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Mini review Open Access

Bioorthogonal Chemistry in Biology and Medicine

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Abstract

Bioorthogonal chemistry and reactions developed from innovations in chemistry, having their excellent biocompatibility can be applied in various biological reactions. As these reactions, does not interfere with other reactions in the biological system, they can be used as excellent tools for tracking and studying dynamics of various biological processes. In this mini review, only the applications of bioorthogonal chemistry in host-microbe interaction and targeted therapy are discussed.

Keywords: Bioorthogonal chemistry; Bioorthogonal reaction; Biomolecules; Microbes; Host; Gene delivery

Introduction

Bioorthogonal chemistry, developed from innovations in chemistry, refers to any chemical reaction that can occur inside living system without interfering with native biochemical processes. Since the introduction of bioorthogonal reaction, it has been applied to diverse classes of biomolecules like glycans, lipids, proteins, nucleic acids of the cells, with excellent biocompatibility and without cellular toxicity [1,2]. Bioorthogonal reactions which fulfill the requirements of bioorthogonality are i) 1,3-dipolar cycloaddition between azides and cyclooctynes, ii) nitrones and cyclo-octynes, iii) tetrazine ligation and iv) oxime/hydrazone formation from aldehydes and ketones (Figures 1A and 1B). The classic azide-alkyne cyclo-addition reaction very effective click reaction and ideal for bioconjugation. These reactions take part in biological system as, first, biomolecules(substrate) labelled with bioorthogonal functional group (like azides) introduced into the cell and then a probe containing complementary functional group (like alkynes) introduced into the cell to react and label the substrate (Figure 2).

Literature Review

Before, bioorthogonal reactions, GFPs (green-fluorescent proteins) were used for the study of protein dynamics and functions in biological systems, however this genetic tagging approach were not suitable for the studies involving other biomolecules such as glycans, lipids, nucleic acids and post-translational modification reactions in biological cells. Since the first appearance of biorthogonal chemistry in 2003, although there are some comprehensive reviews [3-5] on developments of various biorthogonal reactions and applications, no single review todate which focuses on applications of biorthogonal reactions in host-microbe interaction and in targeted therapy. As we were engaged in cell-cell interactions [6-8], and drug targeting in leishmaniasis [9-11], we are planning to apply the biorthogonal reactions in emerging pathogen interaction with the host. It is hoped, that this will be a challenging area for future reseach to understand the mechanism of survival of these emerging intracellular pathogens around the world.

Bioorthogonal chemistry in host-microbe interaction

Suitable receptor-ligand interaction between host and microbe helps to cross the microbe the host cell surface and gain entry inside the host cell. Intracellular localization places the microbe in an environment which is potentially rich in nutrients and devoid of competing microorganisms. However, the intracellular life for these pathogens is not very easy as they have to face or escape the host cell acidic environment or potentially degradative lysosomes. Different intracellular pathogens exploit different locations of the host cells and changeable strategies to sustain their infection [8].

The essential components of microbe cell surfaces are peptidoglycan, lipoarabinomannan, lipophosphoglycan, lipopolysaccharides etc. and these molecules are responsible for pathogen-host interaction and intracellular survival of the pathogens [12,13]. Till date little is known about the synthesis, maturity and dynamics of these pathogen molecules when they are in the intracellular environment, however, there is lots of information when they are outside. Efforts to track synthesis, editing and dynamics of these molecules in the intracellular environment suffer from several drawbacks. These includes species applicability, technical complexity etc.. Recent work on tracking synthesis and maturation of peptidoglycan molecule of bacteria in the intracellular environment in *Listeria monocytogenes*–macrophage model involves bioorthogonal chemistry/bond-formation reaction and metabolic labelling [14]. The technology was the exploitation of D-alanine constituents of peptidoglycan of bacteria, and the bacterial species incorporated azide or alkyne-functionalized D-alanine into their cell walls which was visualized by covalent reaction with click chemistry probes (Figure 2). As eukaryotic cells do not generally produce D-amino acids, this labelling was selectively used for bacteria inside the host cell, and other recent study also demonstrated that this labelling technology could also be used for wide variety of bacterial species. If this technology, could be extended to other glycoconjugates and other microbes then it would be ideal for the study of mechanism of intracellular survival of wide variety of microbes and emerging pathogens.

Bioorthogonal chemistry in targeted therapy

To reduce normal cell toxicity/tissue injury from cytotoxic drugs, targeted therapy is the solution to cure the diseased/infected cells. Targeted therapy involves gene therapy or drug targeting against various critical diseases. Gene therapy have utilized viral-based delivery systems, and in recent years, gene manipulation and delivery

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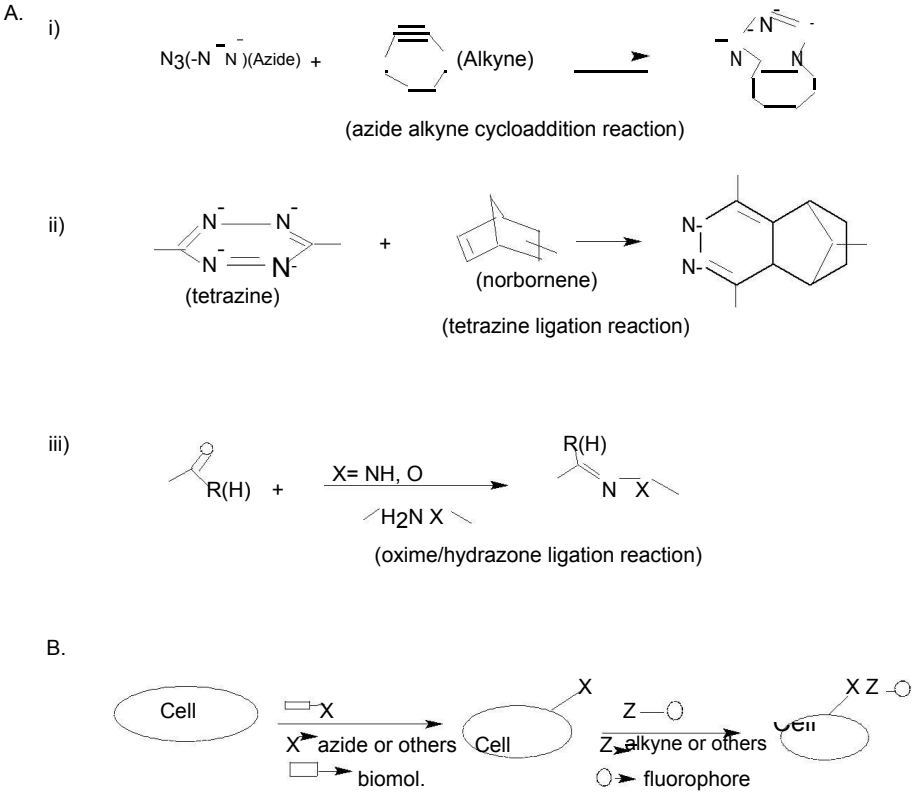

Figure 1: i), ii), iii) Bioorthogonal reactions. B. Azide or other bioorthogonal functional group labelled biomolecules is introduced into the cell. Then cyclooctynes or another complementary functional group containing probe is introduced into the cell to react and label the biomolecule.

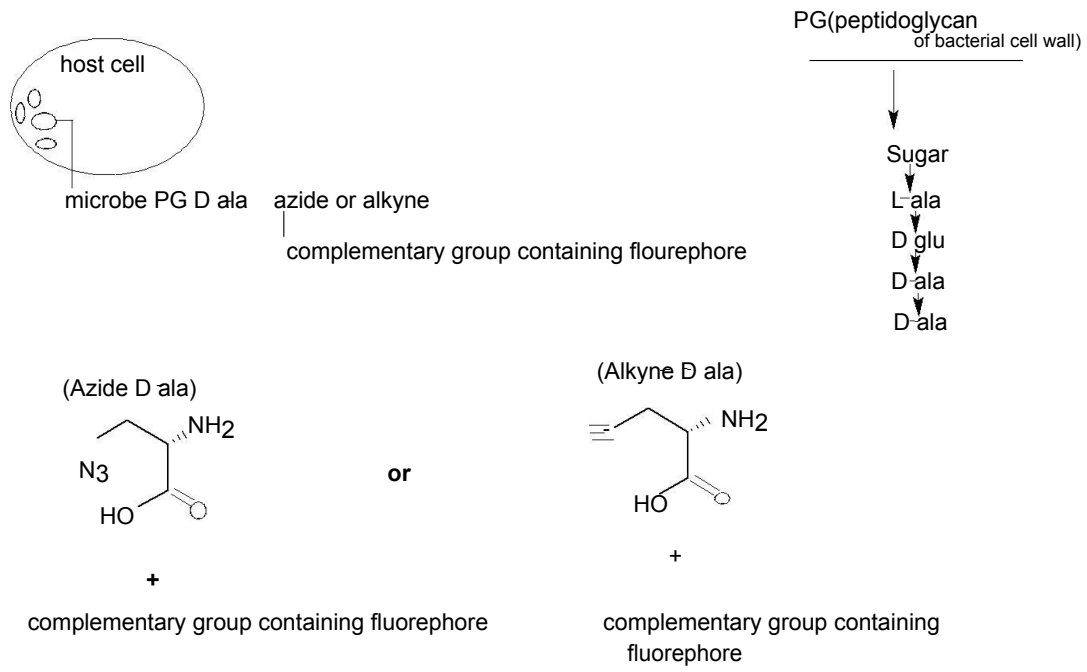

Figure 2: Bioorthogonal reaction in host microbe interaction. Bacterial species inside host cell incorporated azide or alkyne functionalized D alanine into PG of their cell walls and visualized by covalent reaction with click chemistry probes.

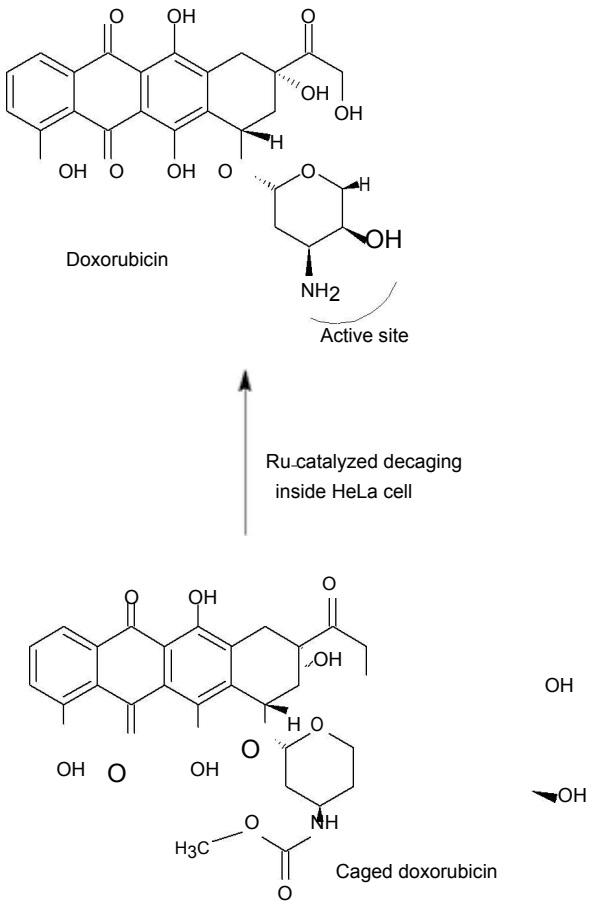

Figure 3: Seletive liberation of potent cytotoxic drugs via bioorthogonal cleavage reactions. Chemically caged doxorubicin was deprotected through bond cleavage reagents.Ruthenium(Ru) catalyzed deallylation reaction was used to activate alloxycarbonyl protected doxorubicin in HeLa cells.

such as CRISPR and non-viral vectors (e.g. liposomes) have been used against hemophilia B, Parkinson's disease, acute lymphocytic leukemia, multiple myeloma, HIV [15,16] whereas drug targeting using neoglycoprotein, antibody and liposome as carriers have been targeted against various infectious diseases [9-11]. However, there are various difficulties/disadvantages associated with these therapies, like inflammatory response of viral vectors, vector viruses infecting more than one type of cell, insertion of a new gene in the wrong location, toxicity etc. Bioorthogonal chemistry here plays a vital role in search of a new system to target drugs to the diseased site specifically. For example, bioorthogonal cleavage reactions have recently been used for selective liberation of potent cytotoxic drugs in a spatiotemporally controlled manner [17,18]. The reaction, Ruthenium(Ru)-catalyzed deallylation was used to activate alloxycarbonyl(Alloc)-protected doxorubicin in HeLa cells (Figure 3).

Discussion and Conclusion

The study of biomolecules in their native environment is a challenging task, because of the huge complexity of the cellular system. In the last few years, among the new technologies developed for studying the modification of biomolecules and their dynamics inside cells are the biorthogonal bond formation and bond cleavage reactions. Non-interference of these reactions with the other biological reactions in the system indicates their great promise in future. Continuous development of further reactions for various kinds of biological cells and tissues would definitely set these reactions as new tools for biology and medicine.

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