Radically Rethinking Biocompatibility: Radical Polymerizations in Living Systems

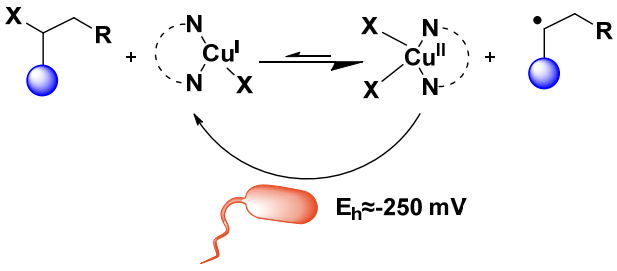
Reported by Dylan Brandt November 15, 2022

INTRODUCTION

The ability to perform chemical reactions orthogonally to biological systems has enabled significant advances such as understanding cell surface glycans and was recognized with the 2022 Nobel Prize in Chemistry for the development of click-chemistry and bioorthogonal chemistry. A new paradigm of bioorthogonal reactions may be evolving within the literature from an area most organic chemists would not think of as biocompatible, radical polymerizations.[1] Polymers are ubiquitous in biology, in naturally occurring polymers such as proteins and polyphosphates (DNA & RNA), as well as synthetic polymers used in pharmaceutical-polymer conjugates and as cell-biology tools. Seminal advances over the last ten years have enabled radical polymerizations to become increasingly biocompatible, from bacteria driven polymerizations, to exploring these reactions as a potential therapeutic for cancer treatment. This literature seminar aims to highlight these advances as well as the unanswered questions which stand in the way of further development of this chemistry and potential clinical applications.

EXTRACELLYULAR POLYMERIZATIONS

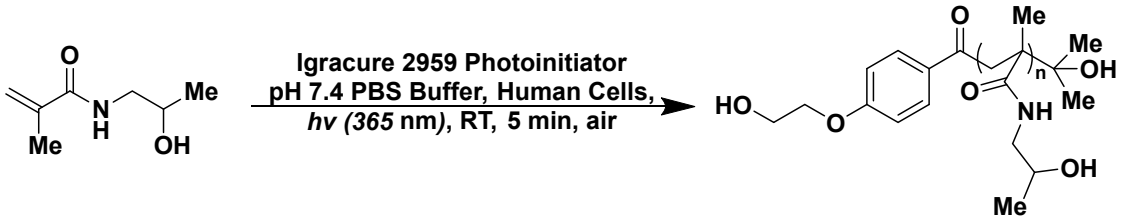
An example of radical polymerizations in a biological context was the use of Cu catalyzed atom transfer radical polymerization (ATRP) by Magennis *et al.* in the bacteria instructed synthesis of polymers.[2] Leveraging bacterial Cu redox homeostasis mechanisms, the reducing gradient generated by the cell was used to drive the polymerization and generate polymers specific to the membrane topology of the host bacteria (**Scheme 1)**. The polymers demonstrated the ability to selectively bind the host bacteria, inducing bacterial aggregation, while incubation with a foreign bacterial strain yielded reduced aggregation. Niu *et al.* demonstrated further extracellular polymerization in the cytocompatible photoinduced electron transfer reversible addiction-fragmentation chain transfer polymerization (PET-RAFT) on the cell surface.[3] Yeast and human Jurkat cells were modified with chain transfer agents and submitted to PET-RAFT conditions, giving polymer-modified cell surfaces with high cell viability.



Scheme 1. Bacterial instructed ATRP for the synthesis of host-specific polymers.

INTRACEULLA R POLYMERIZATION

In 2019, Geng, *et al.* demonstrated that radical polymerizations could occur not just on the surface of cells, but inside cells without a reduction in cell viability.[4] Utilizing a system with a non-toxic monomer and radical photoinitiator, which both showed moderate cellular uptake, polymerization was performed inside of HeLa cells while more than 85% of cells remained viable (**Scheme 2**). Although cell cycle progression and cell viability remained largely unaffected, intracellular polymerization was found to affect the migratory aptitude of the cells as well as actin dynamics within the cell. This principle was further investigated by Zhang *et al.* as a potential treatment for cancer utilizing a different monomer to generate a cytotoxic polymer.[5] Choosing in this case to utilize a PET-RAFT system for increased control over the polymerization event, intracellular polymerization was found significantly decrease cell viability across multiple cell lines. Intratumor injection and polymerization of tumor bearing mouse models showed decreased tumor burden and increased mouse survival, comparable to known therapeutics such as doxorubicin.



Scheme 2. Cytocompatibile photoinitiated intracellular radical polymerization.

CONCLUSIONS AND OUTLOOK

Biocompatible radical polymerization represents a powerful emerging tool in the toolbox of cell biology. Preliminary studies applying this chemistry to enhance the activity of known therapeutics demonstrate the potential of this strategy but remain hampered by the same uncertainties which underly the landmark research. The studies performing this chemistry within human cells lack the fundamental mechanistic understanding of the chemical processes and the biological mechanism of action necessary to further develop therapeutics which utilize this approach. Cross-reactivity studies remain necessary to prove the bioorthogonality of the reactive radicals within these systems.

REFERENCES

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