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Editorial

Immuno-Intervention with Immunoglobulin Y in Alimentary Tract Infections as an Alternative or Adjunct to Antimicrobials or Vaccines

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Editorial

It was only within the past quarter-century that interest surged over immunoglobulin Y (IgY) as an anti-infective clinical material unlike the more well-known mammalian immunoglobulin G (IgG) which has long been the workhorse of passive immunotherapy. IgY is the major immunoglobulin class of birds, amphibians, and reptiles, and possibly shares a common ancestor with mammalian IgE with which it has striking structural similarities. Among IgYs from the avian species, chicken IgY has historically been the most frequently described and studied. By immunizing poultry hens with any viral or bacterial antigen of interest, IgYs are generated in the systemic circulation and accumulate by default in the egg yolk from where they are collected and purified.

The introduction of IgY as a player in the field of gut-related infection control was gradual and without the usual hypes most likely arising from skepticism due to its proteinaceous nature and is therefore perceived as unstable and easily digestible. Pioneering studies conducted in Japan by our group since the early 90's up to the present along with independent studies in Europe and the U.S. yielded promising data on efficacy of orally administered IgY against infectious agents of the alimentary tract from the oral cavity down to the intestines. Data on animal [1] and human clinical trials [2,3] have provided compelling evidence for its critical role in passive immuno-intervention. A noteworthy feature of IgY is its intrinsic resistance to trypsin and chymotrypsin. Hatta observed in 1993 that after 8hr of digestion with these proteases in vitro, about 40% of the IgY molecule remained intact and functional [4]. As such, IgY closely mimics the secretory IgA, a protease-resistant immunoglobulin naturally secreted in the lining of the mammalian gut for mucosal protection. Since then, other investigators have documented the stability and efficacy profile of IgY within the orogastrointestinal tract not only in humans and monogastric animals [3,5] but also in animals with compound stomach upon a virulent challenge dose of enteric pathogens [6]. Although IgY is susceptible to degradation by pepsin at acidic condition, suitable drug delivery systems can protect the active payload from hydrochloric acid in the gastric cavity such as via enteric-coated formulations or delayed release capsules. Simple co-delivery with a buffering material including certain foods such as milk and egg protein also helps protect orally administered IgY from acid degradation.

The use of IgY to confer passive immunity within the gut can be a defining factor in the prevention of certain intestinal disturbances, such as those caused by *Salmonella*, *E. coli* or rotavirus, as it provides an almost instantaneous effect after oral intake whereas active immunization or vaccination relies on the host's immune system to generate an immune response which is usually delayed for several days or a few weeks. By providing a rapid response antimicrobial umbrella, orally administered IgY molecules keep the invading pathogens at bay by suppressing microbial proliferation and preventing damage to mucosal lining while the systemic and local immune systems elaborate their own protective antibodies to eliminate the pathogens and prevent the onset of disease. Suppression of colonization is made possible by the agglutinating or toxin-neutralizing effects of IgY which render the target microbes or toxins unable to colonize mucosal surfaces or perform toxigenic or other functions essential to their virulence or muco-adhesive activity.

The use of IgYas an immuno-intervention agent has distinct advantages over mammalian IgG. A comparative study with IgG has shown that IgY exhibits up to five times more affinity to a specific antigen and reacts more rapidly to the same antigen when tested in competition assays [6].The cost of maintaining poultry hens is comparatively lower than that of cattle if bovine milk or blood are used as IgG source. IgY does not bind human complement and Fc receptors and would therefore not elicit non-specific inflammatory reaction. With IgY, the manner of extracting antibody from the host is through a bloodless physiological process (egg laying) whereas extracting mammalian blood containing IgG involves bleeding and pain issues.

IgY offers various advantages over antibiotics. Being a normal food material in the human diet, IgY is known to be highly safe and can be used in a broader range of subjects from infants to very old patients. IgYs can be designed to recognize unique target molecules enabling them to discriminate between microbial species. As antibodies, IgYs bind virtually irreversibly (under gut conditions) only with the unique mirror-image structures of target microorganisms and not with dissimilar structures of non-target microorganisms thereby selectively decimating only the identified life forms and avoiding dysbiosis in gut microflora. This is quite unlike synthetic antimicrobials that work by collateral killing of both useful and harmful species of bacteria. While antibiotics are effective against only bacteria, IgY can be designed to work against either bacteria or viruses with a high degree

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of specificity. Furthermore, synthetic antimicrobials may generate resistance, immune-suppression or hypersensitivity all of which have not been observed or are not likely to happen in the use of IgY. With the widespread use of antimicrobials, resistance by microorganisms has become a red-hot issue which led to the 2006 European ban on antimicrobial inclusion in feed as growth promoters for livestock and poultry. Unlike conventional antibiotics, IgY is not likely to generate resistance since it is intrinsically polyclonal and are naturally directed against multiple epitopes of microbial antigens produced under the control of several distinct genes. From common observations, simultaneous or en masse antigenic drift or mutation in multiple genetic loci in microorganisms through selection pressure by antibodies is quite unlikely.

In animal studies where IgY was the sole therapeutic agent used against *Salmonella* spp. or *Escherichia coli* [7,8], results indicate that IgY might supplant antimicrobials altogether or at the least it might serve as an auxillary treatment together with antimicrobials to forestall microbial resistance.While IgY may not totally eradicate target microbes within the gut, it can significantly reduce infectious pathogen load to a point where an antimicrobial agent or in most cases the host's own immunity can more easily subjugate the invading pathogen as had been observed in abovementioned studies [7,8].

The successful reduction of bacterial load in pre-existing infection by certain alimentary tract microbes against which vaccines for human use are not yet available is a notable feat achieved by IgY immuno-intervention. The microbial targets investigated to date include: *Streptococcus mutans* which is the major organism responsible for most dental caries [2], *Candida albicans* which is the cause of oral thrush [5], *Porphyromonas gingivalis* [9] which is the major cause of gingivitis and periodontitis, *Helicobacter pylori* [10] which is the major causative agent of gastric cancer and gastric ulcer, human rotavirus which is the major factor in viral diarrhea of infant and young children [3], and *Pseudomonas aeruginosa* [11] which is the major complicating infectious organism in cystic fibrosis. For most of the above microbes, a simple reduction in bacterial or viral numbers in vivo is enough to abolish symptoms of disease or improve an infected person's quality of life since the severity or extent of clinical pathologies is directly proportional to the magnitude of bacterial or viral load. While knocking down these pathogens with IgY is important for the average person, it is considered highly desirable or necessary among the immuno-compromised such as human immunodeficiency virus (HIV)-infected individuals, the very young, the elderly, or the sick and debilitated especially cancer-stricken patients. Considering that oral treatment with IgY helps in preventing or minimizing lung infection by *P. aeruginosa* among cystic fibrosis patients [11], an anti-influenza IgY formulation, designed for oral use against a broad range of influenza virus serotypes including the highly virulent bird and swine flu strains, is currently under study by our group. Vaccination against swine influenza induces an unusual side effect in the form of narcolepsy [12] suggesting that traditional vaccines against this virus with pandemic potential may be impractical. It is therefore of utmost interest to assess the impact of oral IgY in mitigating the sequelae of swine flu infection or in controlling its host-to-host transmission.

Even when vaccines are available for a particular disease, the use of IgY may yet prove to be extremely useful in infectious disease control such as in the case of rotavirus diarrhea among infants and young children. In a hospital-based study conducted in Myanmar among hospitalized patients, IgY has been shown to be efficacious in abbreviating the duration of rotavirus-induced diarrhea by at least 2 days and in significantly reducing the frequency and duration of viral shedding [3]. Inasmuch as the few vaccine strains commercially available will obviously fail to protect against remotely related infant rotavirus serotypes circulating in some endemic areas, it is not surprising that a commercial rotavirus vaccine from the U.S. has been found to protect only 48.3- 51% of vaccinated children in some Asian countries (Bangladesh, Vietnam) [13,14]. It is thus feasible for IgY to be administered orally to susceptible children especially during the peak of diarrhea season even without parenteral rotavirus vaccination. It is worth noting that the IgY formulation used in the Myanmar study in 2011 was prepared using specially selected reassortant serotypes and was shown to be strongly reactive against all major serotypes of infant rotavirus worldwide, a feature not attainable by any currently available commercial rotavirus vaccine. Moreover, the cost of commercial rotavirus vaccines are beyond the reach of the masses in developing countries [15] in which case IgY alone delivered daily to a huge proportion of economically-depressed susceptible population might be a cost-effective solution to control rotavirus diarrhea in a given endemic locality. Comparatively, daily oral IgY during peak diarrhea season among infants and young children is much cheaper (based on the price of a few poultry eggs per dose) than the use of current commercial vaccines [16]. The anti-rotavirus IgY therefore has the potential to be an essential adjunct to protection of children who either failed to mount a protective level of immunity post-vaccination, or who cannot afford the pricey rotavirus vaccines.

As an offshoot of successful clinical trials conducted among human volunteers [16], nutraceuticals or health supplements fortified with IgY have been commercialized in the form of yogurt, lozenge, tablet, capsule, milk formula, etc. for prophylactic intervention against dental caries, gingivitis, oral thrush, infant rotavirus and gastric ulcer. For cystic fibrosis, IgY against *P. Aeruginosa* has been registered as drug rather than food supplement [17,18]. The powder form of delipidated IgY is highly stable at room temperature for at least two years. This feature provides ease not only in transport and storage but also in the design of food supplements such as dry milk and other powder beverages or formulations such as tablets or lozenges.

In animal husbandry, IgY containing supplement products are commercially available in major economies of the world (Japan, U.S., Canada, Europe, Australia and other Asian countries). The target pathogens for IgY in such products include bovine coronavirus, *Salmonella spp.,E. coli, Clostridium perfingens*, porcine epidemic diarrhea (PED) virus, transmissible gastro-enteritis (TGE) virus, swine and bovine rotaviruses, canine parvovirus, and canine corona virus [6-8,19-22]. These supplement products serve as growth promoters and have been used widely in animal feeds to replace more expensive porcine blood plasma, the safety of which has become a concern in pig industry recently as a potential source of live PED virus. IgY preparations are also used along with other non-antibiotic feed additives (probiotics, oligosaccharides, etc) for food producing animals, or as therapeutic regimens to supplant or augment antimicrobials or vaccines to protect herds, flocks or companion

animals against endemic diseases. In New Zealand IgY against bovine rotavirus has been registered as a medicinal product to combat diarrhea in young calves caused by rotavirus.

The science generated in the field of IgY immuno-intervention thus far may mark the beginning of the IgY era as we look forward to IgY intervention studies on several other important human and animal pathogens possibly involving anti-toxin and parenteral applications or as component of antibody-drug conjugates. From the current body of data, it is obvious that synthetic antimicrobials and active immunization are at best inadequate and as yet imperfect approaches vis-a-vis the multitude of real-life challenges prevailing in the realm of infectious disease control. With the need for a more refined model for disease control beyond standard chemotherapeutics and vaccination, the introduction of IgY immuno-intervention promises to be a significant upgrade to the current paradigm particularly in regard to treatment of alimentary tract infections. Clinical and laboratory data have clearly shown that IgY is a safe, host-friendly and efficacious disease-fighting tool that can be employed as a substitute for or as a co-essential adjunct to antimicrobials or vaccines against certain gut pathogens and their disease sequelae.

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