Discuss the role of inflammatory cells in asthma.

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Summary

Asthma is a complex inflammatory disorder of the conducting airways (Holgate 2008) with a common manifestation of localised anaphylaxis characterised by reversible recurring airway obstruction, bronchial hyper-responsiveness to specific or non specific stimuli and airway inflammation. The interaction of the features of asthma determine its clinical manifestations, severity and response to treatment. Asthma is said to be a self amplifying disease stemming from the response of the asthmatic individual to common antigens resulting in a futile immunologic response (Bogaert et al 2009). Asthma is said to be “heterogeneous with respect to immunopathology, clinical representation, response to treatment and natural history” (Holgate 2008). Clinical manifestations may include recurrent episodes of wheezing, coughing, breathlessness and a feeling of tightness in the chest area.

Asthma can be broadly categorised into two main types, allergic or atopic asthma- induced by air or blood borne allergens and intrinsic asthma which can be induced by excessive exercise and cold apparently independently of allergen stimulation. Atopic asthma is the most common form- almost 40 % of the Western world are atopic (meaning they express high IGE antibodies to common allergens), but only 7% of these present with asthma (Holgate 2008). Even so, incidence and severity are increasing in the Western world with up to 300 million people affected worldwide (Fanta 2009)

Asthma is characterised by the chronic infiltration of inflammatory cells and as such, inflammation is a major factor in the pathogenesis of asthma (Vignola et al 1999). Inflammation is found to be present at all stages of asthma (Lemansk and Busse 2003). Inflammation is responsible for the development of airway hyper-responsiveness and airway obstruction characteristic of the disorder and ultimately, the severity of disease (Madison 2000, Busse and Madison 1998). It is the inflammatory cells which are involved in the regulation of inflammation itself and in the initiation of the process of airway tissue remodelling which is a hallmark of severe asthma. The disease process is mediated by the synthesis and release of cytokines (small proteins released by specialised cells that have specific affects on the interactions between cells, on communications between cells and/or on the behaviour of cells, they trigger inflammation and respond to infections) and
chemokines (attract inflammatory cells, involved in the inflammatory response) from these specialist cells. Inflammation has been found to be present at all stages of the disease, whether mild, moderate or severe; the degree of inflammation is dependent on the chronicity and often severity of disease (Lemansk and Busse 2003). The common inflammatory cells namely lymphocytes, eosinophils, activated mast cells, macrophages, their mediators and cytokines are all involved in the inflammatory process and their roles will be discussed individually here.

The asthmatic response is classified as a type 1 allergic response (Bogaert et al 2009) and can be divided into two stages; the early and late responses. The early response begins only minutes after initial exposure to allergen or stimulant and involves T-lymphocyte cells and their cytokines, activated mast cells and the release of their mediators including histamine, leukotrienes and prostaglandin D2 (PGD₂). The late response occurs several hours later (2-24 hours) and involves eosinophils with the release of additional mediators including IL-4, IL-5, IL-16, eosinophil chemotactic factor (ECF), Tumour Necrosis Factor α (TNF α ) and Platelet Activating Factor (PAF).

The Role of T-lymphocytes and Dendritic Cells in Asthma.
There is now overwhelming evidence to support a major role for T-cells, especially the TH₂ cells in atopic as well as non atopic and occupational asthma (Kay 2006). Their role appears to be in the development and regulation of airway inflammation. When first exposed to an allergen, via presentation from dendritic cells (circulating antigen presenting leukocytes with high affinity IGE receptors), the naive T- cell responds by the initiation of sensitization which leads to an immune response. The type of response is determined by the parallel concomitant binding of the co-stimulatory molecules of the dendritic cell with the CD28⁺ receptor on the naive T- cell. The correct activation of the naive T-cell leads to sensitization and differentiation into a TH₂ cell. If not then anergy ensues- or lack of an immune response. This process becomes less important in severe asthma as other co-stimulatory molecules become more important (Holgate 2008)

Dendritic cells also release a IL-12 (cytokine) which allows the TH₂ cells to carry out the following roles:

- Migrate back to the site of allergen sensitisation
- Release a potent range of cytokines IL-3, IL-4, IL-5, IL-6, IL-9, IL-13 and Granulocyte macrophage colony stimulating factor (GM-CSF)

The release of the above mediators stimulates the activation and recruitment of the following
secondary effector cells and enhances their maturation and proliferation:

- Macrophages
- Basophils
- Eosinophils

These inflammatory cells are then able to affect expression and adhesion of molecules on to epithelial cells (Janeway et al 2001).

**TH\textsubscript{2} cells:**

- Synthesise and release cytokines- which attract other inflammatory cells
- Regulate IGE production
- Regulate eosinophilic inflammation

**TH\textsubscript{2} cells are found in high numbers in the airways of asthma patients leading to an exaggerated inflammatory response in asthma patients. The cytokine presence could go some way to explaining the overproduction of IGE which is in part responsible for the exaggerated response and the development of airway hyper-responsiveness.**

There appears to be a defect in the ability of the regulatory T-cells (T- reg) to carry out their usual function of regulating T-cell proliferation and hence dampening down the immune response (Akbari et al 2006). This inability to regulate TH\textsubscript{1} and TH\textsubscript{2} cells may be partly responsible for the pathogenesis of asthma (Seroogy et al 2005). In other clinical disorders, the T-reg cells play an important role in the maintenance of homeostasis which helps promote immune tolerance and protects undue damage to resident cells and tissues, but this mechanism seems to be defective in asthma. Seroogy et al (2005) concluded that this defect may ultimately lead to hyper-responsiveness in asthma due to the exaggerated immune response generated by T helper cells (TH\textsubscript{1} and TH\textsubscript{2}). A study by Matsumuto et al (2009) found not only that the frequency of T-reg cells was markedly reduced in asthma patients as compared to healthy subjects, but also that this was found to be somehow linked to an increase in severity of eosinophilic airway inflammation in mice, suggesting that T-reg cells have a significant role to play in the pathogenesis of asthma.

A simultaneous increase in the presence of NK (natural killer) cells which release large amounts of TH\textsubscript{2} cytokines could also contribute to the airway damage characteristic of asthma (Akbari et al
It can be seen that there is overwhelming evidence for the role of T-lymphocytes in the pathogenesis of asthma. They mediate the immune response and are crucial in attracting other inflammatory cells, regulating IGE production, contributing to airway hyperresponsiveness and regulating eosinophilic inflammation which can develop into a phenotype in and of itself as we will see later.

The role of Mast cells and basophils in asthma.

Mast cells and basophils are granulated metachromatic cells which posses complex and partially overlapping roles in immunity. Both work together to exacerbate and modulate inflammation and to mediate cell repair (Crivellato et al 2010).

Mast cells are the primary effector cells of the early asthmatic response. Airway mast cells containing preformed inflammatory mediators are strategically placed next to lymphatic vessels and nerves and are essential in the regulation of the inflammatory response (Hart 2001). Their proximity to lymphatic and blood vessels allows them to react to the presence of allergens within minutes by (mostly by IGE cross linking) degranulation and release of their multiple powerful preformed mediators, including:

- **Histamine:** - In acute response, mast cells are the primary source of histamine. Apart from causing bronchoconstriction, histamine increases IL-16 production by CD8\(^+\) cells and airway epithelial cells. IL-16 has a role to play in leukocyte recruitment.
- **Proteases:** - Important in tissue remodelling, neuropeptide inactivation and also have a role in the initiation of mucus secretion.
- Powerful bronchoconstrictor mediators such as the cysteinyl leukotrienes (1000 to 2000 times more powerful bronchoconstrictors than histamine Jeffery and Haatela 2006)
- **Prostaglandin D\(_2\) (PGD\(_2\))**: - have an effect on microvascular permeability and can regulate the effect of immune cells
- **TNFa:** - Induces adhesion molecules on endothelial cells leading to migration of inflammatory leukocytes and is also implicated in tissue remodelling.
- **IL-13:** - A cytokine critical to the development of atopic asthma but the mode of action is unclear.

The release of these mediators leads to smooth muscle contraction, airway constriction, increased
epithelial permeability and the release of cytokines resulting in the recruitment of more inflammatory cells, some of which are involved in the late phase of asthmatic reaction. Even if exposure to allergens is limited, mast cells are still capable of releasing enough mediators to illicit a change in the airway environment which results in significant inflammation. Even in the absence of specific allergens, in exercise induced asthma, mast cell degranulation is thought to be induced by osmotic pressure on the mast cell (Brietling et al 2002).

Asthma sufferers tend to have increased numbers of mast cells in the airway smooth muscle, as compared to patients with eosinophilic bronchitis (Jeffries and Haatela 2006). The main difference between the two disorders is that the latter does not display the structural abnormalities of asthma. It has been deduced from this that the infiltration of smooth muscle by mast cells is at least partly responsible for the disordered airway function characteristic of asthma. There is some evidence to suggest that mast cells contribute to the structural changes in asthma by causing inflammation in the airway’s smooth muscle, this is termed ‘mast-cell myositis’ (Berger et al 2005). It is concluded that mast cell smooth muscle infiltration is likely to contributes to airway hyper-responsiveness and airway remodelling, especially in atopic patients (Berger et al 2005). Mast cell numbers have also been shown to increase simultaneously with the increase in T-lymphocytes (Galli et al 2005).

It was initially thought that the mast cells found between the lung basement membrane and epithelium (extracted using BAL) were responsible for most of the mast cell mediated responses in asthma as they may be the first contact for allergens. More recent studies however, demonstrate that the deeper basement membrane mast cells (only extracted from whole lung tissue) may have some influence on the long term response in asthma including the airway tissue remodelling often seen with severe asthma (Bradding et al 2006). Wenzel et al (2003) have also suggested a role for mast cells in airway tissue remodelling; both mast cells and eosinophils (another inflammatory cell to be discussed later) are a source of metalloproteinas which have been indicated in airway remodelling. TNFα, IL-4 and IL-5 and all mast cell cytokines have also been indicated in the ongoing late phase of the inflammatory response.

Basophils constitute less than 1% of peripheral blood leukocytes, so because of their rarity have not been as extensively studied as some of the other inflammatory cells. However, Basophils are known to be effector cells and to carry out similar functions to mast cells in IGE mediated allergic reactions, even though their precise role has never been clearly illustrated in vivo (Yousef et al 2007).

Basophils contain a number of preformed mediators including:
- **Histamines**: Increase bronchoconstriction.
- **Neutral proteases**: Including trptase and chymase which interact with many cells to contribute to airway remodelling.
- **Lysosomal enzymes**: Mediate the inflammatory response and tissue injury (C. Page 2000)

IGE cross linking leads to the de novo synthesis of cytokines and leukotrienes (Youssef et al 2007).

It is interesting to note that Youseff et al (2007) pointed out that 10 times the normal amount of basophils were reportedly found in the lung tissue of patients who died of asthma related illnesses than those who died of other causes, indicating that they may have a role to play in late phase and severe asthma, similar conclusions have been found by Guo et al (1994) and Nouri-Aria et al (2001). Nouri-Aria et al (2001) demonstrated that basophil numbers were significantly increased at 7 and 24 hours after initial antigen activation or late phase corresponding with tissue eosinophilia and IGE synthesis, both characteristics of late stage asthma of the eosinophilic phenotype.

A study by Ono et al (2010) demonstrated that a basophil cell surface marker used to diagnose and monitor certain immune diseases called CD203C increased significantly in patients with asthma exacerbation and decreased when the symptoms were reduced. Although this evidence does not demonstrate a precise role in asthma exacerbation, it does indicate that they may be important.

Increased vascularity is a feature of both mild and severe asthma, Crivellato et al (2010) discussed that both basophils and mast cells are a major source of a number of angiogenic factors. The presence of angiogenic factors causes an increase in blood flow and microvascular permeability followed by a corresponding increase in edema in the airway wall, these are all features which contribute to airway modelling. This evidence combined with the secretion of metalloproteinases and TNFα by mast cells means that there are several lines of evidence to support the hypothesis that mast cells and basophils play an important role in the tissue remodelling that is characteristic of asthma and other inflammatory diseases, although at this stage, it is too soon for a definitive answer regarding the precise role of basophils.

Basophils may also be important in mediating the activity of T-cells and the corresponding secondary response (Pathogenisis of asthma 2008). They share many recruitment mechanisms with eosinophils and may accompany them in eosinophil infiltration as demonstrated by Nouri Aria et al (2001).
The mast cell and the basophil both exacerbate and modulate inflammation, however, the mast cell remains the primary effector cell. Mast cells contribute to increasing mucous production, bronchoconstriction, tissue remodelling and airway hyper-responsiveness which are all hallmarks of the disease. Basophils have been shown to possess the ability to contribute to airway remodelling and may be important in the eosinophillic phenotype characteristic of half of all cases of severe asthma.

The Role of the Eosinophils and Neutrophils in Asthma.

Eosinophils are the prime regulators of late phase asthmatic reactions and are formed in the bone marrow by a process called eosinophilopoiesis under the influence of growth factors including GM-CSF, IL-3 and IL-5 (Jefferey and Haatela 2006). From the peripheral blood, eosinophils migrate into the airways via the microvascular wall where they are selectively retained by TNFα and IL-4 induced upregulation of adhesive molecules. From here, they cross the epithelium attracted by chemoattractants where they are activated and degranulated leading to inflammation (Jefferey and Haatela 2006). Eosinophillic inflammation is a key feature of atopic and intrinsic asthma and there is a direct correlation between the number of activated eosinophils and the severity of disease in mild to moderate asthma (Filipovic and Cekic 2001; Fahy 2009).

Eosinophillic asthma is a distinct phenotype of asthma (even though definitions of asthma have included eosinophilia as a hallmark, only 50% of asthma cases are actually associated with eosinophillic inflammation (Douwes et al 2002)) and is associated with a thickening of the airway basement membrane and pharmacologically with corticosteroid responsiveness (Fahy 2009). Wenzel et al (1999) demonstrated that noneosinophillic asthmatics, including some with severe disease had no thickening of the basement membrane, high neutrophil infiltration and seemed to be relatively corticosteroid resistant. So not all patients with sever asthma have high levels of eosinophils in their peripheral blood and /or sputum with corresponding thickening of the basement membrane. One could deduce that the thickening of the basement membrane is related to the presence of the eosinophils and that neutrophils have a role in severe forms of asthma. Eosinophils do release certain mediators that could induce the thickening of basement membrane. There is some evidence to support the theory that neutrophils are important in the pathogenesis of severe asthma as is discussed below.
The Role of Eosinophils

Approximately seven hours after allergen exposure (late phase) elevated levels of eosinophils can be found in the peripheral blood and asthmatic sputum of asthma sufferers. Upon degranulation eosinophils release:

- cytokines: autocrine cytokines – eosinophil growth factors; immunoregulatory cytokines; proinflammatory cytokines.
- Chemokines
- cytotoxins
- oxygen free radicals
- lipid mediators
- Major basic protein (MBP)
- Eosinophil peroxidase (EPO)
- Superoxidase
- Platelet activating factor (PAF)
- cysteinyl leukotrienes
- Superoxide
- Eosinophil cationic protein (ECP)
- TNFα

(Holgate 2008)

ECP, MBP, EPO and superoxide are all toxic to epithelial cells and their presence following the degranulation of eosinophils leads to desquamation of the cells, ciliary stasis and epithelial secretion and the subsequent damage/repair response that leads to tissue remodelling. Additionally, MBP is a selective antagonist for muscarinic receptors, so its presence, again due to the degranulation of eosinophils leads to a decrease in airway tone, increased bronchoconstriction and an increase in broncho hyper-responsiveness. On top of that, MBP stimulates the release of the bronchoconstrictor histamine from both basophils and mast cells perpetuating the inflammatory response further.

As previously stated in the discussion on mast cells, cysteinyl leukotrienes, also secreted by eosinophils are extremely potent bronchoconstrictors. One author sites them as being 1000 to 2000 times more potent than histamine (Jeffery and Haahela 2006). They also increase vascular permeability, stimulate mucus secretion and decrease mucociliary clearance while stimulating
smooth muscle proliferation causing neuronal dysfunction and stimulating eosinophil and neutrophil recruitment to the site. All of which serve to perpetuate the inflammation further and contribute to the clinical expression of asthma.

PAF is itself an eosinophil chemoattractant and activator, which induces vascular permeability and smooth muscle contraction, again adding to the inflammation and clinical expression. Eosinophils also secrete leukotriene C4, PGE2, and lipoxygenase products, all of which contribute to inflammation and the secretion of mucous into the airways.

Specific cytokines and chemokines released by eosinophils include:

- **Autocrine cytokines**: eosinophil growth factors IL-3, IL-5, GM-CSF.
- **Immunoregulatory cytokines**: IL-2, IL-4, TGF-β, IFNγ.
- **Pro-inflammatory cytokines**: IL-1, IL-6, IL-16, TNFα.
- **Chemokines**: IL-8, MIPα, RANTES.

TGF-β (Transforming growth factor β) inhibits epithelial growth as well as stimulates fibroblast growth and could therefore play an important role in remodelling of the airway tissues and potentially progression of severe disease.

TNFα is mainly produced by macrophages and plays a pivotal role in initiation and perpetuation of inflammation by increasing infiltration by more eosinophils, neutrophils and other inflammatory cells, increasing mucous production by upregulation of mucous producing genes, increasing airway hyper-responsiveness. TNFα is also a contributing factor to airway tissue remodelling by increased proliferation of fibroblasts in the sub epithelial basement membrane. It may also be important in asthma exacerbations related to viral infections as it has been shown to increase in concentration during these times (Holgate and Busse 2008). All of the evidence points to the fact that TNFα may be important in the regulation of the inflammatory response and hence may be centrally involved in the pathogenesis of asthma.

**The Role of Neutrophils.**

Wenzel et al (1999) showed that there are significantly higher numbers of neutrophils than usual in the airway lavage of patients with severe asthma compared to patients with mild to moderate asthma (Chang and Chu 2004). Neutrophils appear to accumulate where there is more severe
airflow obstruction. Eosinophils may also be present as the two cell types are not mutually exclusive (Fahy 2009). Neutrophils have been shown to be present in the sputum of asthma patients after severe asthma attacks where they may be involved in the initiation and the resolution of the attack (Fahy 2009). The lungs of patients who have suffered from sudden onset fatal asthma show an excess of neutrophils and an apparent lack of eosinophils (Chang and Chu 2004) again highlighting that neutrophils may be playing a role in severe asthma. They are eliminated by apoptosis after the attack is resolved.

Neutrophils arrive at the site of allergen exposure early on in the immune response and as such are in prime position to regulate and control the recruitment of other inflammatory cells. The production of chemokines including IL-8 and macrophage inflammatory protein 1α by neutrophils attract more neutrophils in large numbers in a positive feedback loop as well as immature dendritic cells (which secrete more IL-8 attracting even more neutrophils), T cells, monocytes and macrophages.

Neutrophils also engage in cross talk with dendritic cells. When apoptosis of neutrophils occurs in the lymph nodes, their products are taken in by dendritic cells who then present the neutrophil derived antigen to T-cells leading to their activation. On the other hand, neutrophils can also act as antigen presenting cells and present the antigen to the T cell directly.

Neutrophils have not been as extensively researched in asthma as some of the other inflammatory cells. It is noteworthy that netrophils are the first line of defence in bacterial and fungal infections where they have a role in the synthesis and release of a range of very potent cytotoxic agents and inflammatory mediators including:

- Metalloproteinases
- Elastase
- Lactoferrin
- Myeloperoxidase
- Reactive oxygen species
- Eosinophilic cationic protein (ECP)
- IL-8

(Monteseirin 2009)

**Metalloproteinases**
Asthma involves active tissue injury and repair mechanisms which ultimately lead to tissue remodelling, this can be seen to some extent in all stages of asthma. The metalloproteinases are a group of growth factors that have been implicated in this process (Chang and Chu 2004). Metalloproteinases are released by macrophages, eosinophils, epithelial cells and fibroblasts as well as neutrophils. However, in asthma, matrix metalloproteinase-9 (MMP-9) is almost exclusively released by neutrophils and has been implicated in the process of airway remodelling (Monteserin 2009).

Neutrophils also have the potential to synthesise and release TGF-β; basic fibroblast growth factor; platelet derived growth factor and vascular endothelial growth factor among other molecules which have all been demonstrated to contribute to the process of tissue injury and repair through angiogenesis, epithelial damage and fibrosis (Chang and Chu 2004).

**Elastase**

The release of elastase leads to the following:

- An increase in vascular permeability.
- Hypersecretion of bronchial mucous.
- Metaplasia of bronchial mucous glands.
- Bronchoconstriction.
- Bronchial hyperreactivity.
- Stimulates IL-8 secretion and therefore neutrophil transmigration to the lung.
- Stimulates production of eosinophil cationic protein.
- Causes IGE dependent epithelial damage.

All of the above can produce an environment conducive to the development of asthma symptoms (Monteserin 2009).

**Reactive oxygen species, Eosinophilic cationic protein (ECP) and IL-8**

Reactive oxygen species can increase the degree of tissue damage therefore potentially contributing to the tissue injury and repair process seen in asthma. Neutrophils are a major source of these molecules.

ECP is a very potent cytotoxic molecule which has been traditionally associated with eosinophils as previously mentioned. When stimulated by IGE antibodies, neutrophils release this molecule which apart from causing damage to surrounding cells, also causes the release of histamine from basophils.
and leads to an increase in the secretion of bronchial mucus, a frequent characteristic of asthma.

IL-8 is a potent chemoattractant for more neutrophils, therefore contributing to the localised colony and potentiating the overall effects of their presence and prolonging their action.

In atopic asthma, IGE dependent mechanisms can serve to delay apoptosis of neutrophils which normally occurs within one to two days. The extension of the life span of these inflammatory cells in asthma may also contribute to the persistent neutrophillic inflammation now recognised as characteristic of noneosinophillic asthma. (Montseirin 2009)

All of the mediators released by neutrophils in response to allergen stimulation ultimately potentially lead to bronchoconstriction, exudation of plasma, mucus hypersecretion, bronchial hyper-reactivity and airway tissue remodelling, all hallmarks of asthma that can lead to clinical manifestation. The distinct phenotype of esosinophillic asthma is well documented and understood, however, the reasonably sized sub group of noneosinophilic asthma is not as well studied. The increase in neutrophil infiltration associated with severe chronic airway narrowing and severe asthma attacks shows that neutrophils may have a role to play in both the initiation and resolution of such attacks. Current understanding of their precise role is limited to an extent, so more research needs to be conducted into this interesting area in order to potentially target therapies towards this important sub group.

Eosininophillic asthma is a distinct phenotype of asthma. A thick basement membrane is characteristic of the phenotype and points to the possiblity of eosinophils having a role to play in airway remodelling. Eosinophils contribute to bronchoconstriction, hyper-responsiveness and mucous secretions in asthma and may have a role to play in maintaining the chronic severe nature of this phenotype.

There is increasing evidence that neutrophils contribute significantly to mucus secretion, bronchoconstricton, airway hyper reactivity, remodelling chronic severe asthma, acute attacks, and sudden death in asthma.

**The Role of Monocytes, Macrophages and Dendritic Cells in Asthma.**

Alveolar macrophages are the predominant immune effector cell as they are at the forefront of the battleground that is the lungs. Similar to neutrophils, they have to be capable of regulating the
immune response or maintaining a constant environment via homeostatic mechanisms. (Peters and Golden 2004). Their precise role in asthma remains unclear, probably in part due to their heterogeneity (St Laurent et al 2009) but there are many proposed ways in which they could be involved in the pathogenesis of asthma as demonstrated by in vitro tests (Kimpen 2001)

Monocytes originate in the bone marrow and randomly circulate in the tissues in the absence of inflammation. Once in tissues, they can take on a macrophage phenotype specific to the tissue type. With regards to immunologic requirements of asthma, monocytes differentiate into dendritic cells and alveolar macrophages in the lungs.

The proposed roles of macrophages include:
- The release of mediators, although probably not in as large quantities as mast cells and eosinophils.
- The regulation of the inflammatory process via T lymphocytes.

**Mediator release**

Macrophages are known to release:
- Superoxide anion
- lysosomal enzymes
- leukorienes
- Prostaglandin D2
- PAF
- IL-1β
- IL-6
- IL-8
- TNFα
- RANTES- potent attractor of CD4+ cells like lymphocytes and eosinophils

(Pei-Li Yao et al 2005; Holgate and Busse 2008)

The role of the above mediators in asthma have all been previously discussed. The fact that macrophages are known to synthesise and release them in significant quantities shows that they may indeed have a role in the pathogenesis of asthma and thus may contribute directly to the
physiological abnormalities by induction of mucus secretions, smooth muscle tone and bronchial hyper-responsiveness (Holgate and Busse 2008; Ziegler-Heitbrook 2008).

TNFα (Tumour necrosis factor α) is a complex inflammatory cytokine mainly produced by macrophages through an IGE dependent mechanism (Jaymin Marjaria 2008; Holgate and Busse 2008). As discussed earlier, TNFα may be of pivotal importance in the pathogenesis of asthma through its direct effect on other cytokines, inflammatory cells and mucous producing genes.

**Regulation of T cells**

Peter Barnes et al 1998:

“There is a growing consensus that failure to control T-cell immune functions underlies the disease process in hyper-responsive individuals and that the macrophage population plays a central role in the regulation of T-cells”.

Paulter et al (1994) identified a link between T-cell mediated inflammation and bronchial hyper-responsiveness when discussing the progression of asthma:

“An integral factor in prevention of these processes appears to be the regulation of T-cell activity by immunosuppressive lung macrophages. Only when bronchial inflammation and hyper-responsiveness occur in parallel, presumably because of a failure of this macrophage mediated T-cell regulation, will symptoms of asthma develop”.

As has been discussed with eosinophils, macrophages in asthma appear to have a defect in the usual process of apoptosis and hence a prolonged life cycle and presence in the inflamed asthmatic lung. The number of apoptotic macrophages and eosinophils is inversely correlated with severity of disease indicating that a decrease in cell death is linked to clinical severity (Vignola et al 2000).

It can be seen that monocytes, macrophages and dendritic cells potentially play an important role in the pathogenesis of asthma by controlling the immune response through direct interaction with T helper cells and cytotoxic T cells. They perform an important function as antigen presenting cells direct to T-cells which initiates T cell differentiation to TH2 cells. They produce cytokines and other mediators in enough quantities to be significant enough to amplify the immune response in asthma thereby contributing to its pathogenesis.
The precise role of monocytes and macrophages remains unclear but it is known that dendritic cells function as antigen presenting cells and therefore have a regulatory role to play in asthma. The release of mediators is not as large when compared with other inflammatory cells but it may be enough to potentiate inflammation and add to the clinical expression of mucus secretion, smooth muscle tone and airway hyper-responsiveness.

**Conclusions.**

Asthma is a complicated inflammatory disease of the airways involving the infiltration of multiple inflammatory cells and their mediators. The various inflammatory cells synthesise and release various mediators which when activated by common antigens work together with resident cells in a futile attempt to attack common and usually harmless antigens for which most people would usually develop an immunity. For some unknown reason, the normal homeostatic mechanisms that usually dampen the immune response in order to minimise long term tissue damage do not function effectively, leading to prolonged action of certain inflammatory cells such as eosinophils and a corresponding exacerbation of underlying inflammation and subsequent clinical expression of asthma.

The roles of T-cells, mast cells and eosinophils are well documented and understood after extensive in vitro and in vivo studies over the years. The roles of certain other inflammatory cells in asthma like basophils and macrophages are less well understood, never the less, in vitro studies have thrown up interesting and important possibilities for the roles of these and other inflammatory cells in the pathogenesis of this heterogeneous disease.

Although treatments were not the aim of this discussion, it has to be said that to date, treatments like corticosteroid inhalers have been focused on dampening down the symptoms as opposed to actually providing any semblance of a cure. A deeper understanding of the roles of all of the inflammatory cells is required in order for researchers to make advancements in finding a cure for this often debilitating condition whose incidence and severity is increasing in the western world.
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