ACS Chemical Neuroscience

In This Issue

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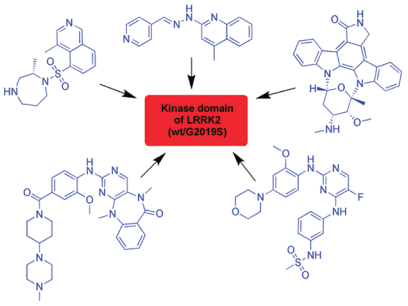
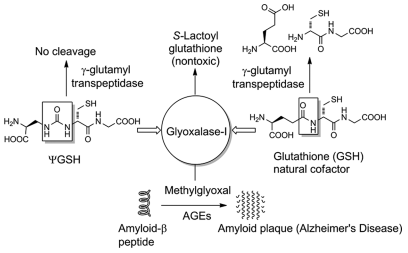
TARGETING PARKINSON'S DISEASE



After Alzheimer's disease, the most common neurodegenerative disorder is Parkinson's disease (PD). Although several genetic mutations have been linked to PD, mutations in the leucine-rich repeat kinase 2 (LRRK2) gene are the most common cause of late-onset PD. This makes LRRK2 an especially good therapeutic target. Kramer et al. (DOI: 10.1021/cn200117j) provide an overview of LRRK2 inhibitors with potential therapeutic benefit.

LRRK2 is a large and complex protein composed of 2527 amino acid residues. The authors describe all published LRRK2 inhibitor classes and their structural motifs that target this complex protein target. Additionally, the biological activities of these inhibitors provide further insight into the mechanism of inhibition.

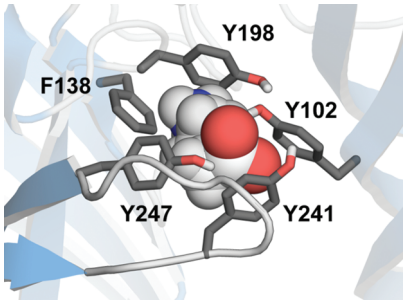
REDUCING AMYLOID-β TOXICITY



Oxidative stress is an important factor in the pathophysiology of neurodegenerative disorders such as Alzheimer's disease (AD). Glutathione (GSH) plays a major role in counteracting oxidative stress in neuronal tissue. In AD, GSH is severely depleted due to degradation by enzymes such as γ-glutamyl transpeptidase (γ-GT). To circumvent this problem, More and Vince (DOI: 10.1021/cn200113z) have developed a degradation-resistant GSH analogue.

The authors synthesized an analogue that functions as a GSH-like cellular reductant. This analogue possesses all the key characteristics of functional GSH such as uptake through the blood-brain barrier, detoxification of methylglyoxal, and protection from amyloid- β toxicity. More importantly, this analogue is nontoxic and resistant to γ-GT degradation. This study potentially opens the door for utilizing similar analogues as a therapeutic for AD.

CHARACTERIZING AN AROMATIC BOX



The Cys-loop superfamily is composed of several receptors, including those of the nicotinic acetylcholine and GABA types. X-ray crystallographic data have established that Cys-loop receptors reveal a cluster of aromatic residues (called the "aromatic box") surrounding a receptor agonist. Understanding of the precise role of these aromatic residues is limited. In the current issue, Lummis et al. (DOI: 10.1021/cn200103n) shed light on the role of the aromatic box.

The authors used a combination of natural and unnatural amino acid substitution and homology modeling to probe the specific interactions of the aromatic residues in the $GABA_c$ receptor binding pocket. Specifically, the roles of several tyrosine residues were explored to elucidate their interactions. This study increases understanding of these aromatic residues across Cys-loop superfamily receptors.

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