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EC GYNAECOLOGY
Short Communication

Different Strategies to Combat Inflammatory Diseases

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Received: March 20, 2019; **Published:** May 13, 2019

Abstract

The main objective of our work is to take our research in the field of drug discovery within the reach of the common people. Our current endeavour involves using various strategies to combat some common inflammatory diseases, to develop new alternative treatment options and ultimately, to make a difference in the lives of people.

Keywords: *Inflammatory Diseases; Inflammation; Idiopathic Pulmonary Fibrosis (IPF)*

The very essence of science and technology is based on community welfare and on the need to improve human living conditions on earth. However, humans share the earth with other living and non-living components, and unless everyone can live in synergy, the human existence may be in jeopardy.

To this end, we firmly believe in working across disciplines in our twin ventures of drug discovery- on the translational aspects of inflammation and degeneration, and on fundamental research on the various aspects of Immunobiology and Regenerative Medicine. Inflammation is the bane of most diseases, where the body ultimately becomes immunodepleted if left unchecked, and progressive tissue degeneration and chronic fibrotic changes are observed in the affected tissues. To address these issues, we have developed various diagnostic, therapeutic and prophylactic strategies that can be used to combat some very common diseases, like asthma, idiopathic pulmonary fibrosis (IPF), inflammatory bowel disease (IBD), peritonitis and atopic dermatitis (AD). Some the strategies that have been developed in our lab and have tremendous potential in the field of pharmaceuticals are antibody therapy using novel camelid antibodies, phytochemicals from natural products, nanoparticles, a novel combinatorial probiotic culture and stem cell therapy.

Antibody therapy

Antibodies are Y- shaped glycoprotein molecules produced by the body's immune cells to fight pathogens. A unique molecule on the pathogen (Antigen) is recognized by the antibody's Fab, or antibody binding, region. This allows the immune cells to recognize the antigen- antibody complex and destroy the antigen. In antibody therapy, an antibody is administered against a specific protein or molecule that is prevalent in a particular disease. The typical antibody (Figure 1A) has 2 identical polypeptide heavy chains, connected to 2 polypeptide light chains via disulphide bonds. Each heavy chain has a variable (Fv) domain, and a constant (Fc) region made of 3 domains (CH1, CH2 and CH3). The antigen binding region is made of the Fv and CH1 domains. Antibody are large glycoproteins, of approximately 150 kDa. Camelids, members of the family camelidae, like camels and llamas, have another type of antibodies (Figure 1B). These camelid antibodies do not contain the light chain or the CH1 domain, but only the variable (VHH), CH2 and CH3 domains of the heavy chain. The

single VHH domain (around 15 kDa in size) (Figure 1C) can be raised against any protein present in diseased conditions, and, due to their small size, have the ability to reach such sites on an antigen that classical antibodies may not be able to reach. Alkaline phosphatase is an enzyme that is normally present in the body, but its levels rise in several disease conditions. Our lab has engineered a novel single domain camelid antibody against alkaline phosphatase. We are also in the process of generating a camelid antibody against asthma specific IgE.

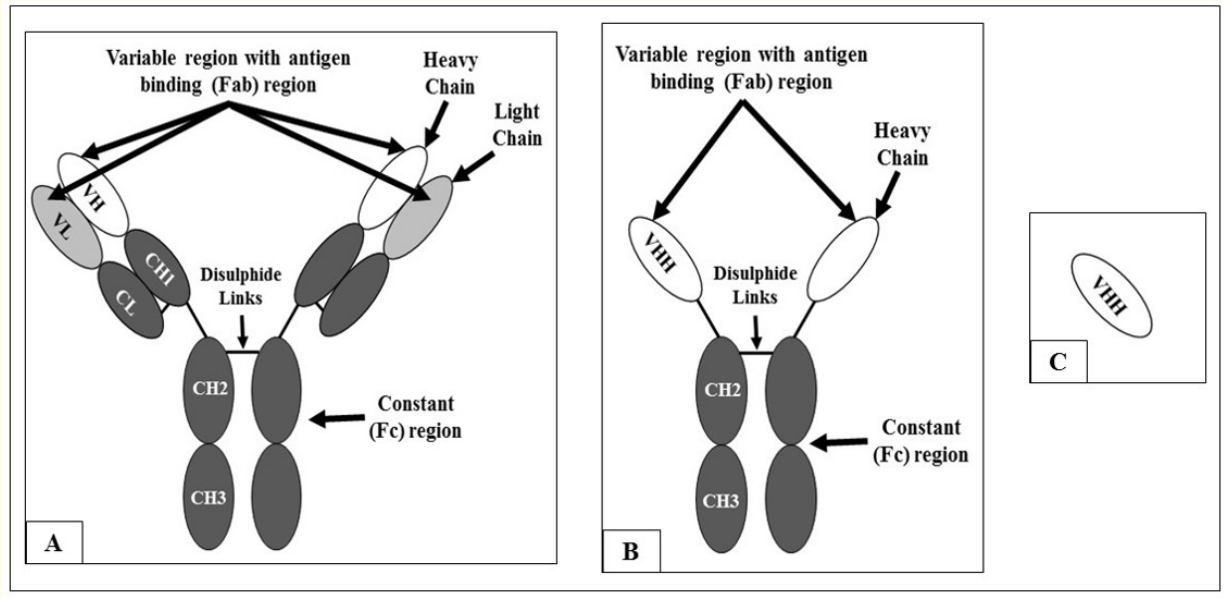

Figure 1: *Structure of antibodies. A: Structure of a typical human antibody (~150 kDa), containing a heavy chain with one variable (VH) domain and three constant (CH1, CH2 and CH3) domains, and a light chain with a variable (VL) domain and a constant (CL) domain; B: Structure of a camelid antibody (~80 kDa), containing only a heavy chain with one variable (VHH) domain and two constant (CH2 and CH3) domains; C: Structure of a single domain antibody (~15 kDa), with only the variable domain of the heavy chain (VHH).*

Therapy using phytochemicals and natural products

Natural products are products/molecules that are found in nature, produced by a living organism. They often have pharmacological activities that may be therapeutic in several diseases. Phytochemicals are a group of chemical compounds with high structural diversity that are produced by most plants. These compounds often attribute to the therapeutic effects of natural products. Many phytochemicals have anti- inflammatory and anti- oxidative effects. Fisetin and curcumin are two such phytochemicals that have been used in our lab, in several *in vivo* models of inflammation. Fisetin is a flavonoid that is found in the plants like the strawberry, whereas curcumin is the main constituent of turmeric. We have used fisetin in mouse models of allergic asthma, IPF, peritonitis, IBD and AD. In all cases, fisetin has been successful in ameliorating the inflammation of the diseases. Curcumin has been tested in mouse models of chronic asthma and IPF and has been found effective.

The betel is the leaf of the vine *Piper betle*. It is very common in Asia, especially India, where it is consumed in various forms, like betel quid or paan (a combination of betel leaf, with areca nuts and tobacco). Paan is known for its stimulant and psychoactive effects, as well as its digestive properties. Paan has been found to have several pro- inflammatory as well as anti- inflammatory factors. Our lab has assessed

different fractions isolated form paan for their anti- inflammatory properties *in vitro*. To examine its effect *in vivo* we plan to administer these extracts in our mouse models of lung and kidney diseases.

Therapy using nanoparticles

Nanomaterials are materials, a single unit of which ranges in size between 1 - 1000 nm, typically between 1 - 100 nm. These nanomaterials can be administered either as nanodrugs or as nanovehicles. They can be natural or made synthetically. Nanomedicines have the advantage of being small devices that are less invasive than normal medicines, that can be targeted to reach a particular site and that can possibly be implanted inside the body. Their also biochemical reaction times are also much shorter. These devices are faster and more sensitive than typical drug delivery systems. We have used mesoporous carbon nanoparticle (MCN), which is a porous nanomaterial of size 100 - 200 nm, and uniform pore size of 3 nm. It is chemically inert, biocompatible, dispersible in water, and can be loaded with drug molecules which are then released slowly. We have used MCN as a nanovehicle, to deliver fisetin in mouse models of asthma, IPF and peritonitis, with the idea that MCN will somehow enhance the therapeutic effects of fisetin. However, our studies have indicated that MCN has not provided any extra therapeutic benefits to fisetin.

We have also used guar gum nanoparticle (GN) in mouse models of peritonitis and atopic dermatitis. Guar gum is a natural polysaccharide gum obtained from the seeds of the leguminous plant *Cyamopsis tetragonoloba*. The guar gum nanoparticle was prepared by acid hydrolysis of the guar gum powder. In peritonitis, GN was administered intraperitoneally. On the other hand, it was administered topically in AD. In both cases, GN was found to have a positive therapeutic effect, especially in AD, where the redness and swelling caused due to AD was seen to have reduced significantly with GN treatment. These results are encouraging and we would be examining its use in other inflammatory diseases.

Therapy using probiotics

Inflammatory bowel diseases (IBD) are a group of diseases of the gastro- intestinal (GI) tract. It is a very common disease, affecting people all over the world. There is no definite therapy for IBD, and conventional drugs include steroids and immunosuppressants, which are often not effective and may cause adverse side effects. Also, rampant use of antibiotics and modern lifestyle leads to disruption in the normal microbiota (*Lactobacilli* and *Bifidobacteria* among others) of the GI tract that usually helps in maintaining host health. This in turn may lead to IBD, where there is a decrease in the normal biota, and an increase in the number of harmful bacteria like *E. coli*, bacteroides and enterococci. Thus, the use of probiotics is an alternative therapeutic strategy. Probiotics are living organisms which are beneficial to the host at specified amounts. We have studied the anti- inflammatory and pro- regenerative effects of a combination of 3 bacterial strains, mixed in a particular ratio, supplemented in food like curd and yoghurt. The exact mechanism by which the probiotics act in IBD is not yet completely clear, but our studies have indicated that they may act by improving the intestinal barrier functions, which are disrupted in IBD. Proteins at the tight junctions are responsible for the selective permeability of the membranes of the cells in the intestine. Probiotics may be involved in upregulating these proteins when there is impaired permeability due to IBD (Figure 2A). The probiotic bacteria may also compete with the pathogenic bacteria for adherence to the epithelial cells, thus ameliorating the inflammation (Figure 2B). Our studies have also indicated that the probiotic cells may be secreting some soluble factors which has a therapeutic effect on the inflammation (Figure 2C). Studies examining the mechanism of action of these probiotics is underway.

Therapy using stem cells

Stem cells are undifferentiated cells that can differentiate into any specialized lineage. Their ability to proliferate, to self- renew (divide but maintain the undifferentiated state), to differentiate and to regenerate make them an excellent therapeutic strategy for degenerative diseases. Stem cells can be of embryonic or adult origin. In tissues, stem cells are present in special microenvironments called stem cell niches, which usually help maintain the stem cells in an inactive state. However, in case of tissue injury, the niche signals the stem cells to proliferate and differentiate, thereby regenerating the injured tissue. Stem cell therapy is the use of stem cells to treat diseases, bone marrow transplant being the most common example. Stem cell therapy has been used in several diseases, like leukemia, Parkinson's disease, Huntington's disease and Type 1 diabetes. Recently, a 'spray gun' has been developed to administer a solution of stem cells to burn wounds. Strategies for degenerative diseases are under investigation. Our lab aims to induce embryonic stem cells to differentiate into

lung and kidney lineages. We have found that human embryonic stem cell (hESC) line H7 successfully differentiated into alveolar epithelial type-I (AE-I) cells, alveolar epithelial type-II (AE-II) cells, as well as Clara cells, *in vitro*. These cells are damaged in case of IPF. When transplanted *in vivo*, the hESCs homed to the small airways of the lung, and markedly reduced the collagen content, which increases during IPF. Administration of mesenchymal stem cells isolated from umbilical cord (UCMSCs) have also been found to be effective in a mouse model of IPF. With the ongoing research in the lab we aim to investigate the effects of other biotic and abiotic factors on stem cells [1-7].

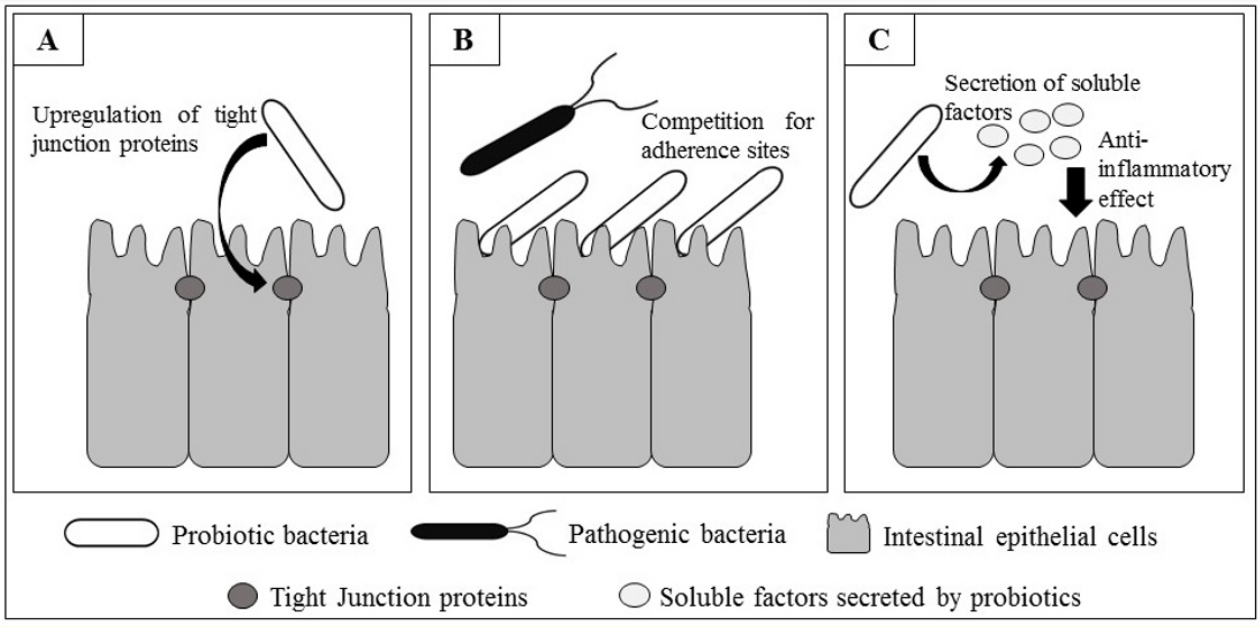

Figure 2: *Possible mechanisms of action of probiotics. A: Probiotic bacteria may improve intestinal barrier functions by up-regulating the production of tight junction proteins. B: Probiotic bacteria may act by competing with pathogenic bacteria for sites of adherence on the intestinal epithelia, thereby preventing the pathogens from colonizing. C: Probiotics may also act by secreting some anti- inflammatory soluble factors which may act on the damaged epithelial cells.*

Conclusion

The essence of laboratory research lies in the ability to generate outcomes which can be translated from bench to bed side and contribute towards improving disease diagnosis, prognosis and treatment. With the use of different measures such as nanobodies, phytochemicals, probiotics, nanoparticles or stem cells we aim to either regenerate the ailing organ or facilitate restoration of normal function by reducing inflammation in the organ. In conclusion, the current research in our laboratory uses a multi-tonged approach to develop new disease treatment alternatives to make a significant difference in the lives of the patients.

Bibliography

1. Pramathadhip Paul., *et al*. "Development of a Novel Format of Stable Single Chain Antibodies against Alkaline Phosphatase as Therapeutic Agents against Immune Diseases". *Journal of Nanomedicine and Biotherapeutic Discovery* 6.2 (2016): 144.

2. Shinjini Mitra., *et al*. "Mesoporous Nano-carbon Particle Loaded Fisetin has a Positive Therapeutic Effect in a Murine Preclinical Model of Ovalbumin Induced Acute Allergic Asthma". *Journal of Nanomedicine and Biotherapeutic Discovery* 5.2 (2015): 132.

3. Shinjini Mitra., *et al*. "Therapeutic use of Fisetin and Fisetin Loaded on Mesoporous Carbon Nanoparticle (MCN) in Thioglycollate-induced Peritonitis". *Journal of Nanomedicine and Nanotechnology* 6.6 (2015): 332.

4. Srabani Kar., *et al*. "Therapeutic use of fisetin, curcumin, and mesoporous carbaon nanoparticle loaded fisetin in bleomycin-induced idiopathic pulmonary fibrosis". *Biomedical Research and Therapy* 2.4 (2015): 250- 262.

5. Rintu Das., *et al*. "Anti-Inflammatory and Regenerative Potential of Probiotics to Combat Inflammatory Bowel Disease (IBD)". *Journal of Biotechnology and Biomaterials* 5.2 (2015): 181.

6. Ena Ray Banerjee., *et al*. "Therapeutic Effect of Combinatorial Probiotics to Protect Intestinal Barrier Function". *EC Microbiology* 9.2 (2017): 84-95.

7. Ena Ray Banerjee., *et al*. "Human embryonic stem cells differentiated to lung lineage-specific cells ameliorate pulmonary fibrosis in a xenograft transplant mouse model". *PLoS ONE* 7.3 (2012): e33165.

Volume 8 Issue 6 June 2019