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MINI-REVIEW ARTICLE

Biocatalysis in Bioorthogonal Reactions: Use of Hydrolases and Transferases for Selective Modifications

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Abstract: Bioorthogonal chemistry explores a set of technologies to incorporate non-native functional groups into biological systems to understand the mechanism of biological processes in living organisms. Among the conjugation strategies available on the bench, the use of biocatalysis as part of bioorthogonal conjugation has been found to be one smart tool to achieve chemoselective functional group installation. The process designing utilizes high substrate specificity of biocatalyst, resulting in a targeted addition of a reactive non-native functional group to a native biomolecule followed by tagging with a suitably detectable moiety and thereby monitoring the salient biological processes involving the conjugated assembly. The present study tries to briefly address the synthetic strategies with mechanistic elaboration involving various transferases with different suitable models and the underlying reactions involved in bioorthogonal processes.

Keywords: Bioorthogonal chemistry, biocatalysis, click reaction, selectivity, transferases and labeling of biomolecules, hydrolases.

1. INTRODUCTION

Bioorthogonal Chemistry involves one of the smartest and most sustainable technologies which involve specific targeted reactions that can take place in biological environments and do not interfere with biochemical processes that run simultaneously or do not give rise to a side product that may affect the system [1-12]. The term "Bioorthogonal" incepts from the Eucleadean (Mathematics) term "*Orthogonal*" which indicates two entities (E-I, E-II) that are perpendicular (vector) and hence contribution or dependence of each entity on the other (as E-I cosine 90 or E-II cosine 90) is zero. Here, these entities are reactions happening in the Biological system. Since the first proposal of the conception by Professor Carolyn Bertozzi in 2003 [13-17], bioorthogonal chemistry has attracted great attention and has been rapidly developed. As an important chemical biology tool, bioorthogonal reactions have been applied broadly in biomedicine, including bio-labeling, nucleic acid functionalization, drug discovery, drug activation, synthesis of antibody-drug conjugates, and proteolysis-targeting chimeras [11, 12, 18, 19]. The 2022 Nobel Prize in Chemistry was awarded to scientists Carolyn R. Bertozzi, Morten Meldal [20, 21] and K. B. Sharpless [22] for their development of click chemistry and bioorthogonal chemistry [23]. These techniques have been used in a number of sectors, including delivering treatments that can kill cancer cells without perturbing healthy cells, as well as sustainably and quickly producing large amounts of polymers to build materials. One click chemistry-based drug is currently undergoing phase 2 clinical trials. Bertozzi is a scientific adviser of the company developing the drug. Bioorthogonal chemistry, known for its outstanding efficiency and accuracy, has broken the boundary between disciplines, bringing the interdisciplinary pace of chemistry, life science, medical pharmacy, and materials science into the functionalism era [24-27]. The past decades have witnessed the fast development of various bioorthogonal reactions, including native chemical ligations, oxime/hydrazone ligations, Staudinger ligations, CuAAC, SPAAC, IEDDA, light-catalyzed bioorthogonal reactions, metal-catalyzed bioorthogonal reactions, *etc.* These unique reactions have shown great potential in biomedicine like biolabeling, nucleic acid functionalization, drug discovery, drug activation, synthesis of ADCs, synthesis of PROTACs, *etc.* Bioorthogonal catalysis was effectively employed in drug delivery across subcellular Lysosomal membranes by Sun *et al.* [26a]. Lysosomal membranes act as intracellular barrier for drug accumulation and concentrations at intended targets. The group used Pd nanozyme which was formed *in situ* followed by nanozyme-mediated lysosomal membrane leakage, which was successfully applied to the design of model prodrugs for anti-cancer therapy [26]. Use of transition metals without biocatalysts, with many compatibility challenges, is also known [27]. The development and application of

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