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FIRST REACTIONS

Tension Promoted Sulfur Exchange for Cellular Delivery

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Using the inherent strain in ETP compounds can shoot cargo across cell membranes without the need for endosomal escape.

Cellular delivery is crucial for the discovery and development of novel drugs and probes. However, the efficient and reliable delivery of bioactive molecules into cells remains both challenging and limited in scope. Therefore, there is an emerging interest to develop conceptually innovative approaches to precisely deliver relevant biomolecules to a target site. With this in mind, Matile and co-workers have taken a significant step forward by using epidithiodiketopiperazines (ETPs) for the nontoxic delivery of model probes to the cytosol and particularly the nucleus, without endosomal capture, making this approach "unstoppable" by all conventional inhibitors of endocytosis.[1]

In their previous studies, Matile and co-workers reported on the use of disulfide ring tension for thiol-mediated cellular uptake (Figure 1).[2−5] These studies indicated that strained disulfides with decreasing CSSC dihedral angles (θ) react best with exofacial thiolates for covalent binding to the cell surface,[6−8] thus increasing the uptake efficiencies. In the current work, ETPs are introduced to drive ring tension to the maximum ($\theta \approx 0°$) (Figure 1), which facilitates the delivery into cells through a novel multitarget hopping mode of action.

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ETPs are a fascinating family of natural products with important biological functions, including cytotoxic, antibacterial, antitumor, antivirus, and antimalarial activities.[9,10] Remarkably, the biological activity of ETPs critically depends on their transannular disulfide bridge, a distinguishing feature of their complex structures. The CSSC dihedral angle near 0° allows for covalent capture by nonactivated thiols and disulfides. Matile and co-workers have employed the high reactivity of ETPs in disulfide exchange reactions for their use as potential transporters for cellular uptake. The corresponding thiol-mediated cellular uptake approach is able to promote highly efficient delivery of model probes to the cytosol and nucleus. This strategy takes advantage of a dynamic covalent disulfide exchange with exposed thiols on the cell surface to allow for the attachment of the transporter and subsequent uptake (Figure 2).

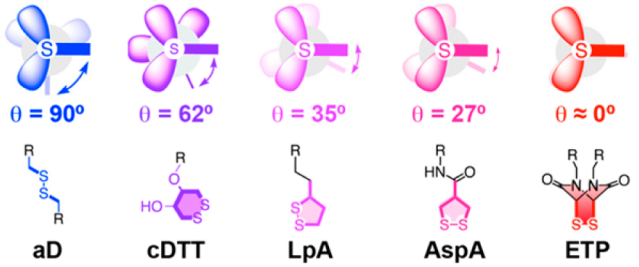

Figure 1. Structures of disulfides with increasing ring tension [aD, acyclic disulfide; cDTT, cyclic derivative of dithiothreitol (DTT); LpA, derivative of lipoic acid; AspA, asparagusic acid; ETP, epidithiodiketopiperazine].

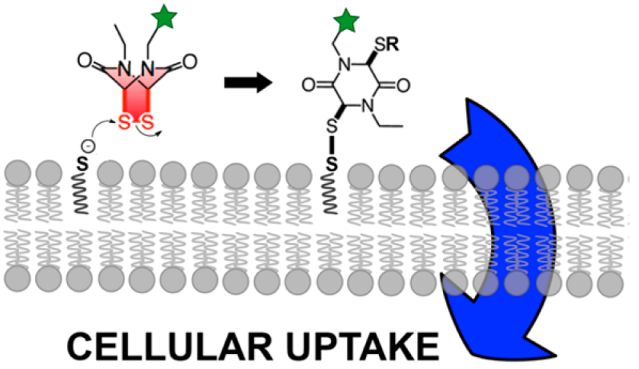

Figure 2. Schematic representation of the ETP-mediated cellular uptake.

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The advantages of the straightforward technology developed by Matile and co-workers are highlighted when it is compared with alternative strain-promoted thiol-mediated uptake methods. According to flow cytometry analysis, the hyperstrained ETPs are much more active than the lipoic acid (LpA) and asparagusic acid (AspA) controls. For instance, ETP-mediated uptake into HeLa Kyoto cells is approximately 20 times more efficient compared to AspA. Therefore, cellular uptake efficiencies increase gradually with increasing ring tension. Moreover, contrary to AspA controls, ETPs have poor response to inhibitors and activators such as cytochalasin B, DTT, or transferrin receptor (TFRC) with siRNA, which indicates that their unique reactivity is decisive for function. Additionally, the results obtained by Matile et al. demonstrate that ETPs can be covalently captured by cellular targets that are otherwise difficult to reach, and suggest that they can change targets during uptake. These stunning characteristics of the ETPs make them potential candidates to be used as efficient delivery transporters.

Matile and co-workers have employed the high reactivity of ETPs in disulfide exchange reactions for their use as potential transporters for cellular uptake.

Although the development of the ETP-mediated cellular uptake approach is still in its early stage, this strategy does have great potential to become a fundamental technology for the efficient delivery of substrates of biological and medicinal relevance.

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