Milk as a protein-protease delivery system: collaborative approaches inspire inquiry into the dynamics and complexities of human milk

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The discoveries that milk contains proteolytic enzymes are compelling evidence that one of milk's key values has been unappreciated. Milk is not a simple mixture of proteins functioning solely as a source of amino acids. Milk can now be viewed as a protein-protease system delivering specific protein fragments to sites along the gastrointestinal tract. The selectivity, specificity and activity of this system can be studied at the level of complexity necessary to appreciating its diverse values to health, yet deciphering such complex protein-protease delivery system is challenging. Current methods of food protein digestion that examine pure proteins reacted with digestive enzymes and measuring hydrolysis *in vitro* are incapable of incorporating the complexity of the milk system and the outcomes. Furthermore, exploration of the bioactivity of hundreds of milk protein fragments in infants is daunting. Integrated approaches are needed to investigate the protein-protease system from these various perspectives to capture the value of milk. A broad collaborative effort is the key to reaching this goal. We have found that this breadth of research objectives provides an unusual educational opportunity in team science for young undergraduates. Therefore, we have assembled a team including undergraduate students with various individual perspectives, utilizing analytical, physiological, biochemical and computational tools to study the protein-protease system of human milk. This collaborative research model has been inspiring young students to develop versatile skill sets and to make novel research discoveries about milk and its properties. Using biochemical models, we have studied interactions between milk enzymes and proteins. With LC-MS/MS, we have identified unique human milk peptides released by its ensemble of proteins and proteases that are distinct from those previously studied. With computational tools, we have constructed databases of the naturally occurring peptides annotated for their protein origins and putative enzymes responsible for their cleavages. Using ontology and evolutionary criteria, we have proposed novel bioactivities for specific peptides. These research successes are building a better understanding of milk as a uniquely complex and effective delivery system to change the value proposition of milk for health improvement.