**ULCER**

Ulcer is the local defect in the surface of organ or tissue. It occurs in the mucosa of mouth, GIT and genital tract.

E.g. Peptic ulcer of stomach.

 **Chronic Inflammation**

Chronic inflammation is the response of prolong duration in which inflammation, tissue injury and repair co-exists in varying condition

 **Causes of chronic inflammation**

The causes include:

* Persistent inflammation
* Hypersensitive reactions
* Prolong exposure to toxic agents

 **Cells of chronic inflammation**

The cells are

1. Macrophages

2. Lymphocytes

 **Macrophages**

Macrophages perform various functions.

* Phagocytosis
* Act as antigen presenting cells
* Responsible for release of inflammatory mediators i.e. TNF-alpha, IL-1 and chemokines.
* Respond signal to T-lymphocytes

 **Activation of macrophages**

There are two pathways for the activation of macrophages.

Classical pathway Alternative pathway

 **Classical pathway**

It is induced by micro-organisms like endotoxins. It is also induced by interferons gamma (IF-gamma) that is released by T-lymphocytes.

After the activation of classical pathway there is increased production of reactive oxygen species and nitric oxide in macrophages and there is upregulation of lysosomal enzymes. As a result there is more phagocytosis and destruction of causative agent.

Classical pathway also leads towards the release of inflammatory mediators from macrophages e.g. IL-1, IL-12 and IL-23 that stimulate the inflammation.

 **Alternative pathway**

This pathway is induced by cytokines i.e. IL-4 and IL-13 that are released from T-lymphocytes. As a result of this pathway, activated macrophages release growth factors that participate in tissue repair process through angiogenesis.

These macrophages also stimulate the collagen synthesis and participate in tissue repair process.

Protective Response:

When macrophages are activated by alternative pathway, it stimulates the production of TGF-beta and IL-10. These mediators have anti-inflammatory properties.

 **Lymphocytes**

 Lymphocytes are the most important cells of the immune system. They participate in cell mediated immune response and anti-body mediated immune response.

During inflammation, lymphocytes migrate towards the site of infection. In tissue, B-lymphocytes differentiate into plasma cells and memory cells and secrete anti-bodies whereas T-lymphocytes release cytokines especially helper T-lymphocytes.

 **Subtypes of helper T-lymphocytes**

There are three types of helper T-lymphocytes.

TH1 cells TH2 cells TH17 cells

* TH1 Cells release TNF-alpha that induce classical pathway for activation of macrophages.
* TH2 Cells release cytokines I-e IL-4 , IL-5 and IL-13. These cytokines activate the eosinophils and induce alternative pathway for macrophages activation.
* TH17 Cells release IL-17 that participates in the chemotaxis.
* TH1 cells and TH17 cells participate in bacterial infections whereas TH2 cells participate in the parasitic infections.

  **Interaction between macrophages**

 **And T- lymphocytes**

Macrophages and T- lymphocytes interact with each other. Macrophages present antigen on their surface and release cytokines I-e. IL-12.

This IL-12 cytokines stimulate the T-lymphocytes especially CD4 T- lymphocytes

 LYMPHOCYTES

 B -LYMPHOCYTES T- LYMPHOCYTES

 Anti-body

 Production

Release TH1

TH2 and TH17

 **3- Eosinophils and Mast cells**

Eosinophils are activated by TH2 cells (IL-4, IL-5, IL-13) and induce alternative pathway for activation of macrophages.

Mast cells release histamine and induce allergic or hypersensitive reactions in ectopic/ allergic individuals.

 Neutrophils are the cells of acute inflammation whereas macrophages and mast cells are involved in chronic inflammation.

 **Granulomatous inflammation**

“Type of chronic inflammation characterized by collection of activated macrophages often associated with T- lymphocytes and sometimes associated with necrotic region”

The site where granulomatous inflammation occurs is called “granuloma”

Granulomatous inflammation occurs in that case in which there is very difficult to remove foreign particles.

Activated macrophages are the important features of this type of inflammation. These activated macrophages resemble to epithelial cells that is why called “epitheloid cells”

When epitheloid cells fuse with each other that results in the formation of multinucleated giant cells.

 **Types of Granulomatous inflammation**

There are two types of granulomatous formation.

 Foreign body granuloma

 Immune mediated granuloma

**1- Foreign body granuloma:**

That usually occurs in case of inert foreign particles e.g. Sutures. These inert particles stimulate the process of phagocytosis. In such types of granuloma, there is no involvement of immune system and these inert foreign particles are destroyed by epitheloid cells.

**2- Immune mediated granuloma:**

This granuloma occurs in case of persistent infection. In such types of infection there is difficult to remove foreign particles so immune mediated response is needed that cause destruction of foreign particles.

 **Morphology of Granulomatous inflammation**

Activated macrophages have:

* Pink nucleus
* Indistinct boundary
* Plenty of cytoplasm

 Activated macrophages resemble to epithelial cells called epitheloid cells.

 Surrounding the activated macrophages, there is a rim of lymphocytes.

The most common example of granulomatous inflammation is tuberculosis TB in which granuloma formation occurs.