and can provide us large amount of knowledge about the state of the cells [3]. Therefore, engineering techniques that can analyze or modify these cell surface materials are highly useful for both biological and biomedical applications [4].

Traditionally, the endogenous target molecules on live cells can be visualized using different binding molecules labeled with imaging probes such as antibodies, peptides, or aptamers. However, the low amount of target molecules on cell surface limited the efficacy of molecular imaging *in vivo* [5]. Furthermore, these target molecules are not homogeneously expressed particularly in tumor tissue, which is well-known as the heterogeneity of tumor cells [6]. Therefore, the insufficient specificity of the labeling techniques using these biological target molecules is always a big problem in many cases, and it can result in non-specific binding or uptake of imaging probes. Recently, in several studies, metabolic glycoengineering and click chemistry showed potential possibility to overcome these disadvantages in current molecular imaging

* Corresponding author. Center for Theragnosis, Korea Institute of Science and Technology, 39-1 Hawolgok-dong, Seongbuk-gu, Seoul, 136-791, Republic of Korea.
** Corresponding author. Center for Theragnosis, Korea Institute of Science and Technology, 39-1 Hawolgok-dong, Seongbuk-gu, Seoul, 136-791, Republic of Korea.
E-mail addresses: kim@kist.re.kr (K. Kim), ikwon@kist.re.kr (I.C. Kwon).
[1] These authors contributed equally to this paper.

http://dx.doi.org/10.1016/j.biomaterials.2017.04.003
0142-9612/



Scheme 1. Schematic illustration of metabolic glycoengineering-based cell labeling and imaging technology.

methods.

Metabolic glycoengineering is a technique that can modify the structure of glycans and introduce various functional groups [7]. When unnatural monosaccharides are treated to cells, the cells use them as building blocks and made their own glycan by intrinsic metabolic pathway. If the monosaccharides are labeled with certain chemical group, these chemical groups can be inserted to the glycan backbone by glycan metabolism with minimum perturbation of cell function. The representative monosaccharides used in metabolic glycoengineering are mannosamine, galactosamine, and glucosamine, and various chemical groups such as azide, thiol, ketone, or aliphatic changes have been introduced to cells by this technique [8]. Among these chemical groups, azide groups are bioorthogonal and can be used for click chemistry *in vitro* and *in vivo*.

Click chemistry is referred to a group of chemical reactions with high yield, fast reaction rate, non-toxic byproduct and can be done in aqueous condition [9]. Therefore, click chemistry has enabled artificial chemical conjugation on cell surface, in cytosol, or in body, which has been impossible by traditional conjugation reactions [10]. Based on these advantages, click chemistry has been paid explosive attention not only from organic chemists but also biological or biomedical researchers until now [11]. Click chemistry has been widely applied to biological mechanism studies, targeted imaging, development of new biomaterials, or drug delivery. Recently, click chemistry particularly showed powerful combination with metabolic glycoengineering in molecular imaging. This combination provided more specific and safe imaging of live cells and it is expected to overcome the current problems in cell imaging that mentioned above. This review will introduce these exciting results based on metabolic glycoengineering and click chemistry in molecular imaging technology including tumor imaging, cell tracking, and so on (see Scheme 1).

2. Tumor cell imaging *in vivo* for diagnosis and therapy

For long time, targeting against cell surface molecules has been a big issue particularly for tumor cell imaging. To target the tumor cells with imaging probes, researchers used biological ligands including antibodies, peptides, or aptamers that specifically bind to the receptors on the surface of tumor cells. However, this type of targeting strategy has intrinsic limitations because the amounts of the receptors could be insufficient for targeting with imaging probes in many cases use [12]. Furthermore, heterogeneity of tumor cells are serious problem for tumor cells targeting because the types and amounts of the receptors are different within the tumor tissue of the same patient as well as in different kinds of tumors receptors [13]. Therefore, it could be highly helpful to find a method to generate large amounts of receptors on tumor cells homogeneously in whole tumor tissue, and the combination of metabolic glycoengineering and click chemistry showed potential possibility to realize it in recent studies.

For tumor cell imaging, the applications of these two techniques are generally performed as follow. First, artificial chemical groups are generated on the surface of tumor cells by metabolic glycoengineering. Then, the generated chemical groups such as azide