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An analysis of the effects of diet on inflammation, the microbiome, and the relation to offspring

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AN ANALYSIS OF THE EFFECTS OF DIET ON INFLAMMATION, THE MICROBIOME, AND THE RELATION TO OFFSPRING

by

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Diet and health are becoming an increasingly important topic in all aspects of society, politics, and everyday life. A growing concern is obesity, which is marked by a large number of circulating fatty acids. This increased number of fatty acids may alter a body’s systems such as immune responses. This makes it even more important to scientifically study the effects of one’s diet on several factors such as disease, inflammation, and the gut microbiota. Several studies and hypotheses have been performed and proposed, respectively, to find the underlying implications of a high fat diet. Some studies explore the similarity between fatty acids and bacterial antigens, and their resulting stimulation of similar cascades. Others explore the effects of diet on the gut microbiome which has many implications in the context of disease. It has been shown that the microbiota share a relationship with the host that is usually beneficial, but alterations may cause it to become harmful to the host. This manuscript aims to explore these studies and analyze their results, as well as the many connections between them. It also aims to connect these studies with those that explore the
far-reaching results of diet, such as the effects it may have on one’s offspring. These effects include disease susceptibility and alterations in the gut microbiome in the offspring.
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<td>Antigen presenting cells</td>
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<td>BSA</td>
<td>Bovine Serum Albumin</td>
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<td>CD14</td>
<td>Cluster of differentiation 14</td>
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<td>COX-2</td>
<td>Cyclooxygenase-2</td>
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<td>LBP</td>
<td>LPS binding protein</td>
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<td>LPS</td>
<td>Lipopolysaccharide</td>
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<td>MD-2</td>
<td>Myeloid differentiation factor 2</td>
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<td>n-3</td>
<td>Omega-3</td>
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<tr>
<td>n-6</td>
<td>Omega-6</td>
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<tr>
<td>PAMPs</td>
<td>Pathogen-associated molecular patterns</td>
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<td>PUFA</td>
<td>Polyunsaturated fatty acid</td>
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<tr>
<td>TCR</td>
<td>T-cell receptor</td>
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<td>TLR-4</td>
<td>Toll-like receptor 4</td>
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<td>TNF-α</td>
<td>Tumor necrosis factor alpha</td>
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INTRODUCTION

The frequency of sepsis, autoimmunity, and allergic diseases in western societies continues to increase (1). Sepsis, for example, is still the primary cause of death from infection (World Sepsis Day). Lipopolysaccharide (LPS), or endotoxin, is a component of microbial cell membranes, and is the main signaling mechanism deployed upon introduction of a foreign microbe to the body. It acts through Toll-like receptor 4 (TLR4) which is part of a group of receptors found on cells of the immune system and which stimulate the body to react to the microbes. The gut contains protective bacteria called the microbiome, or commensal flora, that provides the body with vitamins and maintains homeostasis.

For the past few decades, the diet of western societies has changed immensely. The so-called “Western diet” is associated with a higher caloric intake and dietary fat. This diet has been linked to an increase in both immune mediated and metabolic disease (2). Fatty acids have been linked to different pathways that eventually affect LPS and the microbiome, and thus induces the body to react as it does when it encounter foreign microbes (3).

The literature shows several different mechanisms through which fatty acids stimulate the immune system in autoimmune, septic, and allergic disease. Fatty acids have also been linked to disease by their effects including altering the cell
membrane of several cells and also by direct action on immune cells. For example, they have been shown to affect the fluidity of the cell membrane, as seen in Figure 1, which illustrates fatty acid mechanisms to induce inflammatory cell responses (5). Several studies have shown that fatty acids may cause disease by mimicking the effects of LPS on the body through signaling of TLR-4 (3). When LPS activates TLR-4, a signaling cascade begins that ultimately results in increased cytokines and an increased immune and inflammatory response. When fatty acids mimic LPS, the TLR-4 signaling pathway is activated and results in the same mechanisms as if the body had actually interacted with LPS from a microbe. This induction of the immune system results in disease. For example, in obesity fatty acids are present in large numbers. Through their interaction with TLR-4, they have been shown to produce inflammatory signaling (4). This provides a link between obesity and inflammatory diseases.

Alterations in the gut microbiota can be extremely detrimental to the individual. While the bacteria involved exert protective functions, they are ultimately foreign microbes and any break in the epithelial barrier of the gut or increase in permeability can cause interactions with their components which can stimulate the immune system. Fatty acids have been shown to increase the permeability of the gut to LPS from microbes which can lead to systemic inflammation (6).
Although the majority of the literature links fatty acids with disease, it must still be noted that fatty acids have a beneficial role in nutritional well-being as well (7). For example, saturated and unsaturated fats can have dual roles, one promoting inflammation and the other not, which will be described below.

Through the exploration of human nutrition, the microbiome, and the effects on the immune system such as in inflammatory disease, we can further the analysis to include the effects on offspring. The literature has shown that a mother’s microbiome can be passed on to the offspring. Kau et al explains that the microbiome is something that is passed down from mother to child. This seems to occur at the time of birth (2) but may even occur while the fetus is still in the womb (24). If this microbiome is being passed from mother to child, it is likely that certain exposure the mother has can lead to effects in the child. The effects of alcohol and cigarette smoking on children during gestation are a popular societal notion. Women have been educated on the detrimental consequences these two exposures can have while the child is still maturing in her womb. However, the detrimental effects of diet on offspring is an open field, with much potential for critical results.
Lipopolysaccharide (LPS) and Toll-like receptor 4

Lu et al. describes toll-like receptors as “germline-encoded receptors expressed by cells of the innate immune system that are stimulated by structural motifs characteristically expressed by bacteria, viruses and fungi known as pathogen-associated molecular patterns (PAMPs). Several different types of toll-like receptors have been identified, with the corresponding molecule that activates them. For example, viral DNA stimulates TLR9 while double stranded...
RNA interacts with TLR3 (8). The authors also go on to explain that when these receptors are stimulated, certain cytokines related to inflammation are stimulated as well, in addition to specific cells of the innate immune system. These cells of the innate immune system are called antigen-presenting cells (APCs). These cells take up antigens, engulf them, and then through a specific process place a piece of antigen on their surface. This is to show the antigen to immune cells in the body, and in this way they may react with the APCs to cause a further cascade of the immune system. This cascade involves the recruitment and aggregation of immune cells such as neutrophils, macrophages, and lymphocytes. In addition, APCs activate the release of cytokines, which further recruit more immune cells, or conversely trigger control responses to regulate the immune response. They may also interact with killer T cells which will, as the very name states, kill the associated cell presenting the antigen using another specific process. Thus, toll-like receptors are involved in the immune response to antigens.

Several molecules have been shown to stimulate TLR4, including LPS, which is a part of gram-negative bacteria. Thus, the TLR4 is like a sensor in detecting an invading pathogen such as bacteria and causes an appropriate response by the immune system. There are three parts that make up LPS. One is the called lipid A which is actually the PAMP of LPS (8). The second part of LPS is the core oligosaccharide. And finally the last part of LPS is the O side chain.
Figure 2: The cascade of LPS/TLR4 signaling and the molecules involved. When the body is exposed to LPS, such as when exposed to gram-negative bacteria, LPS binds to the LPS binding protein (LBP), then the cluster of differentiation 14 (CD14), as well as myeloid differentiation factor 2 (MD-2). This signaling can then go two different paths, either MyD88 dependent or independent (Figure taken from Lu, 2008).
As seen in Figure 2, the cascade of LPS/TLR4 signaling and the molecules involved, LPS stimulation involves a variety of molecules that ultimately leads to proinflammatory cytokines and type I interferons. These are molecules involved in a body’s immune response. LPS first binds to LPS binding protein (LBP). These two molecules interact directly and as a result, this binding helps LPS interact with CD14. CD14 then assists in the transfer of LPS to the TLR4 and MD-2 receptor complex. CD14 also ensures that LPS is recognized correctly by the immune system (8).

Studies have shown that CD14 is actually needed for the transport of TLR4 to other organelles and to membranes (9). CD14 was shown to stimulate the endocytosis of TLR4. Zanoni et al. also showed that in specific cells called dendritic cells, which are part of the innate immune system and also considered antigen presenting cells, the induction of endocytosis by CD14 is actually upregulated once an antigen is present. Due to the importance of TLR4 transport to membrane and organelles, and the importance of TLR4 stimulating the immune system, the study of these receptors and associated proteins is extremely important. The process is illustrated in Figure 3 (9).
Figure 3: CD14 and its role in the endocytosis involved in TLR4 signaling. When LPS binds to its LPS binding protein, it stimulates a cascade of events that ultimately stimulates the release of cytokines and production of interferons. The other molecules involved are extremely important for the transfer of toll-like receptors to other organelles and membranes. For example, CD14 has been shown to be the major inducer of endocytosis of the TLR4 receptor complex once it has been induced. CD14 first directs the LPS, which can be part of a gram-negative bacteria, to the TLR4 and MD2 receptor complex. Its next role is to endocytose this complex and into an endosome. This later leads to the stimulation of interferon production (Figure taken from Zanoni, 2011).
The next few molecules involved in the TLR4/LPS signaling are known as adaptor proteins. They include TIRAP, TRAM, TRIF, and MyD88. These help attain the ultimate signaling which is the stimulation of proinflammatory cytokines and type I interferons (8). This signaling pathway is extremely crucial to study because it can lead to an enormous amount of inflammation including chronic diseases involved with inflammation, as well as sepsis.

**The Microbiome**

Many studies, such as Kau et al. and Cho et al., have explored the crucial and important relationship between the immune system, both innate and adaptive, and the gut microbiome. The microbiome is a term used to embody all of the microbial organisms present in one’s body system. The microbiota, or the microbial organisms, predominate in different parts of the body.

It is important to study the microbiome for several reasons. For example, by studying the microbiota present in specific parts of the body, such as at the vagina, scientists can target disease risks associated with these particular microbiota in the targeted area. The microbial-host relationship is balanced, and alterations to this balance can lead to disease or susceptibility to disease. This is because the microbial-host relationship is involved in many host functions including reproduction, metabolism, and immune defense (10). For example, the gut microbiota assist in homeostasis by providing the host with vitamins and
other defense capabilities that helps maintain the host’s health.

The anatomical taxonomic variation is shown in Figure 3. The taxonomic phyla listed are Actinobacteria, Firmicutes, Proteobacteria, Bacteriodetes, Cyanobacteria, and Fusobacteria. These proportions were found from complicated high-throughput sequencing. The microbiota present in each anatomic site varies in proportion and number. For example, in the stomach, the Proteobacteria dominate. On the other hand, in the hair, nostril, and skin, the Actinobacteria dominate. These proportions and variation of taxonomic phyla can be altered by certain occurrences, such as an enteric infection or the presence of antibiotics. Across humans and across different species, variation exists amongst the composition of the microbiota (10).

**The Microbiome and Disease**

Cho et al. delve into several different types of disease states and their relation to the microbiome. The microbiome seems to shift in these disease states, signifying it’s involvement. It seems that studies are still fairly preliminary, but with the advances in high-throughput sequencing, there is hope that more will be discovered pertaining to the relationship between the microbiome and disease susceptibility (10).
Figure 4: Taxonomic phyla and their anatomical locations. There is much variation in the composition of microbiota in specific anatomical locations. High-throughout sequencing was performed to find proportions. This information is important in understanding health risks associated with microorganisms. If *Helicobacter pylori* is in the anatomical site such as in the stomach, or if it is not in the anatomical site such as in other parts of the stomach, this leads to variation in the composition even further (Figure taken from Cho, 2012).
The Microbiome and the Skin

In Cho et al.’s analysis, three skin diseases states were explored. These were psoriasis, atopic dermatitis, and chronic skin ulcers. Psoriasis is a skin inflammatory disease and a shift in the microbiota was seen when samples from psoriatic skin was studied. Similarly, in atopic dermatitis, the frequency with which it arises in places with similar microbiota environments brings up the possibility of a role of the microbiota in the pathogenesis. Finally, in chronic skin ulcers, a similar shift seems to occur (10).

The Microbiome and the Stomach

The existence of *H.pylori* in the stomach has had many implications in different disease states such as peptic ulcer disease (10). This relationship between shifts in microbiota and disease states is especially important in the stomach due to the rising number of peptic ulcer patients seen.

Table 1 shows several other disease states and the relevant microbiota details associated with each.
Table 1: Different diseases and their associated shifts in microorganism compositions. Table taken from Cho, 2012. The table shows the significance of microbiota in different disease states. From skin disorders like psoriasis to gut disorders like inflammatory bowel disease, the microbiota are prominent in a variety of disease cases. It is important to study their relationship to better understand how to target the microbiota for health benefits and decreasing health risks.

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<td>Increased ratio of Firmicutes to Actinobacteria</td>
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<td>Reflux oesophagitis</td>
<td>Oesophageal microbiota dominated by gram-negative anaerobes; gastric microbiota with low or absent <em>Helicobacter pylori</em></td>
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<tr>
<td>Obesity</td>
<td>Reduced ratio of Bacteroidetes to Firmicutes</td>
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<tr>
<td>Childhood-onset asthma</td>
<td>Absent gastric <em>H. pylori</em> (especially the cytotoxin-associated gene A (cagA) genotype)</td>
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<td>Larger populations of <em>Fusobacterium spp.</em></td>
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<td>Cardiovascular disease</td>
<td>Gut-microbiota-dependent metabolism of phosphatidylcholine</td>
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**Fatty Acids**

Fatty acids are extremely important molecules for all species. They are involved in a variety of functions in the body, including involvement in metabolism, function, and structure. For example, fatty acids are components of the cell membrane. When combined with other molecules, such as alcohols, they can become phospholipids, or they can become triacylglycerols (5). Phospholipids make up the standard eukaryotic cell membrane, and they are
very useful because of their hydrophobic and hydrophilic properties.

Fatty acids have a typical structure that consists most readily of a hydrocarbon chain, a carboxylic acid on one end, and a methyl group completing the other end. The carboxylic acid, with the structure of COOH, is what allows the fatty acid to react with other groups such as alcohols. The methyl group contributes to its hydrophobic properties. Fatty acids are then divided into two groups based on if they have double bonds present, or if there are no double bonds and only single bonds. The first group, those with double bonds present, and sometimes with more than one double bond, are called unsaturated fatty acids. If there is more than one double bond, they are called polyunsaturated fatty acids (PUFA). On the other hand, if the fatty acids do not contain any double bonds at all, they are called saturated fatty acids.

The two most common dietary PUFAs are the omega-6 (n-6) PUFA and the omega-3 (n-3) PUFA. Linoleic and alpha linolenic acids are examples of these (5). These are present in butter related products such as margarine and oil. According to Calder, these make up almost the entire PUFA intake in diets eaten by people in the West. The body converts these fatty acids into ones that can then be digested by the body, since linoleic and alpha linolenic acids cannot be. In Figure 5, this process of converting primary PUFAs into digestible ones is shown.
Specific Aims

According to the Centers for Disease Control and Prevention, the US diet has increased in the percent of kilocalories from carbohydrate, as well as the

Figure 5: The breakdown of two polyunsaturated fatty acids, linoleic acid and alpha-linolenic acid. The body cannot break down linoleic acid and alpha-linolenic acid. To solve this problem, the body changes or metabolizes these fatty acids into different ones, such as docosahexaenoic acid, also called DHA frequently. In the process, double bonds are added to the long hydrocarbon chain. In addition, the chain can be elongated so what results is a longer fatty acid with more double bonds. These resulting fatty acids can be broken down by the body (Figure from Calder, 2011).
mean energy intake in kilocalories (32). Along with this change in diet, there has been an increase in inflammation and other disease states described above and below. This suggests a correlation and emphasizes the importance of studying the diet in the context of disease. As shown in previous studies (discussed below), fatty acids have an enormous impact on the susceptibility of individuals to different diseases including allergic disease, sepsis, and autoimmune diseases. Many studies agree to and show the relationships between fatty acids, LPS, TLR-4, obesity, and inflammatory diseases (2). This manuscript aims at describing these relationships piece by piece, but also aims at extending the current research about these relationships to include their role in relation to offspring.

The microbiome is passed down from mother to child and the immense body of evidence linking the microbiome to disease susceptibility and pathogenesis exemplifies the importance of exploring this field as well. Does the microbiome affect an offspring’s disease susceptibility? Does the mother’s diet affect her microbiome and in turn affect her offspring’s?

To answer these questions, this manuscript delves into the details associated with fatty acid intake and diet and its relationship to inflammation, its relationship to the microbiome, and its relationship to an offspring and their inflammation and microbiome. By crossing generations, the significance of this
field is illustrated. It is especially important with the growing concern of our society with health, health benefits and risks, and the association of diet with one’s health.

A very relevant subject is obesity. According to a study by the Centers for Disease Control and Prevention, in 2009 to 2010, 35.7% of U.S. adults were obese, as seen in Figure 6 (11). That is more than one-third of adults in the United States. Labeled as a disease now by many physicians and politicians, the growing epidemic is becoming increasingly alarming in society. Because of this, throughout the manuscript obesity will be touched on to exemplify the direct role of diet and disease and its effects on the immune system. If diet affects inflammatory disease and the microbiome, and those in turn affect offspring, it is crucial to undergo an analysis of these fields and their implications in the world today.
DIET, FATTY ACIDS, AND INFLAMMATION

Inflammation is a process in which the body attempts to protect itself from antigens by activating the immune system. Immune cells are recruited, cytokines are released, and together the machine that is the body works to fight infection, disease, and any foreign microbe. Other molecules released include eicosanoids and chemokines. In addition to recruiting cells and cytokines, inflammation also acts to restore the tissue, both physically and functionally.

Figure 6: Obesity bar graph for US adults, 2009-2010. From the years 2009-2010, about 35.7% of US adults were considered obese (Figure taken from Ogden, 2012)
There comes a point where inflammation has done its job, and any more inflammation will become detrimental to the body. To make sure that inflammation is self-modified, the body has created regulation systems that usually act through negative feedback. This continued effort of the body to repair itself, and then to know when to stop, helps the body maintain homeostasis in the face of adversity. It is when these self-modifying systems break down that pathological inflammation steps in. Too much inflammation can damage tissues.

Fatty acids have been studied in the context of inflammation and it has been shown that they affect inflammation usually by affecting the fatty acid composition of membranes. This alteration in the membranes leads to alterations in signaling, gene expression, receptor binding, and many other functions of the cell (5). This can have serious consequences for the immune system and for the body reacting to infection or foreign microbes. For example, it has been seen that certain n-3 and n-6 PUFAs can alter the membrane composition of immune cells such as lymphocytes (12). By altering the membrane composition, certain elements called lipid rafts are affected. These lipid rafts are involved in cell signaling and the signaling cascades that result from interaction with surface or intracellular receptors. According to Yaqoob et al, one of the complexes they saw affected by PUFAs was the T-cell receptor (TCR) complex. They said that certain signaling by the TCR could be affected by polyunsaturated fatty acids (12). If the membrane is affected, and signaling is thus affected, down the line gene
expression can also be affected (5). This can then have many consequences.

**Fatty Acids, Inflammation, and the NFκB pathway**

Fatty acids are involved in both stimulating inflammation and inhibiting inflammation via the nuclear factor kappa-light-chain-enhancer of activated B cells (NFκB) transcription factor. This transcription factor has been seen before in inflammatory pathways, but it has now been shown that it is affected by fatty acids, both saturated and unsaturated (5). For example, LPS starts an inflammatory pathway that ultimately results in the activation of NFκB and the production of inflammatory cytokines. Some of these cytokines include interleukins. However, n-3 polyunsaturated fatty acids seem to inhibit this activation of NFκB, hence having anti-inflammatory effects. On the other hand, lauric acid, which is a saturated fatty acid, actually activates the NFκB transcription factor in dendritic cells and macrophages (5). Thus, saturated fatty acids seem to promote inflammation.

Another interesting correlation between fatty acids and inflammation is that fatty acids are also precursors of molecules with anti-inflammatory effects. For example, eicosapentaenoic acid (EPA), which is derived from alpha-linolenic acid, and docosahexaenoic acid (DHA), which is derived from either arachidonic acid or EPA, can lead to the formation of protectins and resolvins. These two types of molecules have been shown to have anti-inflammatory effects (5). For
example, resolvins and protectins have been shown in studies to inhibit the production of certain inflammatory cytokines that prevent neutrophils from entering the site of inflammation (Serhan, 2008). By not allowing the neutrophils to enter the site of inflammation, they serve as regulators of the inflammatory process, preventing excessive tissue damage, as seen in Figure 7.
Saturated Fatty Acids and TLRs

Saturated fatty acids have been shown to have proinflammatory influence and act via a multitude of receptors. Interestingly, toll-like receptors, the same group of receptors that are stimulated by LPS, a gram-negative bacteria component, can also be activated by saturated fatty acids (3). When activated, TLR signaling pathways are activated and lead to inflammation. Huang et al. show, through various experiments, that the activation of TLRs is fatty acid specific and not due to remnants of bacterial products. Cells were treated with sodium laurate, a saturated fatty acid made up of 12 carbons, and palmitic acid with bovine serum albumin (BSA), a saturated fatty acid made up of 16 carbons, and the expression of specific inflammatory enzymes and cytokines, cyclooxygenase-2 (COX-2) and tumor necrosis factor alpha (TNF-α), respectively, was seen and is shown in Figure 8 (3). In other words, treatment with saturated fatty acids stimulated an inflammatory pathway.

Figure 7: The importance of resolvins and protectins in preventing excessive inflammation. Resolvins and protectins come from fatty acids such as EPA and DHA. They have anti-inflammatory effects that help prevent tissue damage. They act by not allowing excessive neutrophils to enter the site of inflammation. In doing so, resolvins and protectins become like mediators of the inflammatory process which are necessary in regulating the inflammation (Figure taken from Calder, 2011).
Figure 8: Sodium laurate and palmitic acid with BSA but not BSA alone, increased the amount of COX-2 and TNF-α that resulted. Sodium laurate is a 12 carbon saturated fatty acid, palmitic acid is a 16 carbon saturated fatty acid. COX-2 and TNF-α are proinflammatory proteins (Calder, 2011). When cells were treated with either sodium laurate or palmitic acid with BSA, the levels of these proteins increased, indicating an inflammatory pathway induced by saturated fatty acids. When treated with BSA alone, no increase in levels of the two associated proteins was seen. This study concluded that the results seen were from solely fatty acids, and not bacterial remnants. (Figure from Huang 2012).
Another interesting connection is between CD14, TLR, and diet. As previously described, CD14 is part of the process of moving TLR to the membrane or to different organelles. It helps move TLR to these specific locations. Interestingly, there have been studies that then connect CD14 and the diet. For example, Laugerette et al. divided groups of mice into different groups with different oils in the fatty acids. They wanted to observe the changes resulting from these different oils on the metabolism of endotoxin or LPS. They found that the palm oil group, as opposed to milk fat, rapeseed or sunflower oil groups, had the highest level of IL-6 which as previously described is an inflammatory cytokine, as well as the highest levels of expression of TLR4 and CD14 (30). In other words, the palm group had the highest levels of inflammation. This signifies the effects diet can have on multiple aspects of the inflammatory pathway.

**TLRs and Inflammation in Obesity**

As described previously, more than one-third of US adults are obese. Because of this, it has become extremely important to study the repercussions and consequences in a disease related context of obesity and related syndromes, such as metabolic syndrome. Obesity is characterized by an excess of free fatty acids circulating in the body. This irregularity in adipose tissue causes several things to occur. For example, molecules such as monocyte chemotactic protein (MCP-1) are released. This in turn causes an excess release of macrophages, which leads to an inflammatory pathway. For example, inflammatory proteins are released and initiate a cascade of inflammatory events...
as seen in Figure 9 (14). This has extremely important implications due not only to the rise in obesity, but also the diseases that can result from obesity such as cardiovascular disease.

Furthermore, just like LPS can activate TLRs in the body, so can free fatty acids, as described previously in the study of saturated fatty acids such as sodium laurate and palmitic acid. For example, Youssef-Elabd et al. showed that when adipocytes were exposed to saturated fatty acids, the toll-like receptor TLR4 was stimulated, leading to the inflammatory NFκB pathway (29). This ultimately led to the production of key inflammatory proteins such as TNF-α and interleukin 6 (IL-6) (14).
Figure 9: The toll-like receptors TLR2 as well as TLR4 involved in obesity which ultimately lead to inflammation, as well as insulin resistance. Several molecules can activate toll-like receptors including LPS, part of gram-negative bacteria, or free fatty acids. The irregularity of adipose tissue in obesity causes an increase in macrophages which have TLR2 or TLR4 or both. The macrophages are depicted in blue and green. This increase ultimately leads to an inflammatory pathway. Finally, proteins associated with increased inflammation are released such as TNF-α. This process can ultimately lead to insulin resistance which exacerbates the obesity, as well as related diseases such as cardiovascular disease (figure taken from Jialal, 2013).
DIET AND THE MICROBIOME

Diet and fatty acid intake can affect the microbiome, which in turn has repercussions for one’s health and immune system’s responses (2). There are many instances in science where diet is connected to the immune system and increasingly it appears this connection is due to the microbiome’s role in immune responses. For example, leptin is a protein that modifies the diet by inhibiting one’s appetite. It regulates both food intake and appetite by acting on the brain to control these factors. Interestingly, leptin is also a cytokine which stimulates the increase of T helper cells. In addition, it also increases the amount of neutrophils, as well as macrophages (2). Turnbaugh et al. also showed that leptin deficient and obese mice had different taxonomic microbiota in their gut (15).

Another similarity between diet, the immune system, and the microbiome is seen in the TCR complex described previously. When, for example, there is a foreign microbe present in the body, the body reacts with both the innate and adaptive immune system. Part of the adaptive immune system involves recruiting T cells to the area of infection or antigen presence. When T cells are stimulated by said antigen, the TCR forms a complex involving many other proteins and molecules. This interaction needs sustenance; in other words, an increase in the need for amino acids, as well as glucose, is seen. Without this increase, there is a faulty immune response and the T cells do not have everything they need to become activated (2). This has implications for malnutrition because without the
necessary nutrients, the immune system and its responses may be compromised.

Finally, short chain fatty acids are another connection between diet, the immune system, and the microbiome. The short chain fatty acids are actually the final result of macronutrient breakdown by microbes, since humans cannot break down certain molecules such as plant polysaccharides (2). Thus, these microbes are needed so that they can use their own enzymes to break down these molecules and the links connecting them. Peng et al. describe the link between these short fatty chain acids and the immune system. They show that the short chain fatty acid butyrate helps keep the intestinal epithelial barrier and its function strong. By doing so, it can help prevent extra infections by microbes that get through the barrier or an increased amount of inflammation (16).

Turnbaugh et al further illustrated the importance of the diet on the microbiome and thus a person’s health and immune system. Their model included mice that had human fecal microbes transplanted. These mice were particularly specific – they were germ-free C57BL/6J mice. These mice are particularly imperative because they are grown up germ-free, thus with no exposure to microbes. This way they can be colonized with a variety of microbes and thus studied by scientists in regards to several aspects, in this case diet. As seen in Figure 10, the mouse feces was studied after one day, one week, and
then one month while on a low-fat, plant polysaccharide rich (LF/PP) diet. After this allotted amount of time, the mice were then put on a high-fat, high-sugar Western diet. Every week, their fecal samples were taken and studied. This lasted for about two months. The scientists found that even after just one day, when switching between the two diets, the entire structure of the microbiota was changed and the microbiome gene expression was different as well and this effect lasted about two months (17). So although the microbiota was first given to the mice to represent a mouse microbiome, it was easily changed by diet.
The Microbiome and Cancer

Schwabe et al. describe the relationship between the microbiota and the host as a “super organism” in which both benefit from the relationship, contributing in different ways (18). The most common example is the microbiota’s contribution of vitamins that the host alone cannot attain. Although this relationship is usually beneficial, if there is any dysregulation in the relationship, there is room for disease, infection, and in this case cancer. Table 2 shows examples of different cancers and the microbiota involved in each one.
The body prevents this dysregulation in several ways. For example, the stomach’s pH is extremely low, or acidic, so that it can kill any foreign molecules that may escape from the intestine or that are externally ingested. The gut also

| Table 2: Various cancers and their associated microbiota. Table taken from Schwabe, 2013. |
|---|---|---|---|
| Cancer | Mechanism | Evidence | Refs |
| Gastric cancer | Chronic infection with Helicobacter pylori | *Epidemiology*<br>*Reduction by H. pylori eradication* | 38, 40, 46, 47 |
| *Gastric MALT lymphoma* | Uncontrolled adaptive immune responses in patients with chronic infection with H. pylori, Campylobacter jejuni, Borrelia burgdorferi or Chlamydia psittaci | *Epidemiology*<br>*Antibiotic treatment* | 52–54 |
| *IPSSD* | *Ocular adnexal lymphoma* | | |
| Gallbladder cancer | Chronic infection with Salmonella enterica subsp. enterica serovar Typhi | Epidemiology | 49, 50 |
| Oesophageal cancer | Reduced risk in patients with H. pylori infection | Epidemiology | 48, 48 |
| **Cancers promoted by specific pathogens (in mice only)** | | |
| Breast cancer | Increased inflammation, mediated by T regulatory cells | Cancer promoted in H. pylori infected Apc<sup>min</sup> mice | 94 |
| Liver cancer | Chronic hepatitis | Cancer promoted in H. pylori infected mice | 89 |
| Colorectal cancer | TNF-mediated and NO-mediated | Cancer promoted in H. pylori infected Rag2<sup>−/−</sup> mice | 90 |
| **Cancers suspected to be promoted by commensal bacteria or dysbiotic microbiomes** | | |
| Colorectal cancer | Dysbiosis<br>*Barrier failure<br>*Chronic inflammation<br>*Bacterial genotoxicity | Cancer reduction by antibiotics and in germ-free mice; transmission of dysbiotic microbiota triggers cancer development | 25, 27, 32–34, 36 |
| Liver cancer | Increased hepatic exposure to TLR-activating MAMPs<br>Increased exposure to the secondary bile acid DCA | Cancer reduction by treatment with antibiotics and in germ-free mice | 21, 22, 35 |
| Lung cancer | Increased bacterial infection in COPD? | Cancer increased by treatment with LPS and DCA | |
| Pancreatic cancer | LPS–TLR-mediated increase of pancreatic cancer | LPS treatment increases cancer development | 56–58 |

Apc, adenomatous polyposis coli; COPD, chronic obstructive pulmonary disease; DCA, deoxycholic acid; IPSSD, immune proliferative small intestinal disease; LPS, lipopolysaccharide; MALT, mucosa-associated lymphoid tissue; MAMPs, microorganism-associated molecular patterns; NO, nitric oxide; Rag2, recombination activating gene 2; TLR, Toll-like receptors; TNF, tumour necrosis factor.
has a mucosa layer that helps protect it from invaders as well. These barriers are usually closely associated with the immune system. For example, lymphocytes serve as a barrier in the gut as well as in the skin. One of the best examples that illustrates a break in a barrier is ulcerative colitis, where the barrier in the intestine is broken which increases the risk of carcinogenesis (18).

The toll-like receptors previously described have also been shown to be involved in carcinogenesis. By becoming stimulated by LPS, or another stimulant, their activation leads to certain cell-surviving pathways, such as the NFκB pathway. This makes sense in the context of cancer since cancer is defined as the unmediated growth of cells. They have also been shown to have tumor developing properties by studying TLR4 knockout mice (18).

More specifically, there have been studies showing a relative correlation between the microbiome and colorectal cancer (19). For example, McCoy et al. show that there is a greater amount of Fusobacterium in the mucosa of the rectum in patients that have colorectal cancer as opposed to patients that were healthy and acted as controls as seen in Figure 11 (20). The microbiota in the gut may also cause the release of certain toxic molecules such as phenols or hydrogen sulfide. This may further exacerbate inflammation and the cancer (19).
The Microbiome, Cancer, and Diet

Because the microbiota are closely involved in the host’s metabolism, it is no surprise that there have been correlations between the host’s diet, the microbiome, and cancer. For example, cancer may be affected metabolically by the generation of bile acids which promote the formation of tumors (18). For example, Schwabe et al. describe the process by which the microorganisms in the gut affect the metabolism of bile acid. This is affected by one’s diet because it

Figure 11: The difference in number of *Fusobacterium* found in patients’ rectal biopsies between adenoma patients and non adenoma patients. The adenoma patients had far higher amounts of the microbiota *Fusobacterium* in their rectal biopsises than healthy controls (figure from McCoy, 2013).
was seen that a high-fat diet actually changed the gut microbiome and in turn increased the level of a bile acid called DCA. This bile acid has been associated with certain cancers, including colon and oesophageal cancer (18).

Shapira et al. also show the relationship of diet, the microbiome, and cancer in the context of breast malignancy. Dysbiosis is essentially an altered microbiome that comes after external pressures such as diet or antibiotics. They found that dysbiosis actually lowers the number of lymphocytes, while increasing the ratio of neutrophils to lymphocytes. This in turn caused a lowered survival of women with breast cancers (21). According to Shapira et al., another way that dysbiosis affects breast cancer is its involvement in circulating estrogens in the entero-hepatic system which can contribute to breast cancer.

**DIET, INFLAMMATION, MICROBIOME, AND OFFSPRING**

Several studies have focused on different ways the microbiome can be passed on from mother to child. For example, previously the womb was thought to be a sterile environment, in which the child is born sterile. However, recent evidence shows that the maternal microbiome may actually be passed on during this time. In other words, the child may have an initial microbiome before it’s born because of the mom’s contribution while in the womb and then later on is
affected by breast milk. The authors go through details in which maternal transmission occurs, such as in marine invertebrates, terrestrial invertebrates, and vertebrates, highlighting the fact that throughout the animal kingdom this transmission exists. They also highlight the importance of the microbiome and its contribution to the genetics and function of humans (24).

Breast milk has long been a topic of research due to its direct interaction with offspring and for its many properties. As Kau et al. explains, breast milk contains antibodies necessary for the offspring to fight disease. Breast milk is actually essential in this role, providing offspring with a huge barrier to disease before they can build up their own antibodies. Breast milk may also contain other crucial components that help the body function properly and defend against infection such as antimicrobial enzymes, as well as cytokines and antibodies (2).

Another important aspect is the mother’s diet and its effects on the breast milk. This has been correlated with inflammation and the microbiome in several studies. For example, Hoppu et al. says that “the mother’s diet determines the fatty acid composition and the concentration of vitamins in breast milk, while the influence on mineral, trace element and electrolyte concentration appears relatively limited” (22). Because breast milk is essential to a child’s health, especially an atopic child (a child prone to allergies), the mother’s diet becomes even more crucial since the mother’s diet directly affects the make up of breast
milk. In Hoppu’s study, they measured the food and nutrient intake that mothers had while they were breastfeeding. The offspring in this case were stratified as either low or high risk of atopic sensitization after a year. This group confirmed that the so-called Western diet intake by mothers can increase the risk for atopic sensitization. It is especially important in children whose only source of intake for nutritional resources and immune response resources comes from breast milk. The study team explains that this may be due to other research done that shows that polyunsaturated fatty acids can increase the risk of atopy. One mechanism proposed is by an unsaturated fatty acid being changed into prostaglandin E2 which supports the creation of immunoglobulin E.

In another study, mice mothers were fed the Western diet which created a “toxic” milk that contains fatty acids that are both saturated and that have long chains. This in turn causes inflammation in the offspring that nurse using the toxic milk. The scientists found that this involved TLR4 and the related TLR2, another TLR responsible for sensing bacterial products. On the other hand, they found that the gut microbiota was not involved. They did this in the two ways; they either inhibited the TLRs or they deleted them. In both of these cases, the offspring no longer had the same sensitization. In contrast, when mice were raised germ-free, the sensitization prevailed (23). This causes speculation into the relation of the mother-child barrier, where many things are passed between the two. Figure 12 shows the mice used and their development of alopecia as
well as the skin of the offspring from Western diet moms and their irregular skin.

**Figure 12:** The offspring of mothers fed a Western diet. The top figure is the alopecia they developed, while the bottom picture is the skin dysregulation that resulted (Figure taken from Du, 2012).
Several studies have been done to show the affects of a high-fat maternal diet in other disease contexts as well. One particular study investigated the effects of high fat maternal diet on three systems: the renal sympathetic nerve activity of the offspring, the sensitivity of offspring to leptin and ghrelin, and finally on the blood pressure of offspring (25).

Leptin and ghrelin are diet associated proteins. Leptin is a protein that is involved in sending signals to the brain to essentially stop eating because the body is full and does not need any more food. Ghrelin is like leptin’s counterpart. It essentially tells the body that it is hungry and it needs food. There are higher levels of ghrelin before eating and then it lowers after eating, which correlates with the fact that it tells the body that it’s full.

Prior et al. used rabbits and what was found was that the rabbits with mothers that ate a high fat diet had an altered cardiovascular system because of an irregular sensitivity to leptin and ghrelin. It was found that these rabbits with mothers that ate a high fat diet had an increased mean arterial pressure and heart rate. In addition, they also had an increase in renal sympathetic nerve activity (25). The sympathetic nervous system is associated with “fight or flight” or in other words, an increase in stress. So it makes sense that these rabbits with increased nerve activity in the sympathetic nervous system also had blood pressure. The rabbits that came from mothers that were fed the high fat diet also
had altered response to the leptin and ghrelin. They had higher levels of sympathetic activity to induced by leptin and ghrelin than the control rabbits (25). Figure 13 shows the increase in the three factors, arterial pressure, heart rate, and renal sympathetic nerve activity.

Another study done by Valtonen et al. describes the effects that not just one parent has on an offspring, but that both the father and mother have on the offspring. They studied three factors and the way that the parents’ individual diets, whether a “poor diet” or standard diet, affected these three factors. The poor diet was different in the fact that it had 1/8 the amount of brewer’s yeast that the standard diet did. They first studied the development time and found that the ones that took longest to develop were those that had parents who were both on the poor food diet. By “develop”, the scientists meant to study offspring development time. They then studied the adult body size and found that females who were fed a poor diet had offspring who were larger, as opposed to females that were on a standard diet who had offspring that were smaller. Similarly, those male offspring that had fathers that were on the poor diet actually ended up being larger than the male offspring from standard diet fed fathers. Finally, the last factor of the three was their resistance to the bacteria Serratia marcescens. There was nothing found on the effects of the mother or the father’s diets on the resistance to this bacteria in the offspring (26), indicating that a diet poor in brewer’s yeast does not affect the immune system the way a high fat diet does.
Figure 13: The increase in arterial pressure and heart rate in the group of rabbit offspring whose mothers were fed a high fat diet. Both arterial pressure and heart rate, as well as renal sympathetic nerve activity (not shown) increased in rabbit offspring whose mother ate a high fat diet. This was due to increased sensitivity to leptin and ghrelin (Figure from Valtonen, 2013).
Although this study did not directly deal with a Western diet or fatty acids and their intake by parents and thus the effects on the offspring, this study was very important in understanding several other things. For example, it illustrated that both parents contribute, not just one. The mother may be contributing through her microbiome and the father through gene modifications, or there may be several other factors at play.

It would be interesting to study the effects of a high fat maternal diet in combination with alterations in the gut microbiota on the factors thus far discussed such as an offspring’s weight, the amount of fat or adipose tissue, and the function of the gut. One study did just this by interestingly not only feeding rats a high fat diet, versus a standard diet control group, but also adding *Escherichia coli* (*E.* coli) to the water of some of the offspring (27). The study team measured several factors including the rat offspring’s weight, the amount of fat deposited, the enzymes in the pancreas, the organ growth in the gastrointestinal tract, as well as the intestine’s enzymes and their activity as well as permeability. They found that the factors of weight and fat deposition were actually increased in the offspring who had mothers who ate the high fat diet. In addition, they had a decrease in intestinal proteins and enzyme activity in the small intestine (27). The most unique part of this experiment was the fact that they then added *E. coli* to the water of some of the rat offspring. This addition was found to exacerbate all of the responses found in the offspring with mothers
that had eaten a high fat diet. Additionally, they were found to have an increased intestinal permeability (27). This is especially interesting because although studies in the past have focused on diet effects on offspring, none have gone to this depth in exploring the effects on intestinal function and permeability. Figure 14 shows the effects of *E. coli* on the offspring’s weight and its exacerbating effects.

Figure 14: The exacerbating effects of *Escherichia coli* on the rat offspring’s weight. In this study by Fak et al., the rat mothers were fed either a high fat diet or a standard diet as a control. The rat offspring were then tested at day 14 for several different factors including their weight, the amount of fat deposited, their intestinal activity, as well as the enzymes in both the intestines and the pancreas. Interestingly, this team then added *E. coli* to the water of some of the rat offspring and found that this exacerbated the results, such as higher fat, more fat deposition, and decreased intestinal enzyme activity, that was found in the rat offspring from others fed high fat diets.
In correlation with the effects of diet on the intestinal activity and microbiome of offspring, Perin et al. proposed a study to analyze the effects on postweaning rats and whether there would be similar intestinal activity as the intestinal activity of nursing rats of mothers on high fat diet. Just as different levels of lipids in a mother’s diet can affect the offspring and have modifications in the uptake of lipids as well as sugars by the intestine, the same results were seen in postweaning rats indicating maternal diets alter their breast milk, which can subsequently alter the offspring microbiome (28). They aimed at determining whether if the rats were kept on the same diet that the mother had consumed, they would have the same modifications in intestinal uptake of nutrients. The study found that by changing the lipids in the diet, the intestine actually modifies itself to adapt to this new diet.

**CONCLUSION**

A recent study done by Myles et al. embodies the very concepts explored in this manuscript in a well-rounded and thorough way (33). The group separated mice into two diet groups. The first was called Western diet which aimed to represent the typical western diet with high fat content. The other group was the Low Fat diet which was the standard mouse chow. The breeders, or parents, were on these diets for weeks and stayed on this diet throughout. The offspring on the other hand, were exposed to their parent’s diets during gestation and
lactation, but were weaned on to the low fat diet, and stayed on the low fat diet for three weeks. That way, the only difference between these offspring were the diet they received during gestation and lactation. After about three weeks of these mice offspring on the low fat diet, they were challenged with three different models of disease. The first was infection, in which they were injected with \textit{E.coli} or \textit{Staph. aureus}. The second model used was one of autoimmunity. In this case, the team used an animal model of Multiple Sclerosis. Finally, the last model used was of allergies. In this case, peanut was gavaged into the mice for 4 weeks, and on the 5\textsuperscript{th} week they were challenged. Interestingly, in all three models the western diet mice fared worse. The team additionally studied the reasons for these results. They studied the effects the father may contribute, by studying gene modifications. They also studied the effects the mother may contribute, by studying the microbiome make up. To understand which effect was stronger, they co-housed mice for 3-4 weeks. They found that the father was not responsible, because the immune changes went away with microbiome changes even though the gene modifications did not. So whatever the role the father plays, it is less important than the mother’s contribution. Figure 15 shows Myles et al.’s study set up (33).
The importance of health and diet is becoming increasingly alarming because of the mass amount of studies finding critical evidence of implications involved in high fat diets and its detrimental effects on disease susceptibility and especially on offspring. Over one-third of US adults were found to be obese in 2009-2010 and the number seems to be growing. Thus, it is especially important to explore this field. Another component involved is the microbiome, now known to be affected by one’s diet. Not only can it affect the individual directly, but it
may also affect one’s offspring. This is crucial to study because the microbiome alone contributes much genetic variation to humans. With the new process of high throughout sequencing, it is now easier to find the variability in the microbiota contained in humans, as well as in mice or rats used in studies. By studying the variation in microbiota in different parts of the body, scientists can find new areas to target when attempting to fight certain diseases or states such as inflammation.
REFERENCES


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EDUCATION

Boston University School of Medicine, Boston, MA • 2013
Candidate for Master of Arts in Medical Sciences, GPA: 4.0

Columbia University, New York, NY • 2011
Bachelor of Arts in Economics and Pre-medical Sciences

RESEARCH AND CLINICAL EXPERIENCE

bWell Center, Boston Medical Center Department of Pediatrics, January 2013 – Present
Volunteer
• Improve health and wellness of Boston Medical Center pediatric patients by providing education and social support through the use of the patient navigation model, current technology, and community resources.
• Provide patients, parents, and guardians with free health education and integrate programming and partnerships to create a dynamic and educational experience for patients.

NIH, National Institute of Allergy and Infectious Diseases, Laboratory of Clinical Infectious Diseases, Bacterial Pathogenesis Section. July 2011 – July 2012
Post-Baccalaureate Fellow
• Objective: to use cellular and animal models and patient-based studied to investigate the regulation of IL-17 and related cytokines in the context of infection and the innate and adaptive immune responses against the bacterial pathogen Staphylococcus aureus.
• Head project on the effect of dietary fatty acids on susceptibility to allergic and infectious diseases.
• Perform weekly experimental procedures including PCR and mouse injections.

NIH, Department of Anesthesiology and Surgical Services, September 2011 – July 2012
Patient Ambassador and OR Support Volunteer

- Assist OR staff with transport of patients between the Recovery Room, operating room, and ICU.
- Serve as Spanish translator when needed.
- Visit with patients and their family and friends to communicate updates, answer questions about logistics, and relay messages to staff.
- Improve patients’ and their family’s comfort and overall hospital experience.

NIH, Intensive Care Unit Rounds Shadowing Program and Infectious Disease Unit Rounds, July 2011 – July 2012

- Shadow doctors both in the ICU and Infectious Disease Unit of the NIH hospital on a weekly or bimonthly basis.
- Visit with patients in both departments, and sit in on discussions between the physicians as well as the nurses.

Project Sunshine, NIH Children’s Hospital and Children’s National, October 2011 – Present

Volunteer

- Participate in monthly events such as Sunshine Chef where we make healthy food projects with the children, Arts and Crafts where we help the children create art for their rooms, and Scavenger Hunts with the children.

Columbia University Medical Center, Department of Pathology and Neuroscience, Dr. Carol Troy, May 2010 – December 2010

Research Assistant

- Main Objective: To explore cell death mechanisms in Alzheimer’s Disease, specifically the molecular mechanisms of neuron dysfunction and death with an emphasis on the regulation of caspase activity.
- Perform weekly experimental procedures including western blots, immunoprecipitations, staining, animal dissections, and cultivating hippocampal neurons.

Academic Associates Clinical Research Program at Columbia University, Dr. David Newman, August 2009 – January 2010

Clinical Researcher/Volunteer

- Discuss ongoing clinical trials concerning stroke and pregnancy with patients in the Emergency Department and Fast Track of St. Luke’s and Roosevelt Hospitals and enroll patients in the research studies.

PUBLICATIONS

1. (Journal of Immunology): Ian A. Myles¹, Natalia M. Fontecilla¹,§, Brian M. Janelsins¹,§, Paul J. Vithayathil¹, Julia A. Segre², and Sandip K. Datta¹. Parental Dietary Fat Intake Alters Offspring Microbiome and Immunity.
Nature.

2. (Nature Immunology): Ian A. Myles\textsuperscript{1}, Natalia M. Fontecilla\textsuperscript{1}, Patricia A. Valdez\textsuperscript{1}, Paul J. Vithayathil\textsuperscript{1}, Shruti Naik\textsuperscript{2}, Yasmine Belkaid\textsuperscript{2}, Wenjun Ouyang\textsuperscript{3}, and Sandip K. Datta\textsuperscript{1}. IL-20 receptor signaling inhibits cutaneous IL-1\(\beta\) and IL-17A production to promote methicillin-resistant \textit{Staphylococcus aureus} infection. Nature Immunology.

COMMUNITY SERVICE AND LEADERSHIP

\textbf{Latino Student Fund}, August 2011 – May 2012, \textit{Tutor}

\begin{itemize}
  \item Tutor and mentor a middle school student on a weekly basis, with focus on building mathematics, science, and reading skills, and social responsibility.
  \item Provide workshops, speakers, and informational outreach service to students and their families regarding educational opportunities and community events.
\end{itemize}


\begin{itemize}
  \item Start a program for shadowing doctors around the New York City area.
  \item Organize both P.U.M.P. and Pipeline Mentoring Programs for both high school students in New York City and undergraduates at Columbia University.
\end{itemize}


\begin{itemize}
  \item Responsible for overseeing all the aspects of the team that relate to dance such as choreographing, running practices, cutting music, and overseeing costumes.
  \item Plan, manage, and coordinate \textit{Reléve}, a weekend in which 25 or more underprivileged New York City high school students interested in the performing arts and higher education are hosted by the troupe at Columbia University.
\end{itemize}

SKILLS

\begin{itemize}
  \item Languages: \textbf{Spanish} (Fluent)
\end{itemize}