

## **B cells subset migration to synovium from Lymph node**

Naive B cells travels from Lymph node to Synovium

Memory B cells travels from Lymph node to Synovium

DN2 B cells travels from Lymph node to Synovium

PlasmaBlasts cells travels from Lymph node to Synovium

Plasma cells produces autoantibodies in synovium

Memory B cells expresses CXCR3

## **Cytokines released by Memory B cells**

Memory B cells releases IL-6

Memory B cells releases **TNF- $\alpha$**

Memory B cells releases **GM-CSF**

Memory B cells releases **RANKL**

Memory B cells releases **IFN- $\gamma$**

Memory B cells acts as Antigen presenting cells

## **Cytokines released by plasma blast cells**

Plasmablasts produces autoantibodies in synovium .

Plasmablasts cells releases IL-8 .

Plasmablasts cells expresses CXCR3 .

### **Cytokines released by DN2 B cells**

**DN2 B cells releases TNF- $\alpha$**

**DN2 B cells releases IL-6**

**DN2 B cells releases RANKL**

DN2 B cells acts as Antigen presenting cells

### **Cytokines released by B Regulatory cells**

**B Regulatory cells releases TGF- $\beta$**

**B Regulatory cells releases IL-10**

### **Differentiation of B cells**

Naive B cells differentiate into Memory B cells

Memory B cells differentiate into DN2 B cells

DN2 B cells differentiate into Plasmablast cells

Plasmablast cells differentiate into plasma cells in the presence of IL-6 , BAFF and APRIL which support survival and differentiation of plasmablast cells into plasma cells .

## **Cytokines released by B cells**

B cells releases IL-6

B cells releases **TNF- $\alpha$**

B cells releases IL-10

B cells releases RANKL

B cells releases IL-8

B cells releases CXCL9

B cells releases CXCL10

B cells releases CXCL11

## **Cytokines acting on B cells**

IL-6 acts on B cells and promotes survival and autoantibody production

IL-21 acts on B cells and drives class switching recombination and affinity maturation and hence overall help in autoantibody production and IL-10 release.

**TNF- $\alpha$  acts on B cells and causes activation of B cells**

**BAFF acts on B cells and promotes B cells survival and differentiation**

**APRIL enhances B cells longevity and autoantibody secretion**

**IL-17 acts on B cells and enhances cytokines production by B cells and promotes B cells survival in an inflammatory environment**

**CXCL13 attracts B cells to inflame synovium**

**IFN- $\gamma$  enhances B cells activation and antigen presenting function in B cells**

## Neutrophils move from Lymph node to Synovium

### Cytokines Acting on Neutrophils in RA:

1. **GM-CSF acts on neutrophils and delays its** apoptosis and enhances neutrophil activation . It also promotes ROS production
2. **TNF- $\alpha$  acts on neutrophils** and delays apoptosis at its low concentrations and promoting apoptosis at its higher levels. It also promotes ROS production
3. **IL-1 $\beta$  acts on neutrophils and promotes** neutrophil survival and activation
4. **IFN- $\alpha$  acts on neutrophils and promotes** neutrophil activation in inflammatory conditions
5. **HIF-1 $\alpha$**  indirectly enhances neutrophil survival under hypoxic conditions
6. IL-8 acts on **neutrophils** and guides its movement towards synovium and enhances ROS production from **neutrophils**

### Cytokines released by Neutrophils in RA

1. Neutrophils releases IL-1 $\beta$
2. IL-8
3. TNF- $\alpha$
4. APRIL
5. BAFF
6. Angiogenic factors
7. Pro-inflammatory prostaglandins

**Cytokines released by dendritic cells**

Classical DC1 releases IL-12 and TNF- $\alpha$ . IL-12 promotes Th1 cells responses .

Classical DC2 releases IL-6, TNF- $\alpha$ , IL-1 $\beta$

Plasmacytoid DCs releases IFN- $\alpha$ , TNF- $\alpha$ , IL-6

Monocyte-Derived DCs releases IL-12, IL-6, TNF- $\alpha$

Pre-DC-like Cells releases IL-6, IL-1 $\beta$

**Cytokines acting on dendritic cells**

IL6 acts on Classical DC1 and causes its differentiation and enhance there activation

IL6 acts on Classical DC2 and causes its differentiation and enhance there activation

TNF- $\alpha$  supports the proliferation of Classical DC1 and increase there antigen presenting capacity .

TNF- $\alpha$  supports the proliferation of Classical DC2 and increase there antigen presenting capacity .

IFN- $\gamma$  acts on Classical DC1 and enhances antigen presentation and favors Th1 polarization

IFN- $\gamma$  acts on Classical DC2 and enhances antigen presentation and favors Th1 polarization

IFN- $\alpha$  acts on Plasmacytoid DCs and activates them

IFN- $\beta$  acts on Plasmacytoid DCs and activates them

GM-CSF acts on Monocytes and causes its differentiation to Monocyte-Derived Dendritic Cells

IL-4 acts on Monocyte-Derived Dendritic Cells and promotes there development in specific conditions

TNF- $\alpha$  acts on Monocyte-Derived Dendritic Cells and enhances its antigen presentation capacity

TNF- $\alpha$  acts on Pre-DC cells and promote the expansion and activation of pre-DCs cells

IL-6 acts on Pre-DC cells and promote the expansion and activation of pre-DCs cells