# MLS

Below are the cytokines released by MLS
MLS releases **TNF-α**
**MLS releases** IL-1β
**MLS releases** IL-6
**MLS releases** TGF-β
**MLS releases** IL-8
**MLS releases** CCL-2

Below are the cytokines acting on MLS

1. **TNF-α —> Activates MLS to adapt M1 phenotype and encourage for releasing other pro-inflammatory cytokines (TNF-α ,**IL-1β & IL-6 **)**
2. **IL-6 —> Sustain MLS survival and enhance other cytokines release**
3. IL-1β —> It activates macrophage to release **TNF-α and IL-6 and also support differentiation of osteoclast precursor**
4. IL-17 —> it enhance production of **pro-inflammatory cytokines (TNF-α ,**IL-1β & IL-6 **) by MLS**
5. **IFN-γ —> It activates MLS to become M1 phenotype and enhance** MHC II expression in MLS
6. GM-CSF —> It promotes survival and expansion of MLS
7. TGF-β —> it shifts MLS to M2 phenotype
8. IL-10 —> surpasses M1 phenotype and tissue repair

Cytokines releases by Macrophages that are recruited to synovium

1. **TNF-α**
2. IL-1β
3. IL-6
4. IL-12
5. IL-23
6. IL-8
7. CCL2
8. RANKL

Cytokines acting on Macrophages that are recruited to synovium

1. TNF-α —> Activates recruited macrophage to adapt M1 phenotype and encourage for releasing other pro-inflammatory cytokines (TNF-α ,IL-1β & IL-6 )
2. IL-6 —> Sustain recruited macrophage survival and enhance other cytokines release
3. IL-1β —> It activates macrophage to release TNF-α and IL-6 and also support differentiation of osteoclast precursor
4. IL-17 —> it enhance production of pro-inflammatory cytokines (TNF-α ,IL-1β & IL-6 ) by recruited macrophage
5. IFN-γ —> It activates recruited macrophage to become M1 phenotype and enhance MHC II expression in recruited macrophage
6. GM-CSF —> It promotes survival and expansion of recruited macrophage
7. IL-10 —> surpasses M1 phenotype and tissue repair
8. TGF-β —> it shifts recruited macrophage to M2 phenotype
9. RANKL —> it induces macrophage to differentiate into osteoclasts in presence of M-CSF
10. M-CSF —> It is essential for differentiation of monocytes into macrophage
There is an influx of monocyte in synovium from lymph nodes

## Treg cells

1. It releases TGF-β
2. TGF-β promotes differentiation of Treg cells from T cells in absence or low presence of IL-6 and IL-1β. It also promotes proliferation of Treg cells.
3. IL-6 and **TNF-α causes decreases in differentiation of T cells into Treg cells**
4. **There is a influx of Greg cells into synovium from lymph node**

Osteoclasts cells

1. RANKL initiate differentiation of osteoclast precursors into osteoclast cells.
2. TNF-α works synergistically with RANKL to amplify differentiation of osteoclast precursors into osteoclast cells. TNF-α also prolongs survival of osteoclast cells .
3. IL-1β directly promotes differentiation of osteoclast precursors into osteoclast cells by potentiating RANKL/Rank signalling.
4. M-CSF prepares osteoclast precursors to respond to RANKL signalling . It is essential for the survival and proliferation of osteoclast precursors. M-CSF promotes survival and proliferation of osteoclast cells.

## RANKL

1. Produced by osteoblast cells
2. Produced by synovial fibroblast cells (FLS)
3. Produced by T cells
4. Produced by B cells

## FLS

Below are the CytokInes acting on FLS

1. TNF-α promotes proliferation of FLS
2. IL-1β increases MMP production by FLS and it triggers FLS proliferation and migration .
3. IL-6 enhances survival and resistance to apoptosis in FLS .
4. IL-17 synergise with TNF-α and drives proliferation of FLS
5. TGF-β promotes differentiation of FLS from mesenchymal progenitor cells into FLS .

Below are Cytokines and chemokines released by FLS

1. FLS releases IL-6
2. FLS releases IL-8
3. FLS releases IL-1β
4. FLS releases CXCL12
5. FLS releases CXCL9
6. FLS releases CXCL10
7. FLS releases CXCL11
8. FLS releases VEGF
9. FLS releases GM-CSF and M-CSF
10. FLS releases RANKL

## Th17 cells

1. TGF-β is critical for the differentiation of T cells into Th17 cells either in presence of IL-6 or IL-1β or both.
2. TGF-β and IL-6 together required for the production of Th17 cells from T cells
3. IL-23 promotes survival and proliferation of Th17 cells
4. IL-1β works synergistically with IL-23 to amplify Th17 cells pathogenicity , hence IL-1β promotes differentiation and survival of Th17 cells in inflammatory conditions
5. IL-12 converts Th17 cells into Th1 like phenotype
6. **IFN-γ enhances Th17 cells response to IL-12 . It promotes Th17 cells plasticity and transition into Th1 like phenotype**

Cytokines released by Th17 cells

1. Th17 cells releases IL-17
2. Th17 cells releases IL-22
3. Th17 cells releases GM-CSF
4. Th17 cells releases **TNF-α**
5. Th17 cells releases IFN-γ

Chemokines released by Th17 cells

1. Th17 cells releases CCL20
2. Th17 cells releases CXCL9
3. Th17 cells releases CXCL10
4. Th17 cells releases CXCL11