Protein Chemical Modification Using Highly Reactive Species and Spatial Control of Catalytic Reactions

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Protein bioconjugation has become an increasingly important research method for introducing artificial functions in to protein with various applications, including therapeutics and biomaterials. Due to its amphiphilic nature, only a few tyrosine residues are exposed on the protein surface. Therefore, tyrosine residue has attracted attention as suitable targets for site-specific modification, and it is the most studied amino acid residue for modification reactions other than lysine and cysteine residues. In this review, we present the progress of our tyrosine chemical modification studies over the past decade. We have developed several different catalytic approaches to selectively modify tyrosine residues using peroxidase, laccase, hemin, and ruthenium photocatalysts. In addition to modifying tyrosine residues by generating radical species through single-electron transfer, we have developed a histidine modification method that utilizes singlet oxygen generated by photosensitizers. These highly reactive chemical species selectively modify proteins in close proximity to the enzyme/catalyst. Taking advantage of the spatially controllable reaction fields, we have developed novel methods for site-specific antibody modification, detecting hotspots of oxidative stress, and target identification of bioactive molecules.

1. Introduction

Protein bioconjugation has broad applicability in many research fields such as biomaterials, drug discovery, diagnosis of diseases, and chemical biology research, and new methods are being actively developed. In particular, the modification of antibodies provides tools for imaging, diagnostics, and detection of analytes in biological research. In addition, antibody–drug conjugates, in which antibodies are modified with highly cytotoxic compounds, have been rapidly developing in recent years as a new cancer therapy that takes advantage of the high tumor specificity of antibodies. Bioconjugation is an applied technology that has attracted much attention, but the variation in its methodology is limited. To chemically modify proteins, it is essential to use methods that form covalent bonds with the main chain of peptide bonds or amino acid residue side chains of proteins. Strategies to form covalent bonds between amino acid residues in protein structures and artificial small-molecule compounds are often used. However, among the 20 naturally occurring amino acid residues, only nucleophilic residues such as lysine and cysteine can be modified, and modification of other amino acid residues with high reliability is still a difficult task. In bioconjugates used as drugs, homogeneity of the product is important, so the ideal modification method is one that selectively functionalizes amino acid residues at specific sites. Therefore, a great deal of effort has been made to obtain highly homogeneous products by targeting amino acid residues at specific sites. Current methods using electrophiles alone cannot solve this problem, and a new concept for protein modification is needed. The growing interest and high demand for new bioconjugates have driven the development of new conjugation methods for the selective anchoring of other amino acid residues. Promising methods have been actively developed for the selective bioconjugation of less nucleophilic amino acid residues such as tryptophan, histidine, methionine, and arginine with a specific focus on tyrosine.

Tyrosine residue is an amphiphilic amino acid residue, and the ratio of its exposure on the protein surface is low, making it suitable for site-specific modification. Tyrosine residues have also attracted attention as the third bioconjugation scaffold after lysine and cysteine residues, and the development of novel modification methods has been particularly active in recent years. The chemical modification of tyrosine residues can be broadly classified into nucleophilic and radical reactions. In nucleophilic reactions, approaches such as the Mannich-type reaction, diazonium, phenyl-1,2,4-triazoline-3,4-dione (PTAD), sulfur fluoride, and sulfur triazole have been developed. Among these, PTAD developed by Barbas et al. is one of the most commonly used tyrosine residue modification reagents (Fig. 1A), but the side reaction of electrophilic isocyanate generated by the decon...
position of PTAD in water is an issue to be solved. Gouin and colleagues succeeded in suppressing the side reaction by electrochemically generating PTAD from phenylurazole in situ. In addition to nucleophilic reactions, approaches using radical reactions using oxidants, enzymes, photoredox catalysts, and electrochemistry have been reported. The development of radical-mediated tyrosine modification is closely related to the catalytic proximity labeling method.

**Biography**

Shinichi Sato received his B.S. (2006) and M.S. (2008) degrees from Meiji Pharmaceutical University (Mentor: Prof. Tomomi Kawasaki) and the University of Tokyo (Mentor: Prof. Yuichi Hashimoto), respectively. He then obtained his Ph.D. in pharmaceutical sciences from the University of Tokyo (2011) (Mentor: Prof. Yuichi Hashimoto at the University of Tokyo, and Prof. Mikiko Sodeoka at RIKEN). Subsequently, he worked as a research associate at the group of Prof. Carlos F. Barbas III at the Scripps Research Institute (2011–2012). He was a Research Fellow of the Japan Society for the Promotion of Science (2010–2012). Post this, he was appointed as an Assistant Professor at the group of Prof. Hiroyuki Nakamura at Gakushuin University (2012–2014) and at the Tokyo Institute of Technology (2014–2020). He has been in his current post since April 2020 and is leading an independent research group (Mentor: Prof. Minoru Ishikawa). He received the Pharmaceutical Society of Japan Award for Young Scientists (2021). His research interests focus on protein chemical modifications.
owing to the short-lived radical species generated from the catalyst. While radical-mediated dityrosine formation reactions on tyrosine residues in vivo are known, tyramide 5, which mimics tyrosine residues, has been used as a tyrosine residue modification reagent. Enzymatic activation of tyramides with single-electron oxidation triggers tyrosine modification of the enzyme’s surrounding environment and provides valuable research tools (Fig. 1C). For example, controlling the tyramide-utilizing modification reaction around horseradish peroxidase (HRP)-conjugated antibodies has been applied to the signal amplification technique for immunostaining64–67) and to analyze the clustering of membrane proteins on the cell membrane.68) In addition, the APEX method69,70) which utilizes an engineered peroxidase that is active even in the intracellular environment to label proteins 20 nm around the enzyme with tyramide, has been developed as a technique to comprehensively reveal the cellular localization of proteins at the sub-organelle level and has been actively applied in recent years.71–74)

In addition to enzymatic approaches, small-molecule catalysts have been actively studied in recent years. In particular, small-molecule catalyst approaches enable higher spatial control than enzymes and provide powerful research tools for controlling the localization of the active center of the catalyst at the nanometer scale. Catalytic methods, such as the activation of electrophiles,57,60,86) have been de

Fig. 2. Proximity Labeling Using Hemin and Its Biological Application
A) Oxidative stress hotspot analysis. B) Selective labeling of G4-binding proteins using G4-hemin complex formation and enhanced peroxidase activity.

We have developed a radical-mediated tyrosine-selective modification (tyrosine click) focused on the catalytic control of protein chemical modification. We have also developed a site-selective modification of proteins by utilizing our original modification methods’ characteristics and target protein/site-selective modification based on controlling the positional relationship between the catalyst and protein. This review mainly focuses on the development and application of these tyrosine residue modification methods. Finally, we discuss the novel histidine modifications found based on the common experimental approach of utilizing highly reactive species.

2. Hemin-Catalyzed Tyrosine Click

We focused on the chemical structure of luminol (3) as a molecule with a cyclic hydrazide structure similar to that of the PTAD precursor phenylurazole 1 (Fig. 1A). The luminol reaction is a well-known chemiluminescence reaction used in criminal investigations. In the luminol reaction, the heme structure in the blood’s hemoglobin acts as a catalyst to oxidize luminol. Chemiluminescence occurs due to the denitrification reaction (–N₂) of luminol from its oxidation intermediates. As mentioned above, in PTAD, the electrophilic isocyanate produced by the denitrification reaction induces side reactions that cause a decrease in tyrosine residue selectivity. In contrast, luminol does not produce electrophilic byproducts even after the denitrification reaction, which led us to believe that it would be a tyrosine residue selective modification method. We tested the reaction with various luminol derivatives using hemin as the catalyst. The structure–activity relationship of luminol derivatives as tyrosine labeling agents revealed that N-methylated luminol derivatives (N-Me Lumi, 4) did not exhibit chemiluminescence but instead labeled the tyrosine residues efficiently73) (Fig. 1B).

This reaction was considered to be because of the oxidation of N-Me Lumi by a highly reactive species called compound I ([PPIX]+ Fe(IV)O), which is produced by the reaction of hemin with hydrogen peroxide (H₂O₂). A subsequent investigation suggested that the radical species generated by the single-electron-transfer reaction between compound I and N-Me Lumi occurred because N-Me Lumi is oxidized by one electron at 0.7 V (vs. Ag/AgCl), which is comparable to that of the tyrosine residues.62,88,89) We also hypothesized that the resulting radical species would selectively modify the proximity environment of hemin.

As the activation of hemin is also known as an amplification factor of reactive oxygen species (ROS), we thought that labeling by N-Me Lumi would be a technology to visualize hotspots of oxidative stress (Fig. 2A). We found that tyrosine residues in the hemin-binding site of albumin, which bind to hemin in blood, were efficiently labeled and that the proteins with oxidative damage caused by peroxidase stimulation in mouse liver lysates were visualized by fluorescence labeling.90)

Hemin is also known to form a complex with the G-quadruplex (G4) structure. G4 structures have biological functions, such as transcriptional regulation, telomere elongation, in epigenetics, replication, RNA processing, mRNA localiza-
tion, and translation regulation.\textsuperscript{91,92} G4-binding proteins are thought to regulate each of these functions, but the dynamic nature of G4-binding protein interactions makes it difficult to analyze them. Many of them remain unknown. In the conventional method, G4-binding proteins were identified by pull-down assays and stable isotope labeling with amino acids in a cell culture (SILAC)-based quantitative proteomic method to further elucidate the functions of G4 structures.\textsuperscript{93–95} The photoaffinity labeling techniques for the dynamic identification of G4-binding proteins have been reported very recently.\textsuperscript{96,97} With this research background, we focused on the fact that binding of hemin to parallel G4 structures enhanced hemin-induced peroxidase activity\textsuperscript{98–100} (Fig. 2B). Using a telomeric repeat-containing RNA TERRA, which forms a parallel G4 structure, we demonstrated in an in vitro model experiment that tyrosine residues in the RNA-binding site of the TERRA binding protein UP1 are selectively labeled. In addition, TERRA-binding proteins from HeLa cell lysate were comprehensively labeled with biotin, enriched using streptavidin beads, and identified using nano liquid chromatography-tandem mass spectrometry (LC-MS/MS).\textsuperscript{101}

3. Enzyme-Catalyzed Tyrosine Click

We found that the modification of tyrosine residues by N-Me Lumi was more efficient than hemin by using HRP as a catalyst. HRP has high peroxidase activity and is frequently used in biological research.\textsuperscript{54} In the case of hemin-catalyzed tyrosine click, a high concentration of peroxide, such as 1 mM H$_2$O$_2$, was required. However, using HRP as a catalyst, the reaction could be carried out at a lower concentration of H$_2$O$_2$ (45 $\mu$M), and the efficiency of the reaction was increased while suppressing the oxidative side reactions, such as the oxidation of cysteine residues.\textsuperscript{54}

In the enzyme-based method, radical species are generated close to the enzyme’s active site because of the limitation of the single-electron transfer distance approx. 1.4 nm).\textsuperscript{102} Compared to reactions using low-molecular-weight catalysts such as hemin, the protein structure around the active center behaves as a very bulky catalyst. In addition, tyrosine residues exposed on the protein surface are limited. Tyrosine residues exposed on the protein surface are more likely to be in close proximity to the catalyst than buried residues and are therefore more easily modified.

We focused on the surface exposure levels of tyrosine residues in antibody immunoglobulin G (IgG) structures. Tyrosine residues react with various ROS, such as singlet oxygen, hydroxyl radical, and peroxynitrite, \textit{in vivo}, resulting in protein damage.\textsuperscript{103} Tyrosine residues in the constant region of human IgG are essentially unexposed and probably resistant to oxidative damage and have a long half-life in blood
However, complementarity-determining regions (CDRs) have markedly different sequences among antibodies. When a tyrosine residue is present in a CDR, it may become the most exposed tyrosine residue in the antibody structure. Modification of antibodies with N-Me Lumi catalyzed by HRP specifically labeled tyrosine residues in CDR (Fig. 3A). Surprisingly, the antibodies functionalized with tyrosine residues in the CDR did not lose their antigen recognition ability. At least in the anti-HER2 antibody trastuzumab, the antigen recognition ability was not severely impaired.\(^2,3\) We believe this is because the tyrosine click reaction does not lose the phenolic hydroxyl groups and aromaticity, which are impor-
tant for protein–protein interactions. Antibody–drug conjugates conjugated with the toxic compound DM-1 at tyrosine residues in the CDRs showed antitumor efficacy comparable to that of commercially available ADC Kadcyla in a xenograft tumor model of HER2-positive cells \(^ {62} \) (Fig. 3B).

More recently, we reported a method to convert full-length antibodies into fluorescent immunosensor molecules by taking advantage of their ability to selectively functionalize CDRs. Fluorescent molecules modified near antigen recognition sites (CDRs) are known to have their fluorescence quenched by photoinduced electron transfer (PET) with conserved tryptophan residues in the antibody structure. In contrast, when the modified antibody binds to the antigen, the fluorescent molecules are expelled from the hydrophobic pocket of the antibody, thereby resolving the PET and restoring fluorescence \(^ {104,105} \) (Fig. 3C). Our method of modifying fluorescent molecules via tyrosine residues in CDRs allows for the rapid acquisition of sensor molecules whose fluorescence turns on in response to antigens without the need for genetic manipulation and time-consuming examination of protein expression conditions. \(^ {106} \)

We further developed a laccase-catalyzed tyrosine click to efficiently modify tyrosine residues under mild reaction conditions with minimal oxidative side reactions. Laccase is a copper protein that belongs to the oxidoreductase class, and it catalyzes single-electron transfer with suitable redox potential for the activation of N-Me Lumi. \(^ {107} \) The active site of a laccase comprises four copper atoms and oxidizes a substrate by reducing \( \text{O}_2 \) to \( \text{H}_2\text{O} \). \(^ {108,109} \) In the laccase method, a single-electron transfer reaction consumes molecular oxygen (\( \text{O}_2 \)) in the buffer; hence, adding oxidants such as \( \text{H}_2\text{O}_2 \) is not necessary (Fig. 4A). The reaction conditions using laccase functioned efficiently, allowing tyrosine residues to be labeled with fewer oxidative side reactions and more efficiently than the HRP-catalyzed method. \(^ {55} \) We have shown that the laccase-catalyzed tyrosine click can efficiently functionalize human serum albumin (HSA) with minimal oxidative damage \(^ {110} \) (Figs. 4B, 4C).

4. Photocatalyst-Catalyzed Proximity Labeling

Peroxidase-based methods require \( \text{H}_2\text{O}_2 \) treatment to drive the reaction, which leads to oxidative protein damage and cell invasiveness. However, in the case of laccase, it is difficult to control the timing of the reaction because the reaction driving force, oxygen molecules, are always around the catalyst. We focused on visible light irradiation of a photoredox catalyst, as visible light is an easily controllable external stimulus. The Ru(bpy)\(_3\) complex is excited by visible light stimulation (approx. 450 nm) and oxidized from the excited Ru(II) ([Ru(bpy)\(_3\)]\(^{2+}\)) to Ru(III) ([Ru(bpy)\(_3\)]\(^{3+}\)) under oxidative reaction conditions. The oxidation potential of this reaction is 1.1 V (vs. Ag/Ag\(^+\)), which is sufficient to radicalize the tyrosine residue. Fancy and Kodadek reported a method for generating phenoxy radicals using Ru(bpy)\(_3\) complexes and cross-linking tyrosine residues. \(^ {111} \) After a screening evaluation of various redox-active compounds, we found that tyrosine residues were efficiently modified when the \( \text{N}^\text{A}-\text{acyl-N,N-dimethyl-}
\text{phenylenediamine structure (6) was used as a labeling agent.} \)

The addition of ammonium persulfate (APS) promoted the reaction, and even without the addition of an oxidant, the
tyrosine modification proceeded; singlet oxygen ($^1$O$_2$) generated by the photosensitizing property of the Ru(bpy)$_3$ complex was considered to be the driving force for the formation of Ru(III)$_{112}$ (Fig. 5). The addition of superoxide dismutase (SOD), which metabolizes superoxide anion radical (O$_2^−$) to H$_2$O$_2$, accelerates the reaction, suggesting that $^1$O$_2$ acts as the driving force for the reaction.

When Ru(bpy)$_3$ was used as a single-electron transfer catalyst, the reaction was completed in close proximity to the catalyst, as was the case with hemin or peroxidase. We designed and synthesized carbonic anhydrase (CA)-ligand-conjugated Ru(bpy)$_3$. This molecule binds to CA and catalyzes CA-selective modification of the surface of CA in a protein mixture. However, in the method using N'-acyl-N,N'-phenylenediamine (6), the selectivity of CA was not satisfactory in complex protein mixtures such as cell lysates, where the target protein is a minor component. Electrochemical analysis showed that 6 generated relatively stable radical species. We hypothesized that the labeling reagent, which causes a selective modification with a labeling radius of a few nanometers, must generate unstable radical species. We investigated the reaction with a peptide substrate in which Ru and Tyr residues are forced to be in close proximity, the molecular ruler (Ru-(Pro)$_n$-Tyr), and found 1-methyl-4-arylurazole (MAUra, 7) as a proximity-dependent labeling reagent with a nanometer-scale labeling radius (Figs. 6A, 6B). Although it is not clear whether the formation of tyrosyl radicals on protein is involved in the proximity tyrosine labeling, we revealed that the labeling reagent is catalytically radicalized and is involved in the labeling. The stability of the radical species of the labeling reagent was suggested to be involved in the labeling radius.

In addition to the target protein-ligand conjugated Ru(bpy)$_3$, we thought that selective modification of ligand-bound proteins in a protein-mixed system could be achieved by constructing a reaction field in which Ru(bpy)$_3$ and ligand-bound proteins are forced into proximity. Therefore, we functionalized the surface of magnetic beads with the target-protein ligand and ruthenium photocatalyst. A covalent modification method for the bead surface has already been established using the amidation reaction between an N-hydroxy succinimide (NHS) ester and an amine group.

In the approach using ligand-conjugated Ru(bpy)$_3$, the synthesis stage of the catalyst is a research barrier because its purification is not easy due to its high water solubility and amphiphilic nature. Contrastingly, the beads can be easily functionalized with ligand molecules and Ru catalysts separately, making them highly applicable to a variety of ligands. However, nonspecific protein adsorption on the beads due to the charge of the [Ru(bpy)$_3$]$_{112}^2+$ structure emerged as a problem. By changing the ruthenium complex to ruthenium/4,4'-
dicarboxybipyridine (Ru/dcbpy) complex (10) to neutralize the cation charge by intramolecular COO⁻ groups, we succeeded in selectively binding the ligand-binding protein to the bead surface and selectively labeled it (Fig. 7A).

We then applied protein labeling to low-affinity ligand-binding proteins on the bead surface. The affinity purification method using ligand-functionalized beads can only be applied to high-affinity interactions ($K_D < 10^{-6}$ M). Because many conventional approaches fail to apply weak interactions ($K_D > 10^{-4}$ M), information about weak protein-ligand complexes is still limited. Recently, protein labeling reactions on solid-phase supports have been investigated to identify binding proteins for low-affinity ligands. We have applied this method to selectively and irreversibly label ligand-binding proteins on the bead surface with the labeling reagent MAUra, regardless of binding affinity. In other words, this technique tags the ligand-binding history to the proteins so that even transient binding proteins can be tracked. We labeled peanut agglutinin (PNA) in a protein mixture using lactose ($K_D = 770 \mu$M)$^{118}$) as a ligand (Fig. 7B). Using the beads allowed us to successfully label and identify galectin-1, galectin-3, and protein–protein interaction partners with galectin-3 from cell lysates by nanoLC-MS/MS. To the best of our knowledge, this is the first example of the identification of lectins for specific carbohydrates in a non-biased experimental system.$^{119}$

5. Photocatalyst-Proximity Histidine Labeling Using Singlet Oxygen

We focused on singlet oxygen generated from photosensitizers as a different approach to single-electron transfer-mediated proximity labeling. Singlet oxygen ($\text{O}_2$) is a highly reactive oxygen species generated by light irradiation of a photocatalyst. As the diffusible distance of $\text{O}_2$ is approximately 10 nm, spatially restricted oxidation around the photocatalyst can be controlled.$^{120}$ Chromophore-assisted laser inactivation (CALI) is a known method for generating $\text{O}_2$ to deactivate target molecules and their assembled molecules in living systems.$^{121,122}$ We have also succeeded in target-selective oxidation in mixed-protein systems using the ligand-conjugated Ru(bpy)$_3$ complex.$^{112}$ We believe that developing protein modification using $\text{O}_2$ is a promising method for proximity labeling.

Histidine residues react with singlet oxygen to produce an electrophilic oxidized form.$^{123,124}$ Therefore, we considered the possibility of efficiently supplementing the oxidized histidine using nucleophiles and investigated various candidate nucleophilic compounds. When histidine-containing peptides were selected as the substrate and rose bengal as the photosensitizer, MAUra showed high conversion efficiency. Due to the high nucleophilicity of the hydrazide structure$^{125}$ and the $pK_a$ of 4.7,$^{126}$ the anionic form of MAUra was considered to trap oxidized histidine efficiently (Fig. 8A).

Focusing on the IgG antibody size of 10 nm, a labeling radius of up to 10 nm for $\text{O}_2$ diffusion, antibody Fc region-
selective labeling with MAUra on beads functionalized with photosensitizers, and Fc-binding ligands were performed. As mentioned earlier, ruthenium complexes are also known to act as photosensitizers and generate $\text{O}_2$. We took advantage of the beads described in the previous section. Magnetic affinity beads functionalized with Ru/dcbpy and Fc-ligand ApA,\(^{[27]}\) a non-peptidyl mimic of protein A (Fig. 8B). Trastuzumab was labeled on the beads and cleaved by papain into the Fc and Fab regions. The Fc region was labeled selectively. NanoLC-labeled on the beads and cleaved by papain into the Fc and non-peptidyl mimic of protein A (Fig. 8B). Trastuzumab was functionalized with Ru/dcbpy and Fc-ligand ApA, especially Prof. Hiroyuki Nakamura, Prof. Carlos F. Barbas III, Dr. Kosuke Dodo, Dr. Tatsuya Niwa, Dr. Michihiko Tsushima, and Mr. Keita Nakane. This research was partially supported by Grants-in-Aid for Young Researchers (15K12742), Young Scientists (A) (13K10127), “Homeostatic Regulation by Variational Feedback Control: Zetaplot Stabilizes an Active State”, 2016–2019. The research was also supported by Grants from the Uehara Memorial Foundation, and Tamagawa Seiki Co., Ltd.

6. Conclusion

We described our recent progress toward protein chemical modification using highly reactive chemical species, such as radicals and ROS. We applied these developed protein modification reactions to the functionalization of proteins and the identification of proteins that bind to biologically active molecules. Taking the functionalization of antibodies as an example, we were able to selectively modify tyrosine residues in antibody CDRs by using a reaction that depends on the degree of exposure to the protein surface. Moreover, we were able to selectively modify histidine residues in the Fc region by proximity labeling, in which the catalyst was placed in close proximity to the Fc region. Further studies, including the development of novel protein modification reagents, proximity labeling reactions, and biological applications using new strategies are currently ongoing.

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Conflict of Interest The author declares no conflict of interest.

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