Discovery of cellulose synthase 1 antagonist illuminates the mechanism of cellulose biosynthesis in plants

Background

- Herbicide resistance in weeds, increasingly a problem with the use of similar chemicals in crops, demands the urgent discovery of new classes of herbicides. Additionally, cellulose biosynthesis inhibitors (CBIs) are valuable for studying mechanisms of plant growth and cell wall formation.

Approach

- A robotic platform enabled screening of 50,000 small molecules for new, specific herbicides, using confocal microscopy to observe protein behavior changes upon chemical exposure. *Arabidopsis thaliana*, being a small annual plant with extensive research tools, was used as a model plant. Ethylmethanesulfonate (EMS) mutagenesis helped pinpoint genetic resistance loci. Molecular docking and protein structural analysis were carried out to elucidate resistance mechanisms to targeted CBIs.

Results

- High-throughput screening (HTS) identified fluopipamine as a potent chemical inhibitor of cellulose biosynthesis, with seedlings showing a 70% reduction in [^{14}C]glucose incorporation into cellulose at 20 μM fluopipamine.
- Homozygous resistant F2 plants were identified from the EMS mutagenized population and the genetic resistance to fluopipamine was mapped to a G1009S substitution in cellulose synthase 1 (CESA1).
- Modeling studies suggest that G1009S and other mutations in CESA1 previously associated to CBI resistance create an alternative binding site between CESA1 protomers, enabling continued cellulose synthesis.

Significance

- Experiments show that fluopipamine acts as a cellulose biosynthesis inhibitor within *A. thaliana* and, potentially, to bioenergy feedstocks, such as poplar, with key amino acids within the CESA structures underlying the suggested mechanisms of susceptibility and resistance conserved across species. This combination of HTS and docking modeling establishes a foundation for developing more potent chemicals for agricultural and research applications.

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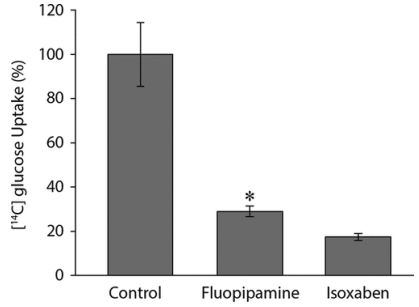
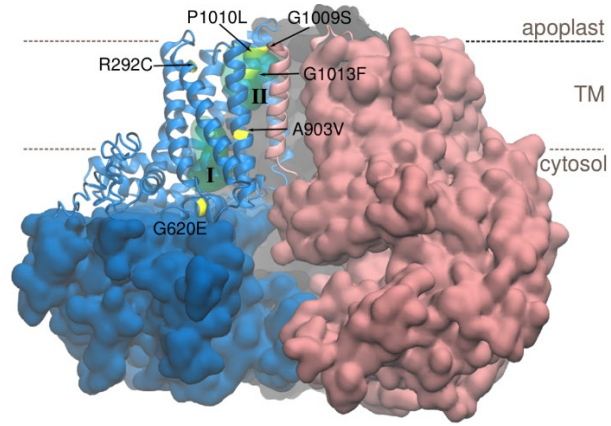
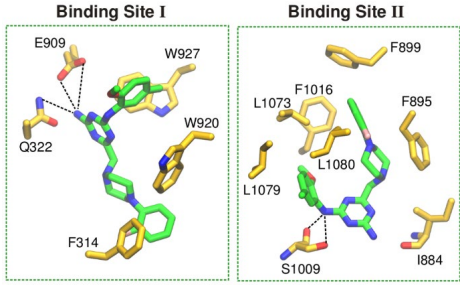


Incorporation of [^{14}C]glucose into the *Arabidopsis* cell wall in the presence of isoxaben (positive control) and fluopipamine.





Structural mapping of CESA1 mutations that confer resistance to CBI and the predicted alternative binding site (II) of fluopipamine.