Deconvoluting redox biology with targeted chemistry

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The ability to dissect multicomponent signaling networks has been the bedrock of numerous biomedical breakthroughs. Despite the emerging importance of redox-dependent cell signaling, studying the regulatory roles of reactive diffusible small-molecule messengers remains devilishly difficult. The only general way to study the consequences of redox events has been through "multi-hit" approaches in which the entire specimen is treated with a reactive entity. Multi-hit strategies have yielded important information about stress-associated pathways, but hitting many targets trips many signaling switches simultaneously. Consequently, functional links between upstream modifications on specific targets and downstream response remain unknown. The impact of a single redox event on a single target has thus been completely unaddressed. My laboratory has introduced a new way to selectively flip a single redox switch in cells at a precise time by selective perturbation with redox-derived signaling electrophiles (see Figure). Here we describe an application of our new methodology in target-specific cell activation that triggers single redox events at a specific protein target. We unexpectedly discover that modest modifications on a single target are sufficient to elicit a pharmaceutically important response downstream that is equivalent to whole-cell-stimulated response. The data suggest that our chemistry-driven targeted perturbation approach is an exciting first step to understanding specificity along individual redox signaling trajectories.