Abstract-. Macrophages play a larger role in our physiology than previously thought. It’s been recently discovered that macrophages influence the central nervous system (CNS) and metabolism through the chemical signals, catecholamines and adipokines allow these systems to interact. The CNS produces catecholamines that can have inflammatory effects due to the interaction catecholamines has with the adrenergic receptors on macrophages. Adipokines are chemical signals secreted from fat cells and recent studies show they influence inflammatory processes due to their interaction with macrophages and the immune system.

Introduction- Our immune system consists of a network of specialized cells that interact through chemical signals known as cytokines. One important cell in the immune system is the macrophage. Macrophages play a vital role in our Immune system and are essential in the transition from innate immunity to adaptive immunity. Their role in innate immunity is to phagocytize potential pathogens. They also are in charge of phagocytizing cellular components and ridding our body of dead and dying cells. Their role in adaptive immunity is important as it allows effector cells to recognize the pathogen. This is accomplished by presenting the pathogen’s antigen to helper T cells, which will release cytokines attracting effector cells necessary for eliminating the pathogen. Presenting the antigen will also lead to the production of antibodies. In subsequent infections the immune system will recognize the pathogen quickly and eliminate it much more easily than when first infected. Until recently, our knowledge of the role macrophages have in our physiology only included the immune system. However, recent studies show that macrophages play a larger role than in just our immune system. It has been discovered that catecholamines produced by the central nervous system (CNS) have the ability to influence the actions of macrophages. These chemicals were previously known to only act as neuromodulators but have now be found to link the immune system, metabolism and central nervous system together . Adipokines are cytokines secreted by fat cells and are regulators of fat metabolism. Adipokines allow the immune system to interact with metabolism. We now know that both these chemicals have multiple roles and act as nontraditional cytokines influencing both innate and adaptive immunity. This discovery has great potential in providing new information that would help develop treatments for diseases that affect metabolism and the central nervous system. The influence these chemical have over macrophages are only beginning to be understood much work is needed to actually develop treatments. However, we now understand the essential mechanisms involved in the interactions of these nontraditional cytokines and macrophages.

Recent Progress- Recent studies allow us to examine the intricacies involved in the role macrophages play in the immune system, metabolism and the CNS. Catecholamines that interact with immunity and metabolism include, dopamine, noradrenaline and adrenaline. These neurotransmitters are produced by adrenal medulla and the CNS and were recently shown to interact with the immune system by eliciting either an anti-inflammatory or pro-inflammatory effect, depending on the receptor on the macrophage they interact with. These neurotransmitters were originally known to only act on the sympathetic nervous system (SNS ) and are involved in the flight or fight response. This response increases heart rate, blood pressure and controls body temperature. Recent studies show these neurotransmitters are released when the vagus nerve is stimulated. The neurotransmitters then cause macrophages to secrete inflammatory cytokines, which in turn can interact with the CNS. Catecholamines act on adrenergic receptors and its signaling is involved in immune cell activation, proliferation and apoptosis. Macrophages, along with other myeloid cells, express alpha and beta adrenergic receptors. These receptors are what allows these two systems to elicit their effects on one another. The following studies show the influence that catecholamines have over the immune system.

Researchers know that macrophages have alpha and beta adrenergic receptors, which bind adrenaline and noradrenaline. This allowed them to test the effects of catecholamines on macrophages by inhibiting the beta adrenergic receptor. When the peritoneal macrophages were treated with lipopolysaccharide (LPS), a component of bacterial cell walls, while the beta adrenergic receptor was inhibited, there was an increase in the secretion of pro-inflammatory cytokines. The same effect was also seen when the adrenal medulla was removed as it lead to a decrease in catecholamines. Having less of a chemical and inhibiting the receptor for that chemical elicit the same responses. Studies show that the beta adrenergic receptors on macrophages have a role in reducing inflammation. Catecholamines influence inflammation by regulating macrophage synthesis and beta adrenergic receptor expression. This effect is seen by removal of the adrenal medulla, which secretes catecholamines. This removal decreases the expression of the beta adrenergic receptor and an increase in tyrosine hydroxylase. Tyrosine hydroxylase modifies the precursor to catecholamines. The loss of catecholamines is compensated by an increase of tyrosine hydroxylase by macrophages. Macrophages are important in the production of catecholamines as they secrete an enzyme that modifies the precursor. As previously mentioned, beta adrenergic receptors are anti-inflammatory. Researches show that the alpha adrenergic receptors activation cause pro-inflammatory cytokines to be produced. The G protein and it’s pairing with the receptors act as a molecular switch and is most likely involved in the different responses in these two receptors. Catecholamines interact with these receptors through inhibition and activation. This allows the CNS to influence the immune system by promoting anti or pro inflammatory mechanisms.

 When it comes to sepsis catecholamines can influence ones likelihood of survival. They can interact with the sympathetic nervous systems, macrophages and influence the parasympathetic nervous system, as well as the cholinergic nervous system facilitated by nicotinic receptors. The connection all these systems have is demonstrated through the molecule acetylcholine. Acetylcholine is released as well as other catecholamines when the vagus nerve is stimulated. Acetylcholine promotes the downregulation of tumor necrosis factor alpha (TNFa) and other pro inflammatory cytokines. Researchers show a certain subset of T cells can secrete acetylcholine causing a decrease in inflammation in the sepsis mouse model. Decreasing pro-inflammatory cytokines allows this pathway to elicit this effect. Studies show that the removal of the vagus nerve or the adrenal medulla causes a lethal sepsis due to the decrease in catacholanime. When treated with dopamine the sepsis is not lethal. The mouse model of sepsis shows the importance of the cholinergic pathway in regulating the inflammatory immune response. Inflammation is an important mechanism in some places it a necessity and others it is lethal. Catecholamines regulate inflammation pathways making them a possible therapy in infections that cause sepsis.

Catecholamines can influence other life threatening illnesses. For example, macrophages exposure to dopamine plays a role HIV virulence. In the CNS, macrophages are the cells that HIV attacks. When human peripheral blood derived monocyte macrophages were treated with dopamine there was an increase on HIV entry into the cell and its replications. Drugs that increase dopamine are also believed to influence HIV virulence. This information could be helpful in developing new HIV treatments.

These chemicals can influence so many processes in the body. Another system that catecholamines plays a role in is wound repair. This is especially true of the catecholamine, adrenalin, in extreme burn injuries. When treated with adrenalin, burn wounds from excised human skin showed delayed reepithelization. This neurotransmitter negatively effects wound repair by preventing the migration of keratinocytes which express beta 2 adrenergic receptors. Treatment of an antagonist to the beta 2 adrenergic receptors lead to rescued wound repair. Furthermore, the macrophages in the CNS, microglia are responsible for maintaining neural synapses. If microglia are chronically activated the dysregulation can lead to neurodegeneration, neuropathic pain and a decrease in cognitive ability. This is due to norepinephrine activation of the beta adrenergic receptor leading to a decreased response to pathogenic molecules and altered microglia surveillance. Macrophages are able to regulate physiological homeostasis by secreting catecholamine’s precursor when it is low.

Catecholamines role in metabolism involves the process of thermogenesis, a physiological response involving temperature control. In the mice model cold temperatures caused alternative activated macrophages (AMA) to secrete catecholamines. Mice lacking these macrophages are unable to maintain their body temperature when exposed to cold. AAM are involved in the development of beige adipose tissue. This development causes an increase in energy consumption by fatty acid metabolism. The influence macrophages have over different systems and disorders depends on the site, development and environment the macrophage is in.

The other newly discovered chemical signal is adipokines. These are adipose derived hormones and play a role in metabolic processes and function as an Immunomodulator. In metabolism they regulate lipid and glucose uptake. The cytokines produced, whether it be pro or anti-inflammatory, by macrophages depends on the adipokines involved which are lipoprotein, leptin and adiponectin. Lipoproteins form high density lipoproteins (HDL) and low density lipoproteins (LDL). HDL promotes cholesterol efflux from cells which contributes to arterial plaques. When HDL is decreased these plaques increase. HDL has anti-inflammatory properties. LDL is susceptible to oxidation and can form aggregates. Those aggregates form fat droplets that are recognized by scavenger receptors on macrophages. This recognition leads to macrophage foam cell biogenesis which contributes to plaque formation on artery walls. Macrophage dysfunction in macrophage’s lysosomal activity is due to the oxidation of LDL, causing atherosclerosis. Oxidation of LDL can also influence plaque formation by contributing to the expression of adhesion molecules and the cells adhering to endothelial cells. The immune system involvement in heart disease could be a potential target in the treatment of these types of diseases.

Another adipokine involved in the interaction of metabolism and macrophages is leptin. A hormone produced by adipose tissue that affects the hypothalamus. It is involved in signaling that control hunger by negating the effects of the hunger hormone. It also promotes energy consumption involved in thermogenesis. An increase in leptin levels leads to leptin resistance and can also effect glucose metabolism and insulin signaling. Researchers show that its involvement with the immune system influences activation, chemotaxis and survival of cells. Studies show that expression of leptin is related to the amount of adipose tissue. The cytokine interleukin 6 (IL-6) is structurally similar to leptin. IL-6 binds to the lepin receptor and causes the secretion of pro inflammatory cytokines that are associated with obesity. Adiponectin regulates the level of glucose by decreasing its production and increasing its uptake. Through beta oxidation of lipids it participates in fat metabolism as well.

Adiponectin influence over the immune system involves the reduction of pro-inflammatory cytokines which in turn decrease phagocytic activity in macrophages. Macrophage foam cell biogenesis is also decreased by this molecule by increase cholesterol efflux. Resistin and resistin like molecules have hormonal and immune functions. They play a role in the immune system by regulating the transcription factor NFkB which mediates production of pro-inflammatory cytokines. In metabolism it contributes to insulin resistance by impairment of insulin metabolism and increasing hepatic glucose levels. These chemicals like catecholamines have many effects and interaction between these systems is necessary for life.

Discussion-The discovery of catecholamine and adiponectin acting as nontraditional cytokines in addition to their role as hormones has been seen in numerous studies. Targeting the discussed pathways could have a far reaching effect on more than just one disease. This new information can help researchers target diseases of metabolism, the immune system and central nervous system in a more effective way than the treatments available now. People afflicted with diseases such as HIV, coronary heart disease and obesity could benefit from more research concerning these systems and the role catecholamines and adipokines play. However, much work is still needed because the effects that these chemicals elicit depend on the many aspects of the macrophage itself. These include the tissue the macrophage is located in, its state of devolvement and its environment to name a few.

Barnes, MA, Carson, MJ, and Nair, MG. "Non-traditional Cytokines: How Catecholamines and Adipokines Influence Macrophages in Immunity, Metabolism and the Central Nervous System." *Pubmed* (2015): n. pag. Web. Jan.-Feb. 2016.