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Opinion Article

Applications of Genetic Code Expansion in Drug Discovery and Development

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DESCRIPTION

The Genetic Code Expansion (GCE) technique allows for the site-specific insertion of an Unnatural Amino Acid (UAA) into proteins. By requiring the presence of a UAA to prevent the premature termination of protein synthesis in response to an amber codon Uracil Adenine Guanine (UAG) this controls mRNA translation. A gene to be expressed that has the amber stop codon within its open-reading frame, a tRNA that contains the correct anticodon, a tRNA synthetase that has a binding pocket for the amino acid to be inserted and can recognize the tRNA, and the amino acid to be inserted make up the total of four components of GCE by amber suppression.

Target cells can express a protein that contains a UAA in a site-specific way by adding the genetic components. Numerous translation-regulated applications, such as biological activation and inactivation, functional control of proteins, and the expression of therapeutics, have been made possible by recent advancements in GCE approaches. GCE modifications on the basis of the complete mRNA transcript control transcription and translation. Compatible UAAs were delivered to target cells and labelled with a fluorescent dye site-specifically using bio orthogonal click chemistry.

Due to their superior reaction kinetics, biocompatibility, and high orthogonality, amino acids that may conduct an inverse electron-demanding Diels-Alder reaction are the focus of click labelling in particular. This led to the discovery of several aaRSs and TRNAs that allow the inclusion of such amino acids. The protein turnover rate, UAA addition to the cell, absorption, tRNA loading, and integration into the target protein *via* the ribosome are the only constraints on the efficiency of this fusion approach. As a result, when UAAs are added to target cells, any conventional or optimized aaRS/tRNA system could activate protein characteristics encoded downstream of a PTC, potentially allowing re-localization or re-functionalization of the target protein. The tRNA cassette frequently has varying numbers of copies. The assumption that tRNA copy number scales with improved GCE efficiency is still up for a debate in the scientific community and has not been fully demonstrated. Unexpectedly, a Nuclear Localization Sequence (NLS) was discovered in the protein sequence of the most common *M. mazei PylRS*, which can cause the *PylRS* to accumulate in the nucleus of target cells. Because of this, an approach to compel a higher cytoplasmic localization of the *PylRS* in more recent GCE systems has been to fuse an N-Terminal Nuclear Export Sequence (NES) to the *PylRS*. Since the N-Terminal Domain (NTD) of the *PylRS* plays a crucial role in tRNA recognition and changes at the enzyme's N-terminus can disrupt the complex formation between *PylRS* and tRNA, it is still unclear whether and how much this modification proves to be advantageous.

Different sets of mutations within the *aaRS IPYE, HRS*, as well as tRNA sequence optimization (M15) and tRNA copy number, as well as other factors like reengineered termination factors, were introduced in an effort to increase GCE efficiency and UAA incorporation. Additionally, it was discovered that the structure of the UAA and the site of incorporation within the polypeptide sequence both had a significant impact on GCE effectiveness. However, there is a lack of comparative evaluation of how each improvement affects GCE efficiency, and its combinatorial optimization potential is unrealized. Complete maskings of receptor epitopes or a restriction on antibody penetration into the cell-cell interface where a GPCR and its ligand are expressed are possible outcomes of this. As a result, Immuno histochemical analysis of their co-localization in tissues and cell cultures is rendered unreliable or, in the worst case scenario, useless, which can have an impact on how experimental data should be interpreted.

Despite being much smaller than antibodies, novel immunoagents like nano- and monobodies that target G protein coupled receptors (GPCRs) may also be impacted by this situation. Alternative labelling techniques, like receptor fusions with genetically encoded fluorophores or enzymes, can solve this issue but are limited by their size. The effect of these labels on receptor structure and function restricts their application inside the receptor protein. The structure-function balance of GPCRs has previously been successfully maintained by the minimally invasive placement of UAA using GCE, even within individual domains.

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The comparison of a broad range of properties, including receptor/ligand dosage and stoichiometry, the testing of binding interfaces on complex formation, the effects of receptor/ligand engagement on GPCR signals and biochemical processing of the receptor molecules, and the impact of pharmacological adhesion process modulators, can now be made in conjunction with time-controlled surface anchoring of ligands through GCE. The labelling of difficult-to-access protein complexes at cellular interfaces as well as the induction of protein complex formation at a specific time point upon addition of a UAA are both made possible by GCE of GPCR-ligand complexes in living cells, which together represent a significant advancement in the field of GPCRs. This offers up new avenues for studying protein complex formation with high temporal control and visualizing PPI, which had been inaccessible using normal immunolabeling methods.