Toward a pill to enable celiac patients to eat foods containing gluten

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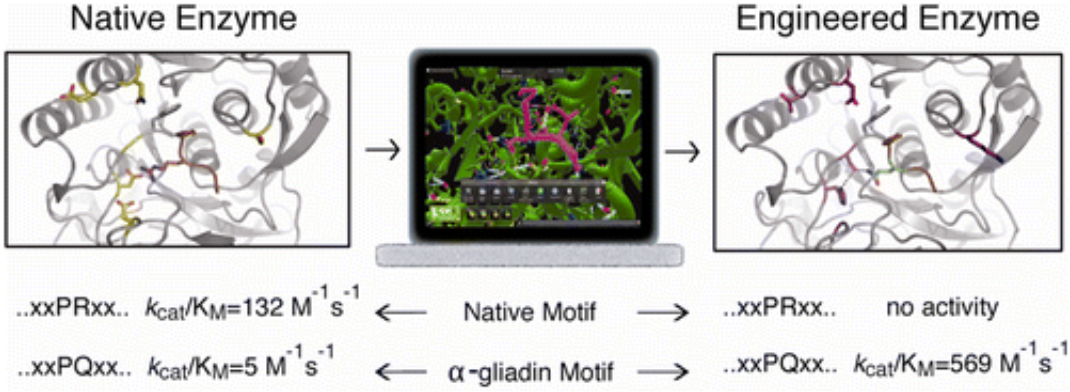

Scientists are reporting an advance toward development of a pill that could become celiac disease's counterpart to the lactase pills that people with lactose intolerance can take to eat dairy products without risking digestive upsets. They describe the approach, which involves an enzyme that breaks down the gluten that causes celiac symptoms, in the *Journal of the American Chemical Society*.

Justin Siegel, Ingrid Swanson Pultz and colleagues explain that celiac disease is an autoimmune disorder in which the gluten in wheat, rye or barley products causes inflammation in the digestive tract. Enzymes in the stomach break down gluten into smaller pieces, called peptides. For most people, these peptides are harmless. But for the 2 million-3 million

Americans with celiac disease, the peptides trigger an autoimmune response and painful symptoms. Currently, the only treatment is a gluten-free diet. However, the scientists reasoned that if an enzyme could further break down the offending peptides in the stomach, celiac patients might be able to eat gluten-containing foods.

They describe discovery of a naturally occurring enzyme that has some of the ideal properties for doing so. The scientists modified the enzyme in the laboratory so that it would meet all the necessary criteria. The new enzyme (called KumaMax) broke down more than 95 percent of a gluten peptide implicated in celiac disease in acidic conditions like those in the stomach. "These combined properties make the engineered [enzyme] a promising candidate as an oral therapeutic for celiac disease," say the researchers.

More information: "Computational Design of an α-Gliadin Peptidase" *J. Am. Chem. Soc.*, 2012, 134 (50), pp 20513–20520. DOI: 10.1021/ja3094795

Abstract
The ability to rationally modify enzymes to perform novel chemical transformations is essential for the rapid production of next-generation protein therapeutics. Here we describe the use of chemical principles to identify a naturally occurring acid-active peptidase, and the subsequent use of computational protein design tools to reengineer its specificity toward immunogenic elements found in gluten that are the proposed cause of celiac disease. The engineered enzyme exhibits a kcat/KM of 568 M–1 s–1, representing a 116-fold greater proteolytic activity for a model gluten tetrapeptide than the native template enzyme, as well as an over 800-fold switch in substrate specificity toward immunogenic portions of gluten peptides. The computationally engineered enzyme is resistant to proteolysis by digestive proteases and degrades over 95% of an immunogenic peptide implicated in celiac disease in under an hour.

Thus, through identification of a natural enzyme with the pre-existing qualities relevant to an ultimate goal and redefinition of its substrate specificity using computational modeling, we were able to generate an enzyme with potential as a therapeutic for celiac disease.

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