Multi-Ontology framework of Maternal Milk for Immune Systems (MOMMIS) - Extended Abstract

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Abstract

We propose a multi-ontology framework modeling the impacts of milk composition on immune health outcomes, using maternal milk as a case study. We evaluated the wide array of immune-health promoting bioactive factors in mammalian milk and existing ontologies relevant to food, nutrition, and health. From here, we are aligning existing ontologies and developing new ontologies to fill notable gaps. MilkOligoDB, which allows for the comparison of milk oligosaccharide profiles among mammalian species and across the literature, demonstrates how the MOMMIS framework can be instantiated. MOMMIS will be useful for interdisciplinary and translational research at the intersection of food and health science disciplines.

Keywords

Maternal Milk, Milk Composition, Immune Systems, Immune Health, Ontologies

1. Immune Health vs. Immune Disease

Neonatal immune cells, with little immunological memory, a developing immune system, and increased vulnerability to a vast array of infectious and non-infectious diseases and conditions, must simultaneously mount responses against environmental stimuli while maturing (1–3). Establishment, development, maturation, optimization and maintenance of immune system functions leads to improved disease resistance, healthspan, and longevity (4,5). Current immune system ontological structures annotate immune system components relative to their corresponding disease states and drug treatments (6,7). Ontological structures are needed, which are capable of annotating immune health system development, maturation, and improvement including both intrinsic and extrinsic factors.

2. Development of Ontologies at the Intersection of Milk Composition and Immune Health

Maternal milk provides the perfect case study to ontologically model food composition impacts on immune health. As mammals' first food, milk confers health from one generation to the next in ways that no other food or biological fluid does. Transmitting evolutionary knowledge via milk, mothers catabolize their own bodies to create and deliver a food providing everything an infant needs, and nothing more. Maternal milk is the only substance consumed through the course of a mammal's lifetime informed by millenia of Darwinian selective pressure to nourish and improve the immune system of its consumer while also setting the stage for improved healthspan and disease resistance (8,9). Children need milk for bone growth, and infants rely on it for crucial immune function as they develop (10,11).

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Annotating milk is a worthwhile pursuit because milk plays a crucial role in the growth and development of mammals. An ontologically based maternal milk ⇔ infant health informatics framework offers the opportunity to links bodily tissues and fluids, as well as their packaging and delivery into nutritive foods with the metabolic processes and health outcomes of the consuming organism. Specifically relating to organismal immunological function, ontologically modeling maternal milk and its consumption affords the opportunity to better understand establishment, development, maturation, optimization and maintenance of immune system functions across molecular, cellular, organ, and systems levels. It will also be crucial for interdisciplinary translational research efforts, i.e. determining how an increase in oligosaccharide content in milk affects immune-mediated health outcomes or what immune health-promoting bioactive factor(s) affect the development and/or treatment of emerging viruses such as COVID-19.

2.1. Mammalian Milk Immune Components

Mammalian milk contains a variety of immune-health promoting bioactive factors (milk immune components) including but not limited to: hormones, cytokines, chemokines, lymphocytes, macrophages, neutrophils, T cells, immunoglobulins, lactoferrin, lysozyme, bioactive peptides, antibodies, stem cells, human milk oligosaccharides (HMOs), the microbiota, and microRNAs capable of the mechanisms by which they drive immune maturation (11,12). For example, HMOs play an important role in the prevention of necrotizing enterocolitis, a disease occurring in sick or premature babies (13)(14). *Bifidobacteria infantis*, a probiotic that grows selectively on specific HMOs, is currently used to treat necrotizing enterocolitis (15).

2.1.1. Existing food, nutrition, and health ontologies related to milk immune components

Annotating maternal milk components for their relationships to immune health using ontologies lays the groundwork for a comprehensive food, nutrition, and health informatics framework describing any food components and their corresponding immune health outcomes. Connecting multiple ontologies by building multi-ontology food informatics frameworks allows researchers to ask and answer more interdisciplinary questions (16–19). The Multi-Ontology framework of Maternal Milk for Immune Systems (MOMMIS) connects the following biological ontologies: FoodOn (20), Uberon (21), Compositional Dietary Nutrition Ontology (CDNO) (17), the Mass spectrometry ontology (HUPO) (22), the Mammalian phenotype ontology (23), and the Gene Ontology (GO) (6). Ontologies related to nutrition interventions and personalized nutrition experiments will also be crucial. These include but are not limited to: the Ontology of Precision Medicine and Investigation (OPMI) (24), the Ontology for Biomedical Investigations (OBI) (25), the Ontology for Nutritional Epidemiology (ONE) (26), the Ontology for Nutritional Studies (ONS) (27), the Food Biomarker Ontology (FOBI) (28), the Human Disease Ontology (DO) (29), and the Medical Action Ontology (MaXO) (7), and the Ontology of Host-Microbiome Interactions (OHMI) (30).

2.1.2. Connecting UC Milk and MilkOligoDB: Oligosaccharides as key milk immune components

UC Milk is an ontology that was developed to characterize mammalian milk components and the biological processes giving rise to their creation. The ontology describes both the production and processing of milk itself as well as the role of milk throughout the life cycle, including during three key stages: infant, pregnancy, and lactation (31). MilkOligoDB allows for the comparison of milk oligosaccharide profiles among mammalian species and across the literature. It demonstrates the considerable variation in oligosaccharide profiles both between species and within species (32). Building off of the data model for MilkOligoDB (32), we extend CheBI oligosaccharide classes to cover known classes of mammalian oligosaccharides and then instantiate these classes in the oligosaccharide class (prebiotics) to probiotics in the gut that confer immunological health benefits, including for different types of mammalian milks. Ontologies that allow us to model milk processing conditions such as pasteurization, which are especially relevant for mothers who cannot breastfeed, are being built as well (33).

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