Inducing Changes to Cell Signaling via the Application of Macromolecular Hydrogen Sulfide Donors

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The gasotransmitters (nitric oxide, carbon monoxide and hydrogen sulphide) are a family of otherwise gaseous molecules which are intimately involved in many cell signalling processes. Among these, hydrogen sulfide (H\textsubscript{2}S) has been implicated in a wide array of cell signaling cascades which trigger physiological events ranging from vasodilation to cell proliferation.\textsuperscript{1} Further, perturbations to H\textsubscript{2}S signaling have been associated with a number of different pathologies.\textsuperscript{2} As such, there is considerable interest in the development of materials that can release H\textsubscript{2}S in a cellular environment. This presentation will report the synthesis of macromolecular H\textsubscript{2}S donors which can trigger cell signaling pathways in both the cytosol and at the cell membrane.\textsuperscript{3} The macromolecular donors were synthesized by first preparing copolymers having pendent oligo(ethylene glycol) and benzonitrile groups, and then transforming the benzonitrile groups into primary aryl thioamide groups via thionation with sodium hydrosulfide. The thioamide groups were successfully incorporated into (i) a hydrophilic copolymer or (ii) a block copolymer. In the case of the block copolymer, the thioamide groups were successfully inserted into either the hydrophilic or hydrophobic domain. Amperometry was used to demonstrate release of H\textsubscript{2}S under simulated physiological conditions, with the release kinetics being impacted by both the molecular architecture of the donor and the presence or absence of a suitable trigger for H\textsubscript{2}S release (L-cysteine).

The macromolecular H\textsubscript{2}S donors were subsequently applied to HEK293 cells, and were shown to elicit a slow and sustained increase in cytosolic ERK signalling (monitored using a FRET-based biosensor). Additionally, the macromolecular donors were shown to induce a small, fast and sustained increase in plasma membrane-localized PKC activity immediately after addition to cells. By using an H\textsubscript{2}S-selective fluorescent probe in live cells, we confirmed release of H\textsubscript{2}S from the macromolecular donor over time scales consistent with the signaling observations. These results demonstrated that the use of macromolecular H\textsubscript{2}S donors enabled the instigation of spatiotemporally confined cell signaling events.

References