No HAT Required! Unusual Radical-Trapping Antioxidant Mechanisms Provide New Strategies for Preventing Oxidative Cell Death

Derek A. Pratt

Department of Chemistry and Biomolecular Science, University of Ottawa, Ottawa, Canada
dpratt@uottawa.ca

The radical-mediated autoxidation of the phospholipids of cell membranes drives ferroptosis, the cell death process that is believed to underlie neurodegeneration and the damage that occurs upon reperfusion of ischemic tissue following stroke or organ transplant. Radical-trapping antioxidants (RTAs) are small molecules which inhibit lipid autoxidation by intercepting chain-propagating peroxyl radicals and have emerged as the most promising therapeutic candidates for pathologies wherein ferroptosis has been implicated. The vast majority of potent anti-ferroptotic RTAs are aromatic amines, which react with peroxyl radicals via H-atom transfer (HAT) from their labile N-H bonds. We recently characterized and/or designed scaffolds that do not rely on HAT for inhibition of (phospho)lipid peroxidation and associated cell death. The first are metal thiosemicarbazones, which undergo ligand-based radical addition and subsequent radical combination reactions that occur largely independently of the metal centre, enabling the paradoxical design of potent platinum-based cytoprotective agents. The second are boronic esters and amides derived from catechols and diaminonapthalenes. The former have previously been developed by Renaud as powerful radical precursors for use in elegant radical chain processes, but which we show can be engineered to undergo interrupted homolytic substitution to trap radicals instead. Both of these new radical-trapping scaffolds suppress ferroptotic cell death in multiple cell lines and can be optimized to achieve potent cytoprotective activities that are on par with some of the most promising pre-clinical and clinical candidates to treat ferroptosis-related conditions. These results underscore the central role of radical reactions in a key pathological cell death process and highlight how radical chemists' mechanistic understanding can be exploited for the design and/or development of seemingly absurd bioactive compounds.