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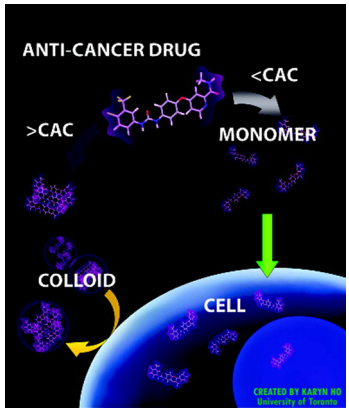
COLLOID CHARACTERIZATION

In aqueous solution, many small organic molecules can form colloids, or microscopic aggregates that are evenly dispersed throughout the solution. When in solution with proteins or other biomolecules, colloids can alter protein activity and cause nonspecific inhibition, suggesting that this phenomenon could skew the interpretation of small molecule activity in various high-throughput screens. Owen *et al.* (DOI: 10.1021/cb300189b) now explore the tendency of 7 anticancer drugs and 1 diagnostic agent to form colloids and assess the biological consequences of their colloid formation.

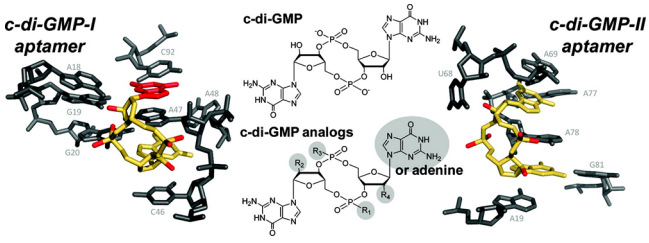


All 8 of the molecules studied were found to form colloids in biochemical buffer and in cell culture medium. Moreover, in cell-based assays the activity of the colloidal form of 3 of the drugs was found to be dramatically reduced compared to the monomeric form. In addition, investigation of the colloidal properties of the diagnostic compound revealed surprising new details regarding how this compound functions as an agent to measure vascular permeability. This study offers compelling insights into how colloidal formation affects biological activity and could lead to new strategies to manipulate colloid formation and behavior.

SWITCHING UP BACTERIAL TARGETING

Bacteria produce a circular RNA dinucleotide, c-diGMP, that has been implicated in the regulation of numerous processes including biofilm production, motility, and virulence. While some of these activities are mediated via interactions with various bacterial proteins, c-di-GMP also binds to riboswitches, RNA elements that reside within bacterial mRNAs and regulate gene expression. Riboswitches are an attractive target for the design of novel antibiotics, especially in light of the growing resistance to drugs targeting commonly pursued pathways such as bacterial cell wall synthesis. To gain insight into how best to target c-di-GMP-binding riboswitches, Furukawa *et al.* (DOI: 10.1021/cb300138n) examine the interactions between numerous c-di-GMP analogues and two classes of riboswitches derived from different species of pathogenic bacteria.

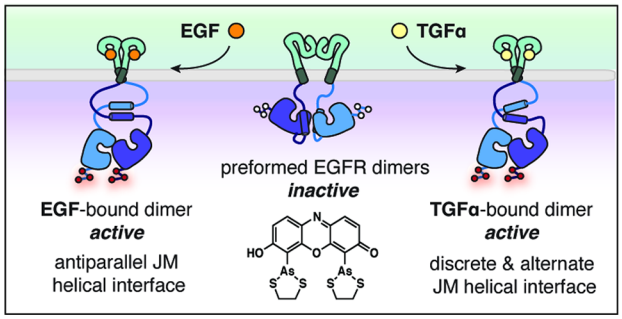
Binding interactions between over 20 c-di-GMP analogs and the riboswitches were characterized. These characterizations shed light onto how c-di-GMP might modulate transcription



termination, and the analogues served as valuable tools toward the development of high-throughput screens for small molecule riboswitch binders.

JUSTIFYING THE JUXTAMEMBRANE DOMAIN

Receptor tyrosine kinases such as the epidermal growth factor receptor (EGFR) are important liaisons between the outside and the inside of a cell, transmitting information from extracellular ligand binding events to the intracellular environment. While the functional consequences of these binding events have been intensively studied, the structural changes within the receptor that accompany them are less well understood. Scheck *et al.* (DOI: 10.1021/cb300216f) now report the use of a clever chemical tool called bipartite tetracysteine display to characterize conformational changes in EGFR that take place in response to ligand binding.



In bipartite tetracysteine display, a fluorescent signal is produced when a structure of interest is folded and assembled properly. Using this approach, the structure of a key intracellular region of EGFR called the juxtamembrane domain was examined. Intriguingly, when the EGFR binds one of its ligands, EGF, the juxtamembrane domain adopts one structure, but when it binds a different ligand, TGFα, it forms a different structure. These findings offer insight into how structural changes within receptor tyrosine kinases might influence the functional ramifications of distinct ligand binding interactions.

Published: August 17, 2012

   dx.doi.org/10.1021/cb300365t | *ACS Chem. Biol.* 2012, 7, 1307–1307