Design and Application of "Smart" Polymers for Separations, Diagnostics and Drug Delivery

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We have been combining stimuli-responsive or "smart" polymers with biomolecules to yield biohybrid compositions that can: (a) "switch" the solubility of proteins and other biomolecules to cause reversible phase separation, (b) "switch" protein recognition processes *on* and *off* reversibly by blocking and unblocking protein recognition sites, or (c) "switch" *on* transport across lipid membranes by disrupting the membrane. These actions are stimulated by small changes in local environmental conditions, eg, by thermal-, pH- or light-driven changes in the smart polymer solubility. (eg, see Hoffman, 2000 and Stayton, 2005)

In the first case, we have used the smart polymer-protein conjugates to thermally-phase separate an affinity protein along with its binding partner, similar to affinity chromatography done in solution. We have also conjugated the smart polymer to an antibody, allowed it to bind its antigen, and then added a second, labeled antibody to form the immune complex "sandwich"-polymer conjugate. When we thermally-phase separate this complex-conjugate and wash the precipitate, we can redissolve it in fresh buffer and assay the signal from the label. This is like doing ELISA in solution, without the microtiter plate or plate reader. More recently we have conjugated the smart polymer to nano-beads, and also linked affinity proteins or enzymes to the beads. We are using these smart nano-beads in microfluidic devices, for diagnostic assays and lab-on-a-chip enzyme bioprocesses. (Malmstadt, 2003, 2004)

In the second case, we have conjugated temperature-, pH-and light-responsive polymers at specific sites on recognition proteins near the active site of the protein. When the polymer is stimulated to collapse by changing temperature, pH or light, it will phase separate, or in the case of site-specific conjugates, the active site is blocked, and the reverse of the stimulus restores the protein activity. We are applying this principle to affinity separation and enzyme processes. (Shimoboji, 2001 and 2002)

In the third case, we have combined pH-responsive polymers with protein or nucleic acid drugs that are to be delivered to intracellular targets such as the ribosomes or nucleus. When the polymer + drug formulation is taken up into a cell by endocytosis, the acidic endosomal environment causes the polymer to partition into the endosomal lipid bilayer membrane, leading to its disruption and allowing the drug to escape into the cytosol. In this way, the drug avoids degradation by lysosomal enzymes. We are using these pH-sensitive polymers for intracellular delivery of a variety of therapeutic biomacromolecules, including proteins, antisense oligodeoxynucleotides (ODNs), siRNA and DNA. (Stayton, 2005)

This talk will cover these three smart biohybrid systems.

Selected Recent References

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