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IP Indian Journal of Immunology and Respiratory Medicine

Journal homepage: https://www.ijirm.org/

Review Article

Macrophage death induced cellular mechanisms and some regulatory pathways of macrophage death related diseases

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ARTICLE INFO

Article history:
Received 06-12-2023
Accepted 10-01-2024
Available online 27-01-2024

Keywords:
Macrophage
Apoptosis
Autophagy
phagocytosis
immune system

ABSTRACT

In mammalian physiology the dead cells of body and cellular debris could not be digested by body's own cellular mechanism. Macrophage is a component living inside the cell sometimes engulf the unrequired cell debris by phagocytosis and became dead by its own, this type of death inside macrophage is called "Macrophage Death" which has been done for our good cytosolic condition. Macrophage death is about many types those have been disclosed later and referred as "Programmed Cell Death."Apoptosis, Autophagy, Necrophagy all are different types of cell death associated with macrophage. When cytotoxicity of a cell condition leads to a cell destroy by its own then often it's referred as a "Cellular Suicide" where cells die by itself.Macrophages death is a complicated mechanism which directly involves with ER stress, oxidative stress, lost mitochondrial functional ability, lysosomal outburst and other cell particulates dysfunctioning.

1. Introduction

Macrophages in our body system are associated with innate immunity or natural immunity system. When an infection or outside particle enters within body cells then macrophages destroy the host pathogenic cells by engulfing the entire area of infection. Either the dead cells and cell debris are removed by phagocytosis or it often produce plaque area and necrosis which then removed the unnecessary particles outside the cell.

If the dead cells are not engulfed by the macrophages then it causes inflammation to body's damage area and also damage the cell tissue. Macrophages are the derivative of White Blood Cells which removes foreign bodies by releasing a pathogen clearing compound known as Nitric oxide which destroys the harmful microbes from body. [1–3]

Besides Nitric oxide macrophages also secrete some proteolytic enzymes that causes cellular damage and tissue destruction and further leads to cell death.

1.1. Macrophage death

1.1.1. Macrophage

This is a typical White Blood Cell component that destroys microorganisms and surrounded by the cellular derivatives present in every cell types of all organs in the body like liver, brain, bones, lungsand also in blood specifically at the site of infection.

1.2. Macrophage death pathways in disease

Macrophage Death has been reported in certain diseases such as

1. Tuberculosis
2. Sepsis

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https://doi.org/10.18231/j.ijirm.2023.026

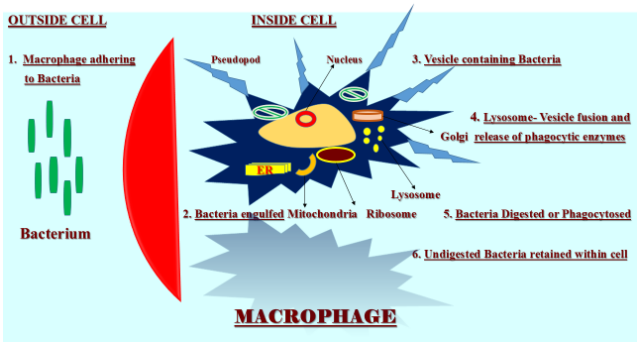

Figure 1:

3. Inflammation
4. Atherosclerotic Plaque Development
5. Viral Infections

1.2.1. Tuberculosis - Induced Macrophage Death

The significant agent of Mycobacterium tuberculosis (Mtb), causes tuberculosis is destroyed by the Host- Defending mechanism of macrophages. But after phagocytosis Mtb grows resisting power against macrophages. CRISPR – Cas9 genome wide screening proved that the macrophages die due to the Mtb infection that has been identified by the systematic progress of autocrine or paracrine signalling that occurred by type –I IFNs derivatives of macrophages. The type –I IFN signalling augmented the Mtb infection in mice through drugs that affects first line TB and in in- vitro condition the effect of rifampin is accelerated throughout the pathway.[1]

Novel mechanism followed by the Mtb induced macrophage death:

Here, Tumor Necrosis Factor – α (TNF– α) initiates that main potential for in vitro and in vivo mechanism of defending or retaining of the host which causes the induction of pathogenic infection of mycobacterium.

1. Apoptosis**:** Cycloheximide or TNF- α alltogether proceeds to apoptotic initiation in large number of cell types by the caspase- 3 and caspase- 8 mediators that cleaves throughout the process.[1]
2. Necroptosis**:** TNF- α and NF- Kβ combinedly inhibit caspase activation through relevant phosphorylation of (RIPK- 1 &3) and (MLKL- pseudo kinase) to initiate necroptosis. Infection caused by Mtbhasindirectlyinitiatednecroptosis through MLKL in consistent with RIPK -1 & 3 inhibitor thus blockade of death in Mtb infected BMDMs occurred.[1]
3. Ferroptosis**:** Ferroptosis inhibitor Ferrostatin-1 is activated to being exposed with Mtb infected Macrophages to inhibit classic Ferroptosis which is induced by Erastin and RSL3.[1]
4. Parthanatos**:** Hyper activation of PARP-1 that causes DNA damage is a component of the DNA damage mechanism and Rucaparib are often initiated by the inhibition of Parthanatos.[1]
5. Autophagy**:** Autophagy knock down by using CRIPSR- Cas9 mechanismin Wild Type BMDMs that helps certain cell death. But Mtb induced macrophages totally not hindered by Casp1and Casp11 combined genetic imbalance of Gasdermin D (Gsdmd).[1]

Observation: So, Mtb induced macrophage death could not be restricted by Q-VD-OPHthat inhibits pan-caspase or with combined mechanism of Q-VD-OPH and the suppression of Necroptosis and Ferroptosis.[1]

So, Host Directed Therapy of TB is a more appropriate selection over the systematic prevention of Type -1 IFN signalling.

1.2.2. Sepsis

A systematic inflammatory response that is Sepsis syndrome and that leads to Acute Kidney Injury (AKI) which is among one of the serious death complication in world. Pathophysiological basis of sepsis includes Programmed Cell Death mechanisms of Apoptosis, NecroptosisPyroptosis and Autophagy which triggers Sepsis induced AKI process.Though there is no specific treatment can help to cure Sepsis AKI except supportive dialysis.[2]

ROLE and mechanisms of macrophage autophagy in Sepsis

1. Sepsis is caused by Immuno dysfunction in cellular bodies.
2. Enhancement in Sepsis can play multiple roles:
   (a) Negatively regulating abnormally Macrophage activation.
   (b) Modulating macrophage polarization phenotype.
   (c) Reducing activation of inflammasome and releasing inflammatory factors.
   (d) It is also affecting “Macrophage Apoptosis”.

1.3. Categories of programmrd cell death occurence in sepsis induced AKI

1. Bacteria with drug resistant capacity, effects of drug formulation and different procedures showcase more critical situation to the Sepsis induced AKI. Kidney dysfunction is associated with the Sepsis augmentation process. Approximately, ~50% Acute Kidney Injury (AKI) is caused by severe Sepsis.[2]
2. PAMPs or DAMPs secreted from tissue damaging that are active and accelerate the phenotypic inflammation of (M1) macrophages and produce pro- inflammatory cytokines such as interleukin (IL -1), (IL -6) Tumor Necrosis Factor –α (TNF –α), chemokines and

Reactive Oxygen Species (ROS) that causes tissue damage in kidney injury.[3]

1.3.1. Apoptosis

(From kidney biopsy samples for histological samples)**:**Apoptotic cells are present in distal and proximal tubules of cell tissues in sepsis through TdT –initiation d UTP Nick End Labelling (TUNEL) in an alternative of caspase-3 staining procedure.[3,4]

(Sepsis animal models during Cecal Ligation and Puncture –CLP, LPS or AKI mediators bacterium):According to Aslan et al. renal tubular cells are found with Apoptosis in response to receptor specific stimuli and signals.[3,4]

Fas-associated death domain (FADD) and TNF receptor associated death domain (TRADD) are conjugated with LPS and TNF-α through Death Effector Domain (DED) and initiated the caspase -3, 6 and 8 activation.[4,5]

According to Chen et al. inhibition by resveratrol of pro inflammatory macrophages initiates apoptosis and eliminate LPS induced renal inflammation in Sepsis –AKI animal model.[6,7]

1.3.2. Pyroptosis

Tissue damage by developing septic shock is the main cause for programmed necrosis associated with PAMPs, DAMPs and other inflammatory factors leads to Pyroptosis.[8]

Pattern Recognition Receptors (PRRs), Toll Like Receptor- 4 (TLR- 4) of the surface cell mediators of macrophages and phagocytes are highly expressed and during Sepsis in enhanced condition these are highly activated. Interleukin- 1 Receptor Associated Kinase- 1 (IRAK- 1) and TNF Receptor Associated Factor- 6 (TRAF-6) are arranged on an alignment with Interleukin-18 leads to the caspase- 11 dependant macrophage inflammation, Pyroptosis and tissue damage with the release of PAMPs, DAMPs and other secretory factors during Sepsis.[9,10]

Intermediates of downstream signal amplification, TNF-α, IL- 1β, NF- Kβ activation increases the expression during Sepsis. By induction of transcriptional NF-Kβ an intracellular receptor NLRP3 and activated inflammationleadsto macrophage Pyroptosis during Sepsis.[11]

Reactive Oxygen Species (ROS) assembles NLRP3 inflammasomes to increase inflammation, mitochondrial dysfunction to the oxidation of mtDNA in cytoplasm and interaction with NLRP3 assembles and activates NLRP3 inflammasome.[12]

Upon LPS activation in macrophages, 4 hydroxycinnamaldehyde galactosamine (HCAG) suppresses activation of NLRP3 inflammation and inhibits the caspase- 1 exposure, NLRP3, IL- 18, IL- 1β, TLR 4 in renal tissue of mice by elimination of LPS mediated inflammation in renal tissue.[13,14]

According to some research findings, hyper activation of caspase- 1, GSDMDs, IL- 18, IL- 1β and cytokines are expressed in human TECs mediated mouse kidneys, but caspase- 1 inhibitors suppresses the NLRP1 activation thus Pyroptosis of TECs are reduced. Also the activation of NLRP3 and GSDMD in kidney injury and caspase- 11 is silenced in mice and TECs which is directed to inhibition of LPS induced Pyroptosis.[14]

1.3.3. Necroptosis

Programmed Cell Death known as Necroptosismainly causes nephrotoxicity after activating Receptor Interacting Protein Kinase 1 (RIPK1) with TNFR to initiate Necroptosis. Upon activation of Mixed Lineage Kinase Domain (MLKL) and RIPK3 phosphorylation of MLKL protein leads to cell surface swelling, rupture and secretion of DAMPs after translocation on cellular plasma membrane.[15]

Also GSDMD mediated pyrolysis triggers tissue and organ damage by enhancing inflammatory receptor stimuli that macrophages possess significantphenomena in Sepsis induced kidney injury byNecroptosis and pyrolysis.[16,17]

1.4. Observation

1. The gene expression levels of NLRP3/Caspase-4/AKT2/STAT3 are inhibited by Septic infected macrophages. Also, Pyroptosis associated protein level balance, NLRP3, Caspase- 4, GSDMD and NT GSDMD are also suppressed by PD-1 antibody treating.[18,19]
2. So, mitochondrial functional error, oxidative stress and DNA modification are the main causes of regulation of programmed cell death in Sepsis induced kidney injury.[18,19]

1.5. Apoptosis, pyroptosis and necroptosis interrelated properties

In Sepsis- AKI Apoptosis, Pyroptosis and Necroptosis related phenomena of Cellular Death function with different cell biology, morphology and biochemical characteristics excluding Ferroptosis and Parthanatos.[19]

From intensifying Apoptotic cascade to inhibiting Necroptosis this Caspase- 8 acts with ASC and other immunogenic components.[19]

MLKL deficiency also causes lethality in Caspase-8 treated mice but stimulates Pyroptosis but inhibits Apoptosis and Necroptosis consequently.[19,20]

Again, the lethality and premature death through the treatment of Caspase- 8, MLKL, Caspase- 1, ASC in mouse model proves that Caspase- 8 is a immunogenic switching element.[19,20]

1.6. Cellular pathways involved with Macrophage induced PCD

1. Epigenetic regulation**:** Both eukaryotic and prokaryotic cells undergoes epigenetic modification thus helps to cure kidney disorder, Sepsis- AKI. The genetic modifications are stated below:

   (a) Proteic Acetylation
   (b) DNA Methylation
   (c) RNA m6A Methylation
   (d) Autophagy
   (e) Mitophagy
   (f) Carbonylation
   (g) Glycosylation
   (h) MicroRNA expression

1.6.1. Proteic acetylation

Reverse process of Histone de-acetylases (HDACs)

1.6.2. DNA methylation

By affecting DNA catalyzation of DNA methyltransferases (DNMTs) processed to CH3 (methyl) group of DNA nucleotides at cytosine or adenine residue. Cytosine-phosphate-guanine (CpG) methylated at dinucleotide cytosine domain that modifies the cell death during Sepsis-AKI.[19,20]

MHC class proteins and other methyltransferaseproteins associated DNA methylation of monocytes in In vitro condition was confirmed the IL-6 and IL-10 related seriousness in organ failure during Sepsis. Also the monocytes were identified by TLR stimulation and the levels of inflammatory cytokines forming changes in epigenetic regulation in Sepsis- AKI.[20,21]

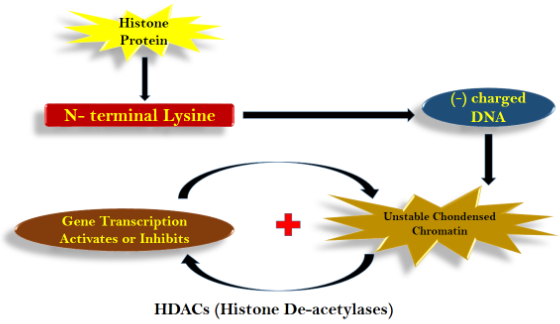

Figure 2: :

1.6.3. RNA m6A Methylation

RNA modification in post transcriptional level interacts with N6-methyladenosine to affect RNA processing, stability, RNA translation and immune-physiology of cells.[21]

Enzymes related to m6A Methylation**:**

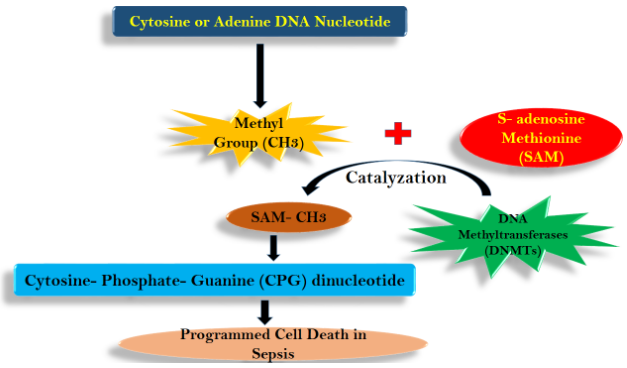

Figure 3: :

1. Methyltransferase that encodes methyl group of adenosine residues.
2. De-methylase that eliminates methyl group.
3. A protein that identifies and incorporates with m6A.[21]

Excessive activation of SOCS1 regulated macrophages can be allocated for the phenotypes of in vivo and in vitro macrophages. Overactive expression of METTL3 stimulation of LPS in macrophages also shows anti-inflammatory effect that determines m6A activation in macrophage inflammation.[22,23]

1.6.4. Autophagy

Sepsis- AKI in relation to autophagy dysfunction proceeds to LPS self-repairing activity through the pathogenesis od Sepsis. According to Yang et al. after treatment with dexmedetomidine autophagy can be enhanced by alleviation of Sepsis with the inhibition of NLRP3 inflammation.[24] But the effects of dexmedetomidineis eliminated by 3-methyladenine (3-MA) that inhibits autophagy. Meanwhile, in in vitro and in vivo condition of Sepsis related kidney injury autophagy can be inhibited by the RIPK3 mediated signal induced from Necroptotic stimuli.[24,25]

1.6.5. Mitophagy

If that mitochondria is divided into the damaged condition so, after the essential break down mitochondria got damaged and its derivatives got used again by the cyclic process of Mitophagy.[26]

In early stage of CLP a subcellular activation of fission between mitochondrial mitophagy occurs in kidney on CLP regulated cells of sepsis-AKI but after cellular fission of mitochondrial mitophagycessation occurrence of Apoptosis ad Pyroptosis is observed.[27,28]

1.7. Macrophage death and inflammation

Steatohepatitisregulates cell death and inflammatory diseases in macrophages through RIP1 kinase activity.

1.7.1. HFD NASH model

High Fat Diet Non-alcoholic Steatohepatitis Model.

Kinase activity promotes inflammatory disease reaction, apoptosis and necroptotic cellular degradation through in vivo in vitrolipotoxicity and palmitic acid modification both in BMDMs and mouse primary kupffer cells.[29,30]

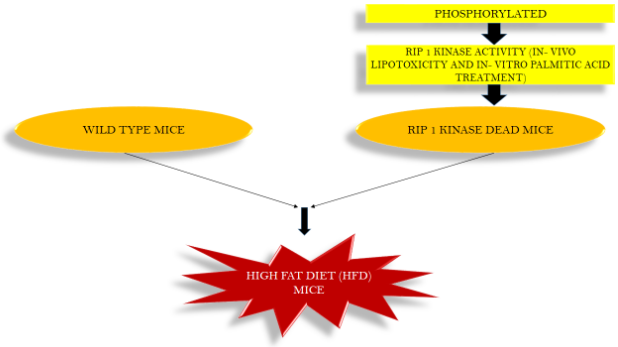

Figure 4: HFDNASH model

1.7.2. NASH murine model

Murine model of NASH shows RIP1 kinase activity which occurs in macrophages of kupffer cells as an indication of double stained procedure of immunofluorescence.[29,30]

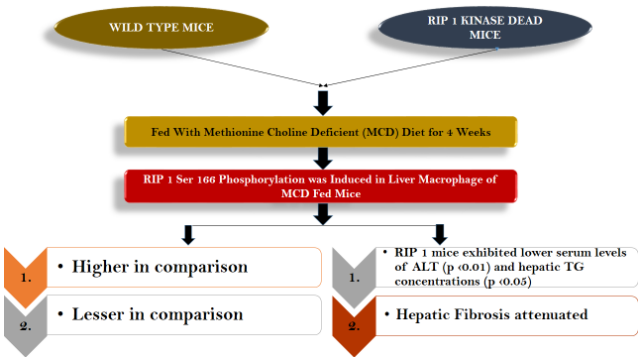

Figure 5: NASH murine model

2. Results

1. RIPK1 kinase activity promotes palmitic acid induced cellular degradation and inflammation activity shown on macrophages of kupffer cells.
2. Moreover Palmitic Acid regulates the activity of caspase-8, cleavage of caspase-3 those are all eliminated for the Rip1 regulated Bone Marrow Derived Macrophages (BMDMs).[29,30]
3. Apoptosis and necroptosis both were induced by RIP1 kinase activity that was introduced by fatty acid regulation and correlation by in vivo condition of cells.
   (a) Palmitic acidinduced NF-Kβ pathway in IL-1β secretion

Palmitic acid regulates IL-1β release that blockade happens in NLRP3 negative BMDMs in contrary to palmitic acid triggered NLRP3 inflammatory activity and IL-1β secretion in Pyroptosis.[29,30]

So, RIP1 kinase activity generated palmitic acid regulated Apoptosis, Necroptosis and Inflammatory activity.

2.1. Mirna mediated macrophage polarization

1. Introduction**:** Myeloid Progenitor cells of bone marrow are the key source of macrophages. After diffusing in peripheral blood stream monocytes are migrated to body tissues and regenerated as macrophages.[31]
2. Biogenetic process of MiRNA**:** Transcription of genes for mediating biogenetic process of miRNA through type II RNA polymerase of cell nuclear region occurs that helps to cleave primary miRNA (pre-miRNA) by endoribonuclease activity and gain pre-miRNA. In preliminary incidents, target gene first get affected by miRNAs.[32,33]
3. Macrophage polarization
   (a) M1 Activation
   (b) M2 activation: On the basis of stimulation of other stimulus M2 macrophages are the categories of M2a, M2b, M2c and M2d whose unicity in geneticprofiling show hyper activity of IL-10 and IL-1 and lesser level of IL-12 production. But the M2 types of subset release Arginase-1 enzyme which degraded into L-arginine to suppress T cell responses by the enzyme-substrate reaction by Inducible Nitric Oxide Synthase (iNOS).[34]

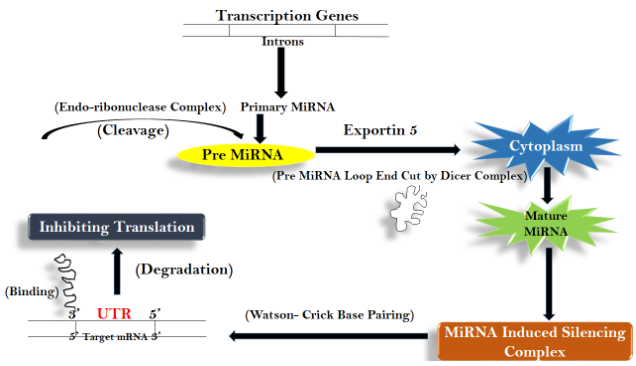

Figure 6: Mechanism of action of miRNA

2.2. Regulation of MiRNAs in M1 polarization

The Classical pathway related to macrophage activation which also the pro inflammatory components responsible

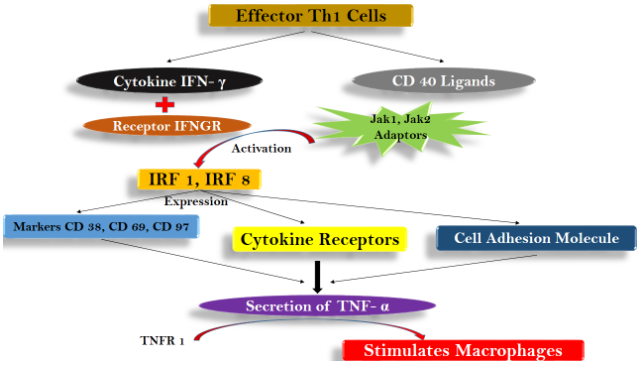

Figure 7: :

for the inhibition of several mediators are progressed by the promoting factors miR-9, miR-127, miR-155, miR-125b.[35,36]

1. miR-9: miR-9 induced macrophage subtype polarization is activated through triggering (PPAR-δ) according to Thulin et al. PPAR $-\delta$ is a receptor factor which regulates lipid and glucose homeostasis by the activation of protein B cell lymphoma- 6 that also regulates inflammation as an anti inflammatory transcriptional suppressor. [39] That suppression of PPAR $-\delta$ activity prevents BCL -6 induced anti-inflammatory effects by enhanced level of miR -9 expression. Simultaneously this condition resulted in higher level of PPAR $-\delta$ expression through transfection of anti-miR -9. [39]
2. miR-127: miR- 127 also increases the expression level of Classical Activation of macrophages but the antagonist mediated suppression inhibits miR-127 to prevent activation of macrophage subtype genes to accelerate transcription of macrophage marker genes.[37]
3. miR-155: According to O'Connell et al. the activity of miR- 155 was higher for the stimulation of macrophages by the ligands named TLR2, TLR3, TLR4.[38] But uponactivation of NF- KB signalling upregulation is affected through reactivation of MyD88 and TRIF. At the initiation of JNK pathway JNK inhibitor degraded elevation and activation of TNF- α due to miR- 155 regulated macrophage polarization. To promote M1 polarization miR- 155 inhibits STAT6 activation through targeting the IL-13 receptor α 1 (IL13Rα1).[39]
4. miR-125b: Macrophage subtype M1 polarization is upregulated throughmiR- 125b but the excessive expression of miR- 125b elevated the macrophage response to induce M1 polarization through inducer IFN- γ by stimulating IRF4.[40]

2.3. Regulation of MiRNAs IN M2 polarization

Macrophage subtype M2 polarization and anti- or pro-inflammatory responses are mediated by the factors miR-124, miR- 223, miR- 34a, let- 7c, miR- 132, miR- 146a and miR- 125a-5p.

1. miR-124: According to Sun et al. cholinergic agonists in LPS triggered macrophages enhances miR- 124 expression level. TNF-α and IL-6 are diminished by transfection of miR- 124 in macrophages. IL-6 and TNF-α are decreased in production through miR-124 directed STAT3 and TNF-α converting enzyme (TACE) in M2 macrophages.[41]
2. miR-223: miR- 223 is the inert component of myeloid and monocytic segments of bone marrow myeloid cells. LPS induced secretion of IL-6 through triggering STAT3 were suppressed through excessive expression of miR- 223 in M2 macrophages.[42]
3. miR-34a: miR- 34a has an inverse effect in M2 macrophages as the blockade of pro-inflammatory induced macrophage subtypes is the occurrence for mentioned. The lesser amount of TNF-α, IL-6 shows the reduced pro-inflammatory responses by the transfection of miR- 34a in LPS induced macrophages which in turn reduced miR- 34a expression level.[43]
4. Let- 7c: let- 7c targeted p21 activated kinase 1 (PAK1)to promote M2 phenotypes in M1 polarized macrophages. For instance, 1) The reduction of expression amount of macrophage subtype genes TNF-α, IL-6, IL-12a, IL-12b in LPS induced PAK-1 and BMDMs. 2) The initiation of let-7c reduces the levels of PAK m RNA.[43,44]
5. miR-132: LPS treated rat alveolar macrophages enhanced miR- 132 expression by hyper activation of IL-1β and IL-6. Pro-inflammatory responses was suppressed by miR- 132 in macrophages by suppressing NF- KB and STAT3 molecular mechanism.[44]
6. miR-146a: Release of M1 regulated proteins were reduced with M2 associated genes were enhanced by transfection with miR- 146a in LPS treated peritoneal macrophages. Thus miR- 146a targeted NF-KB signalling mediators to prevent pro-inflammatory responses such as IRAK-1, TRAF-6.[45]
7. miR-125a-5p: miR- 125a-5p suppresses M1 subtypes and induces M2 subtypes in macrophage polarization by targeting Kruppel-like factor 4 (KLF4).[45]

*2.4. Macrophage Polarization **i n** Mirna Regulation to **t**he Potential of Inflammatory Response*

1. Macrophages are the specialized cells for eliminating pathogens which is an innate immunity or adaptive immunity response by presenting antigens.

2. MiRNA regulation profiling in M1 and M2 subtypes of polarized human is detected by microarray or RT-PCR array mechanism.[45]

2.5. Propofol induced caspase-1 Dependant macrophage pyroptosis by NLRP3 atherosclerotic inflammatory response

1. Propofol infusion syndrome (PRIS) that is a hyperactive condition in receiving high dose of propofol, thus this phenomena damage immune-system.
2. Thus immune-regulatory macrophages play a vital role in anaesthesia and sedation.
3. So propofol directly induces cellular mortality through inflammasomes.[46]

   (a) Primary Cell Culture of (BMDMs) Cells and Murine Macrophage Cell lines are required.

2.6. Atherosclerotic plaque development

1. Atherosclerotic plaque development is a multifunctional disease that causes chronic inflammation in the artery which act as a source of drug delivery system in coronary arterial disease, cardio-vascular disease that influenced by inflammation and metabolic dysfunction and lipid derivation.
2. Small Heat Shock ProteinHsp 27 that activated through several modulators which supports in directing apoptosis. Also it participates in autophagic process.[47]

2.6.1. Apoptosis: Molecular mechanism

1. Apoptosis a PCD mechanism that is augmented through cysteine proteases or caspases.
2. Caspases which are active further induces apoptotic pathway and simultaneously reduces unrequired or damaged cells of the body. Extrinsic and intrinsic and stress related pathways lead to apoptosis.[47]

*2.6.2. A**ut**ophagy: Molecular Mechanism*

1. Autophagic process is an example of catabolism that helps to eliminate or remove unnatural cell debris, like as mis-folded or contained proteins, degraded organelles through lysosomal redundancy.
2. Autophagic pathways are divided into three categories Macro Autophagy, Micro Autophagy and Chaperone Mediated Autophagy.[47]

2.6.3. Apoptosis with Atherosclerosis

1. Macrophages, (VSMCs), Endothelial cells undergo autophagy.
2. IAutophagy has a cyto-protective effect on atherosclerosis.
3. IExcessive or autophagic functional error can be highly effective on cellular condition upon survivality or mortality, by causing atherosclerotic plaque development.[47,48]

2.6.4. Heat shock protein Hsp 27

1. Hsp 27 (27 kDa) is a protein and also a molecular chaperon that associated with energy metabolism is found by natural phenomena.
2. Human cells are all accumulated with Hsp 27 which is predominant in cardiac muscle cells.[47,48]

Conclusion: Regenesisof cell and atherosclerotic plaque development can be happened by apoptotic pathway but modified autophagic pathway can postpone atherosclerotic plaque development.

2.7. Macrophage death related drug delivery system in atherosclerotic plaque development

1. Anti-inflammaomes helps to treat or prevent atherosclerosis so macrophage death has an effect on atherosclerotic plaque development with stability.
2. Insufficientcell death promotes apoptotic cellsto cleave through neighbouring cells through a phagocytic pathway, called**"**Efferocytosis**".**[48]
3. Autophagy is a major cell sustainability pathway of plaque development in macrophages which prevents cell death, but triggering autophagy stimuli regulates different death procedure, which is known as **"**Autosis**".**[48]

2.7.1. Apoptosis target mechanism by macrophages

Atherosclerotic plaque development has macrophage death pathways like apoptosis that induced through several modulators like as oxidative stress, hyper activation of cytokine TNF- α, regulation ofFasligand and (ER) stress.

2.7.1.1. Observations. a) Lesion area is less required in Macrophage Apoptosis to get rid of severity of macrophages in spreaded plaques.

b) Also this result clarifies that phagocytic elimination of apoptotic macrophages that called **"Efferocytosis "** which clearly distinguished in primary lesions.[49]

c) The explanation said that **"**Efferocytosis**"** proved to be ineffective and the lesion area of apoptosis which get minimal for substrate-inhibition in **"**Efferocytosis**".**[49]

2.7.1.2. Conclusions. Erroneous phagocytic cells of apoptosis has been a consequence which regulates progressions or complexity in atherosclerosis.

2.8. Efferocytosis

2.8.1. Objectives

Induction and augmentation of efferocytosis activity that is an overwhelming pharmacological pathway that regulates

inflammatory objectivity and eliminates temporary plaque formation which is susceptible to degradation.

2.8.2. Gautier et al. experiment

CD11c Diptheria toxin (DT) receptor (DTR) in transgenic mouse model will proved that macrophage undergoes apoptotic pathway after attenuation of DT.[50]

2.8.2.1. Observation. Sustainable apoptoticpathway is accompanied with attenuated plaque development and augmented inflammatory diseases.

Table 1:

CD11b- DTR MICE	**CD11c- DTR MICE**
1. Induction of macrophage apoptosis was without effect in plaque stability and content.	1. Induction of macrophage apoptosisv had increased plaque inflammation and accelerated.
2. Monocytes are high in CD11b- DTR MICE, so it is possible for most frequent depletion. (50% reduction in circulating monocytes).	2. Monocytes are less in CD11c- DTR MICE, so there is a less chance to deplete extensively in compared to CD11b- DTR MICE.
3. No elevation in plasma cholesterol.	3. High elevation in plasma cholesterol.
4. Decrease in lesion size.	4. Increase in lesion size.

2.9. Observation

Metabolism is high in activity for plaque development so very susceptibe to protein synthesis modulators in comparison with many cells including VSMCs and endothelial cells.[49]

2.9.1. Drawbacks

1. Blood monocytes in periphery get depleted that might be eliminated as it has vital roles in acquired and augmented immunity.
2. Macrophage degrading drugs can have neighbouring cell site accumulation that eliminates or reduces unnecessary system adaptation.
3. Simultaneously pro-efferocytic treatment can be necessary for inhibiting accumulation of free-floated and non-phagocytic cells of apoptosis. For which the engulfing capacity in plaques get suppressed through the depletion of macrophages.

2.10. Targeting macrophage NECROSIS

1. (a) Passive Necrosis
   (b) Necroptosis
   (c) Autophagy
   (d) Pyroptosis
   (e) Ferroptosis
   (f) Parthanatos

2.10.1. Passive necrosis

1. Necrotic PCD is supported through augmented cell multiplication (oncosis), bulging of organ subsets and chromatin saturation promotes thickness that prevents membranous degradation and secretion of intracellular components.[49,50]
2. DAMPs secrete to regulate inflammasomes in plaque therefore plaques are prone to be degraded.[50]
3. High Mobility Group Box 1 protein (HMGB1), the most important DAMPs for Atherosclerotic study**.**

DAMPs Inhibition Stimulates Necrotic Cell Death through Anti-oxidant Therapy by Vit- C, E that known as an Effective Strategy for Stabilization in Plaques.

2.10.2. Autophagy

1. Severalautophagic stimulus mobbedin plaques developed by atherosclerosis, like as Reactive Oxygen Species (ROS), LDL, inflammasomes and (TNF- α).[50]
2. Oxidative stress, cellular stress and ER stress continues to less amount of autophagic adaptation in VSMCs that regulates cellular occurrence through deprive of degraded organelles and proteins.[50]

2.11. Ferroptosis

1. It is characterized by non apoptosis dependant cellular death that redirects peroxidation of lipid based iron based lipid.[50,51]
2. LOXs and PHD are the enzymes that metabolizes phospholipid more by oxidatingphosphatidyl ethanolamine that required polyunsaturated fatty acids also contribute to ferroptosis.
3. Radical those are encaged by antioxidants like vitamin E, ferrostatin 1 express resistance over oxidation and ferroptosis and directly trap peroxyl molecules without inhibiting LOXs.[51]

2.11.1. Resistant factors of ferroptosis

1. Ferroptosis resistant factor FSP 1 acts as an oxireductase conferring against protection for ferroptosis that catalyzes the regeneration of ubiquinine which encaged those radicals of lipid peroxyl by inducing lipid peroxidation.[51]
2. GTP Cyclohydrolase 1 (GCH 1) with the metabolite compounds are another molecules that protects against ferroptosis.[51]

2.11.1.1. Conclusion. The membranous plaques formed to contribute against altering outer matrixwhich gives cellular bulginess after thatferroptotic cells die outburst.

2.11.2. Parthanatos

1. High regulation in Poly ADP Ribose Polymerase- 1 is directed to parthanatos pathway and proceed by

oxidation of cells that helps in DNA damage. But excessive activity of PARP- 1 degrades cellular matrix of (NAD+) and ATP, thus another cause for cellular death.[52]

2. PARP- 1 binds to Apoptosis Inducing Factor to further release cytoplasmic fluid. After a large amount of DNA fragmentation and chromatin condensation it translocate into nucleus.[52]
3. Plaque inadequacy causes non coupled translocation of NF- Kβ inside nucleus, thus inflammatory mediators do not promote monocyte recruitment that effects on lipid metabolism and increased cell death in atherosclerosis.[52,53]

2.12. Cross talk in PCD related programmatic pathogen defence mechanism

1. Apoptosis is a non-immunogenic cellular death which regulates actual growth and tissue equilibrium also pyroptosis, necroptosis are the cellular death mechanism induced through host pathogen which is activated by inflammatory immune system.
2. So, these researches described well this programmatic cross talk and raise question about apoptotic, pyroptotic and necroptoticmechanisms by immunogenic clarification.

2.13. Objectives

1. Valid proof of practical and upgraded cross talk between cellular death mechanisms.
2. Immune modifications of cell death attachment regarding host defence mechanism.

2.13.1. Cross talk and Up-gradation through programmatic Cell Death

The separation between cellular death mechanismssuppose the necroptotic stimuli attached with pyroptotic modulators which are obviously the example of canonical law that are suppressed. That refers a chain of cellular death mechanisms to prove that cellular altercation by different mechanism with the pathogen regulated suppressors in primary mechanism.[54]

2.13.1.1. Apoptosis- Necroptosis CROSS-TALK. Apoptosis or necroptosis are highly assembled through caspase- 8 activation. It is a constant activation in external apoptosis though suppresses necroptosis mediated signalling to split RIPK 1 and probably RIPK 3.[54]

2.13.1.2. Apoptotic- Pyroptotic interrelated CROSS-TALK.

1. Apoptotic and pyroptotic activity regulate caspase family of proteases and share a common evolutionary origin.
2. In contrary to the reversible signalling of caspase-1 and casppase-8 protease with activenecrosome is attenuated to regulate atherosclerosis by caspase-8 dependant activation of pyroptosis.[54]
3. This above mentioned scaffolding activity is diversified through catalysis by defective caspase-8 that allows atherosclerosis with caspase-1 related pyroptotoic or inflammatory dysfunction.
4. Together this signalling compound with apoptotic, pyroptotic and necroptotic modulators (i.e. caspase-8, Caspase-1, RIPK1/3) are specific to forming 3 types of cell death.[54]

2.13.2. Necroptotic- Pyroptotic interrelated CROSS-TALK

1. The lysis pathway is ensured by both Necroptotic and pyroptotic mechanism to the potency of inflammation that is morphologically acceptable. This interplay within these mechanisms is essential to the cross-talk ability.
2. Pyroptosis intimated through NLRP3 inflammatory pathway that is accumulated to the context of performing ion equilibrity inside cells.[54]
3. So, necroptosis may drive pyroptotic activity in the absence of it.

2.14. PCD of Macrophages and Cellular Suicide in Host Defense against Pathogens

Acquired immunity which encourages normal factors which deliver sustainability to protest host pathogenic inter-stages towards actual counteraction behind adaptive lymphocyte receptors todirect the longevity of molecular specificity to recognize and binding epitopes that are prelim of any infectious disease.

2.14.1. Viruses

1. The intracellular pathogens for sustaining host cell physiological mechanisms the activation of viral replication is important, then deletion of pathogenic cells to support PCD which is a strategic host defence mechanism while exploring the virus to immune recognition.[55]
2. Cytotoxic immune cells triggers PCD associated infected cells which regulates Apoptosis that is very essential for suppressing infection through pathogenic defence like virus.[55]

2.14.2. Bacteria

1. Bacteria are followed as facultative pathogens or circumvent replicator which is intracellular but replicate like extracellular microorganisms.In Bacterial pathogens PCD assembles up-regulation and cross linkage with bacterial APCs (Antigen Processing Complex) by active cytokine.[55]

2. Apoptotic signalling regulates pathogenic defence to get rid of bacterial infection for instanceMycobacterium tuberculosis infected apoptosis in alveolar macrophages suppose to protest against replicationinsideimmature phagosomes thus to repress M. tuberculosis proliferation.[55]
3. Similarly macrophage attachment into the apoptotic bodies can activateSalmonellaenterica, Listeria monocytogenesorM. tuberculosis inside vesicles to enable phagocytosis, digestion to up-regulate and cross link with antigens that triggers adaptive immunity.[55]
4. Secreted effector prolins such as Legionellepneumophilainhibits intrinsic apoptosis.
5. In modulator activated apoptosis suppression thus bacterial PAMP enhances inflammatory signalling that induces excessive innate immunity for signalling towards apoptosis.[55]
6. Inflammatory activity andPyroptosis are triggered with bacteria associated PAMPs on virulence activities of bacterial disease.
7. Such as Citrobactorrodentium, Legionella sp., S. flexneri, S. typhimurium, Yersinia sp. etc.[55]
8. Apoptosis, Pyroptosis and Necroptosisall are less certain about its complication in host pathogenic defence mechanism against bacteriogenecity.[55]
9. Such as S. typhimurium, Y. pseudotuberculosis, C. rodentium, Staphylococcus aureus are virulent against caspase inhibitor that regulatesnecroptosis.[55]

2.14.2.1. Conclusion. PCD helps against replication of intracellular pathogens still this connections interfere inflammatory signals that proceed into cellular death at infected areas thus prevent from case-sensitive deadly immune pathology.

3. Macrophage Death and Cancer Pathways

3.1. Metabolic regulatory CROSS-TALK between tumor microenvironment and tumor associated macrophages

1. Macrophages that borne on TME are called Tumor Associated Macrophages (TAMs).[56]
2. **Fro**m scientific studies TAMs are known for predominantly M2 like phenotype which is regulated through IL-4 and IL-13. It brings immunosuppression towards pro tumorgenic activity.[56,57]
3. According to research articles based on PCD mechanism the primary functions related to macrophages get a reactive anti-tumor immunity by targeting CD-24, CD-47, PD-1/ PD-L1 pathways.[58,59]

3.1.1. Uptake and Metabolism CROSS-TALK from TME to TAMs

Metabolites are accumulated in the TME and cellular recycling are actual for cellular contact, inhibition, metabolism that generated from TME cells, T cells, Mast cells, Fibroblasts, adipocytes excluding TAMs for changing phenotype and function.

1. Tumor cells or TME cells

   (a) Thus for development several tumor cells lack of Glu than TME so the TAM cells are not exchangeableto oxidative phosphorylation thus relying upon (OXPHOS) that generates ATP in cell functions.[60,61]
   (b) Scientific report says treatment with lactic acid eliminates from releasing TNF in mammalian monocytes by repressing glycolysis.
   (c) Tumor cells that produce lactic acid expressed Vascular Growth and M2 associated polarity and influence HIF- 1a.[60,61]
   (d) According to that, tumor acidosis activated through (GPCRs) that induce btrancriptional repressor ICER i.e. (CAMP early repressor) that accelerate pro-tumorgenesis, macrophage polarity by which they have hyper Melanoma condition.[60,61]

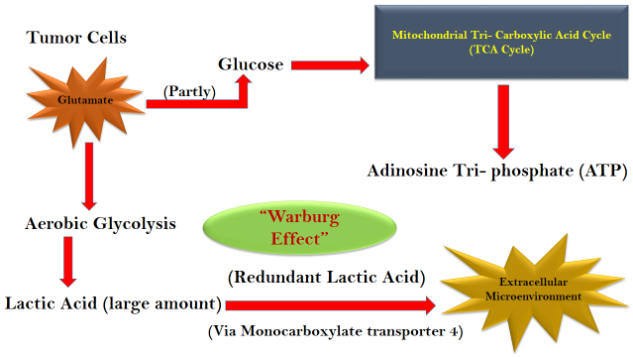

Figure 8: TME cells or tumor cells

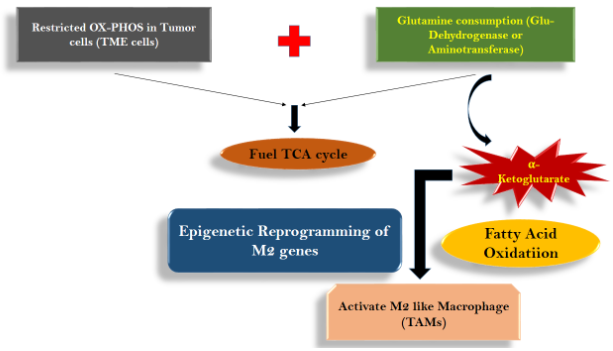

Figure 9: α-Ketoglutarate sensitivity in tumor cells and TAMs

3.2. Energy Accumulations in ATP in TME

ATP is an energy generator whereas hypoxia or chemotherapy recovers excess ATP that is earlier found in tumor cells through connexions etc.

1. ATP is an energy generator whereas hypoxia or chemotherapy recovers excess ATP that is earlier found in tumor cells through connexions etc.
2. Regarding to the unstable nature of ATP which is readily transformed into adenosine and excessively gathered at Extra-Cellular Matrix of solid tumor cells.[62]
3. Adenosine receptors are suitable for sensing tumor specificity and immune susceptibility.
4. According to reports, CD39 it generally attenuated by HIF-1a.[62]

3.3. Lipid and fatty acid accumulation

1. Lipid derived from prostaglandin causes tumor development which is a synthetic oxygenase that proceed onto immunological relief.
2. Science journals proved PGE2 association in M2 polarization by cAMP attenuated CREBs cycle.[62]
3. Fatty acids are more TME cells dependant.
4. It is found that stearic acid produces CDC 11c+ functions in free state through activating cytoplasmic reactivity of proteins.

3.4. Another types of metabolites in TAMs

1. Keto-acids transporter-1 (MCT- 1) processed by TAMs that eliminates unnecessary tissue engulfing through TAM to progress immune susceptibility.[62]
2. In articles it is found that HRG derived cellular inhibition of tumor evasiveness through induction of M1/M2 polarity by down regulation of (PIGF).[63]

   (a) T-cells: T cells for their cytotoxicityas they persist on the immune response so the production of toxicity factors proceed into tumor initiation and recurrence which diminish the tumor cells.[63] These phenomena based on metabolic support mainly utilize the OXPHOS pathway to generate ATP.[64,65]

   (b) Mast cells: These cells after maturation by enhancement of PGD2/ DP pathway the tumor growth is suppressed through modulation of tumor hyper-permeability and angiogenesis. Though lower PGD2 pathway lack of PGDS accelerates tumor sensitivity and must cell mediated pathway reverse metastatic development.[66,67]

   (c) CAF: Cancer associated fibroblasts (CAFs) are the fibroblasts cells residing at living cells which is substantial to accelerate tumor evasiveness and metastasis. Fibroblast specific protein 1 (FSP 1), CD 90, Neuron glial antigen 2 (NG 2) are the markers to identify CAFs.
   Stanniocalcin-1 (STC-1) is a derivative of CAFs which is an inflammatory protein that released by uncoupling protein -2 (UCP-2). Though inhibition of anti tumor chemokine secretion in TAMs is suppressed to proceed anti tumor T cell infiltration.[68,69]

   (d) Adipocytes: Another adipokine Leptin maintains the TME structure and mediates tumor development. Leptin mediation and high clustering through mTOR pathway and TAMs mediated phenotypic changes via leptin is unknown though, but JAK/STAT, MAPK, PI3K pathways related activity was modulated by receptors to induce tumor evasiveness.[70,71]

3.5. Metabolic CROSS-TALK from TAMs to TME

1. TAM1 replicate the TME well, as mentioned earlier, consume in glycolytic pathway to release ATP.[72]
2. Accelerated glycolytic pathway and down regulated apoptotic pathway also extra cellular non coding mRNA those up-regulation held in tumor micro-environments.[72,73]
3. Clear renal cell carcinoma based on glutamine derivative are limited to retain which also increase immune-modulatory activity.[72,73]
4. So, metabolites developed tumor growth and evasiveness.[73]
5. Micro-vesicle packed micro RNAs help to promote brast cancer cell invasion.[73,74]
6. Recent studies suggested that ABHD-5 (Abehydrolase) dependant initiation from TAMs that mediates tumor metastasis.[74]

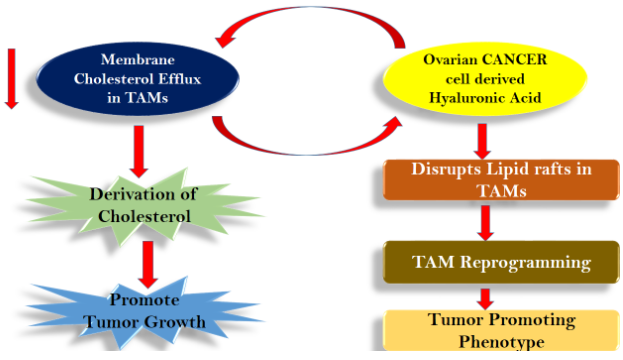

Figure 10: Metabolic cross-talk from tams to TME

4. Conclusion

1. So, Antibody Dependant Cellular Cytotoxicity (ADCC can destroy tumorgenic micro-environment
2. M2 phenotypes in TAMs down regulate Vit-D metabolic activity which results as a deprived cytotoxic affinity.
3. So, that phenomena says TAMs based initiation of antibody dependant cytotoxic susceptibility

**Note: All images provided in this article are created by D.S.

5. Conflict of Interest

None.

6. Source of Funding

None.

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Cite this article: Samanta D, Bhattacharya M. Macrophage death induced cellular mechanisms and some regulatory pathways of macrophage death related diseases. *IP Indian J Immunol Respir Med* 2023;8(4):120-132.