Role of Cytokines in neonatal Respiratory distress syndrome: A review article

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Abstract

Background: Cytokines are non-structural proteins that have a molecular weight of less than 30 kilodaltons and are known to exert complex regulatory effects on immune response and inflammation. Biomarkers for a wide variety of diseases can be derived from cytokines, which are important mediators that regulate immune and inflammatory responses via complex networks. Macrophage migration inhibitory factor, also known as MIF, is a pleiotropic cytokine that has a structurally unique profile. It plays an important role as an upstream regulator of both innate and acquired immunity, as well as the regulation of the inflammatory response through both extracellular and intracellular processes. Research has shown that the innate cytokine known as MIF is essential for the development of the embryonic lung. They also reveal that the concentration of MIF and mutations in the MIF gene both have a role in the onset of multiple lung illnesses as well as the severity of those ailments.

Objectives: The following topics will be discussed in the review article that we are writing: the potential role of cytokine (MIF) in respiratory distress syndrome (RDS) in neonates; the correlation between circulating MIF levels and RDS in neonates; genetic variations in macrophage migration inhibitory factor as a predictor of RDS in neonates and the clinical severity of RDS in neonates.

Conclusion: Because of the immense promise that cytokine (MIF) holds as a biomarker in predicting the susceptibility of preterm neonates to RDS and the severity of the disease, more study has to be done on the topic.

Keywords: Neonatal respiratory distress syndrome; RDS; Cytokines; Macrophage migration inhibitory factor; MIF.

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Introduction

Previously referred to as hyaline membrane disease, respiratory distress syndrome (RDS) is the leading cause of illness and mortality in premature newborns. RDS, which stands for respiratory distress syndrome in infants, is one of the most common causes of respiratory distress in neonates. Although a low birth weight and a short gestational period both increase the risk of RDS, neither of these factors, on their own, is sufficient to forecast how the disease will progress (**Rodriguez et al.,2002).**

Clinical Features of neonatal RDS

Till few hours after birth RDS symptoms can be observed , According to Reuter et al. RDS is characterized by tachypnea (more than 60 breaths per minute), intercostal and subcostal retractions, nasal flaring, head bobbing, sweating, grunting, and cyanosis in room air (**Reuter et al.,2014**). Hypotension, hyperkalemia and acidosis are all possible additional clinical characteristics. After an initial improvement brought on by resuscitation and stabilization, an uncomplicated course is typically characterized by a gradual deterioration that lasts for between forty-eight and seventy-two hours. Recovery often takes place alongside diuresis following an initial phase of oliguria that may have been present.**.**

Pathophysiology of neonatal RDS

Surfactant deficiency is assumed to be the primary cause of neonatal respiratory distress syndrome (RDS), which is caused by the immaturity of the lungs. Pulmonary surfactant is a mixture of phospholipids and proteins that are secreted by Type II alveolar epithelial cells (pneumocytes). In addition to its role in reducing surface tension to prevent lung collapse at the end of expiration, pulmonary surfactant also plays a role in the innate host defense mechanism against inhaled infections (**Jobe et al.,2008).**

Diagnosis of newborn respiratory distress syndrome and evaluation of the severity of the condition

The presence of two or more clinical symptoms of the disease that appeared within the first 48 hours of an infant's life, in addition to radiological indicators that are supported by laboratory tests, is required to make a diagnosis of respiratory distress syndrome (RDS)(**Martin et al.,2013**). The severity of neonatal respiratory distress syndrome can be determined in a number of different ways, including using the Downes' Score, the Silverman-Anderson Score, the Chest Radiography Grade, the Type of Oxygen Therapy or Assisted Ventilation Needed, and its Duration. (**Shrestha et al.,2021**).

Differential Diagnosis of neonatal respiratory distress syndrome:

A newborn infant may experience respiratory distress for a variety of reasons, some of which are pulmonary in nature, such as newborns' transient tachypnea (TTN), Meconium Aspiration Syndrome (MAS), pneumonia, or other non-pulmonary causes like anomalies of the chest wall, heart conditions, neuromuscular conditions, metabolic conditions, or even newborn sepsis. One of the most common causes of respiratory distress in newborns is neonatal respiratory distress syndrome (RDS) (**Warren et al.,2010**).

Complications of newborn RDS

The most common complications of RDS are pneumothorax, pulmonary hemorrhage, broncho-pulmonary dysplasia, apnea of prematurity, neonatal sepsis, necrotizing enterocolitis, intracranial hemorrhage, neurological impairment, and

death. **(Fanaroff et al.,2007).**

Preventing newborn respiratory distress syndrome (Antenatal Care):

The following are the benchmarks of prenatal care:

A) Efficient and effective prevention of premature birth by early identification of pregnancies at high risk.

B) Provide the most effective therapies possible, beginning before delivery, in order to enhance outcomes and reduce the risk of RDS.

According to Diguisto et al. research receiving inadequate prenatal care raises the risk of suffering a severe morbidity or passing away altogether **(Diguisto et al.,2018)**. It is extremely difficult, if not impossible, to avoid having a baby prematurely, even with good antenatal care . Nevertheless, it is made available to expectant moms who will have babies born prematurely prenatal corticosteroids have been shown to improve survival rates, reduce the risk of neonatal respiratory distress syndrome, necrotizing enterocolitis (NEC), neonatal encephalopathy, and intraventricular hemorrhage, and do not appear to have any significant adverse effects on either the mother or the baby in the short term. **(Roberts et al.,2017).**

Management of RDS Syndrome in Newborns. The goal of managing an infant with RDS is to:

(1) Prevent the occurrence of hypoxemia and acidosis.

(2) Ensure that the patient receives enough amount of fluids in order to prevent hypovolemia, as well as prevent overload and pulmonary edema.

(3) Decrease the number of cases of lung injury caused by volutrauma and oxygen toxicity.

In the past few decades, there have been two significant advancements in the treatment of newborn RDS:

1) Exogenous surfactant.
2) Positive end-expiratory pressure (PEEP) and assisted ventilation .

- **Surfactant replacement therapy**: Surfactant therapy has been found to minimize overall mortality in preterm neonates by enhancing oxygenation, minimizing air leaks, and significantly reducing the risk of infant death from respiratory distress syndrome (RDS) **(Soll et al.,1990).**

A) Surfactant preparations and timing: Cochrane has conducted systematic reviews and direct randomized comparison studies on a wide range of synthetic and natural surfactant compositions, including poractant alfa and beractant ((survanta)). According to the findings of the meta-analysis, preterm children diagnosed with RDS who were treated with natural surfactant had more favorable outcomes. The use of natural treatments resulted in a decrease in mortality and the number of pneumothorax cases **(Speer et al.,2012).** When to administer surfactants? According to **(Rojas et al.,2012)** there have been two approaches taken, and they are referred to as preventative treatment and rescue therapy respectively.

B) Prophylactic administration: Involves treating the baby by surfactant as soon as he is stable upon birth. To facilitate establishment of functional residual capacity (FRC) in immature, surfactant-deficient lung and protect it from injury. **(Soll.,2012).**

C) Rescue administration Treatment of established respiratory distress syndrome in preterm neonates using Exogenous surfactants will improve both of oxygenation and ventilator requirement. **(Reininger et al.,2005).**

Oxygen therapy and assisted ventilation

A) Oxygen therapy

The goal of oxygen therapy for preterm newborns diagnosed with RDS is to supply just enough oxygen to keep the saturation level (as measured by pulse oximetry)

RDS but do not yet have respiratory failure, nasal CPAP is the treatment of choice **(Subramaniam et al.,2016)**, CPAP has several advantages over mechanical ventilation for preterm newborns diagnosed with RDS. These advantages include the maintenance of spontaneous breathing, the elimination of the need for endotracheal intubation, and a lesser risk of lung injury.
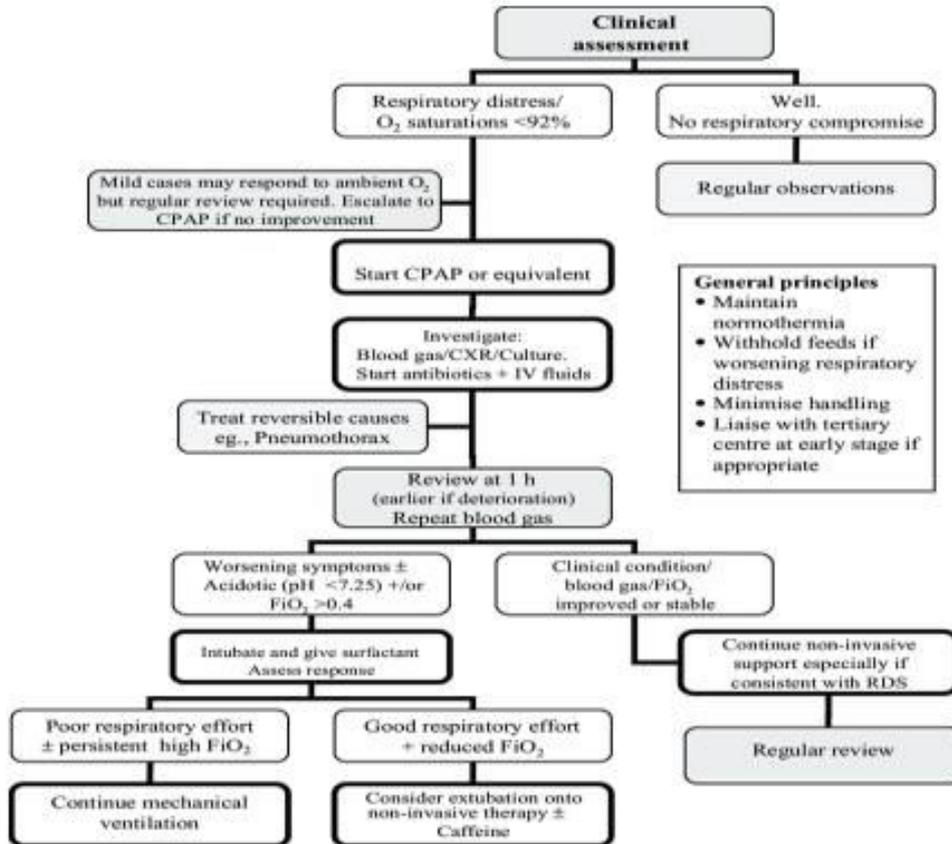

Figure1 : Algorithm for the management of respiratory distress in the moderately preterm infant in the newborn period.(**Miall and Wallis 2011**)

between 50 and 70 mmHg **(Saugstad.,2018)**, and to prevent any lung injury or other complications For instance, retinopathy of prematurity is a consequence of increased O2 concentration **(Manley et al.,2016)**.

B) Assisted ventilation
- **Continuous Positive Airway Pressure (CPAP):**

For premature infants who have respiratory distress syndrome (RDS) or are at risk for

Early use of CPAP cuts down significantly on the need for exogenous surfactant therapy, and using CPAP also brings the risk of developing Bronchopulmonary Dysplasia down to a lower level. The purpose of continuous positive airway pressure, or CPAP, treatment is to keep the patient's SpO2 level between 90 and 95% and PaCO2 level

between 45 and 65 mmHg **(Fig.1) (American Academy of Pediatrics.,2014).**

- **Mechanical Ventilation(MV)**

Infants who are very premature or extremely ill often require a technique known as mechanical ventilation (MV), which can save their lives. However, MV should only be used when absolutely essential to prevent the development of major lung injury that could lead to long-term issues. This is to ensure that the patient does not experience any adverse effects. Additionally, the aim of MV is to make an effort to lessen the lung damage caused by the ventilator while still maintaining adequate oxygenation and ventilation. There are a few different strategies that can be utilized to mitigate the negative effects that MV has on the lungs. Some of these strategies include permitting a small amount of hypercarbia (also known as permissive hypercarbia), avoiding excessive O2 levels, and keeping PaCO2 levels between 45 and 55 mmHg **(Miller et al.,2008).** To further reduce the risk of volutrauma, it is recommended that the tidal volume be maintained at 4-5 mL/kg during the procedure. Adjuvant treatment with exogenous surfactant will improve lung mechanics (lung compliance) and increase oxygenation. This will be accomplished by reducing atelectasis and increasing FRC. **(Sweet et al.,2013).**

Other lines of treatment

Include thermoregulation, caffeine for a condition known as apnea of prematurity (CAP), prophylactic antibiotics, good nutritional support, and supportive care (including appropriate fluid management and support of the circulation to maintain adequate blood pressure and tissue perfusion) **(Kim et al.,2010).**

Prognosis of RDS

The progression of RDS in a newborn can be affected by a wide variety of circumstances, including gestational age, weight, use of prenatal steroids, maternal history, and the presence of any associated diseases. The prognosis for newborns who receive the best treatment is favorable; with modern care, mortality rates in countries with advanced medical services can fall to under 10%, and survival rates can reach as high as 98%. In contrast, the mortality rate for premature newborns diagnosed with RDS in nations with low levels of income is quite high, and in certain cases it can even be 100%. **(Kamath et al.,2011)**. When just breathing support is provided, surfactant synthesis will eventually begin, and after four or five days, the RDS will begin to improve along with the beginning of diuresis. When left untreated, a disease that strikes within the first few days of a newborn's life and causes severe hypoxemia can have devastating consequences, including death.

Cytokines (Description and Introduction)

Cytokines are small, non-structural proteins or glycoproteins with molecular weights of less than 30 kDa (about 200 amino acids). They are secreted by cells in the immune system. Leukocytes, which are one type of cell that express cytokines and are responsible for regulating immunity, inflammation, and hematopoiesis, are an example of a cell that can do so. Over 200 different cytokines have been discovered up to this point. There are cytokines that promote inflammation as well as those that reduce it. **(Deverman and Patterson.,2009)**.

Cytokine is a generic name for several proteins. There are also other names for subgroups, such as:

a) Lymphokines, which refers to the cytokines that are expressed by lymphocytes.
b) Monokines, are a type of cytokine that are produced by monocytes.
c) Chemotactic activities are exhibited by Chemokines, which are a type of cytokine.
d) Interleukin, which is a type of cytokine that is produced by one leukocyte and acts on other leukocytes.

Cytokine action can take place on the cells that produce it (known as autocrine action), on cells that are close by (known as paracrine action), or on cells that are located further away (known as extrinsic action) (endocrine action).

Pathologies of the lungs related to cytokines

Lung disorders that are caused by immunological or inflammatory processes might emerge owing to exposure to injurious factors (such as an infectious agent or hazardous chemicals). These diseases impede the lung from performing gas exchange as effectively as possible. The lung responds to noxious substances by activating host defense mechanisms that are regulated by cytokines **(Fig.2).**

Cytokines are produced in the lung by epithelial cells of bronchi, bronchioles and alveoli , also produced by alveolar
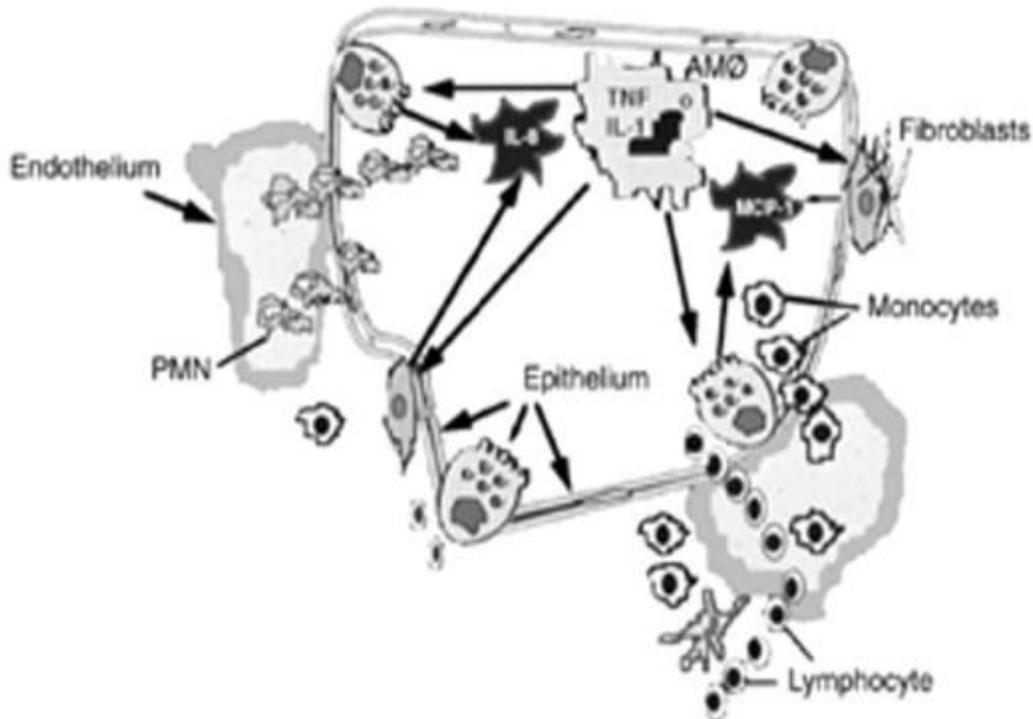

Figure 2: Development of an inflammatory response. (Toews 2001).
Innate immune cells such as alveolar macrophages and monocytes recognize microbial products and secrete chemotaxins which recruit polymorphonuclear neutrophils (PMN's) to the airspace. Innate immune cells also secrete early response molecules such as interleukin (IL)-1 and tumour necrosis factor (TNF), which activate alveolar epithelial cells and fibroblasts to produce chemokines. The development of an inflammatory response requires the induction of a coordinated network of cytokines, which involves cells throughout the alveolo-capillary wall. AM: alveolar macrophages; MCP: monocyte chemoattractant protein.

maintenance of immunological and inflammatory responses.

Cytokines are in charge of determining how a defense system should react to harmful agents and what effector mechanism should be employed.

Intracellular mediators known as cytokines provide cell networks with the instructions necessary to carry out the following functions:

a) The division of everything in the cosmos into agents that cause harm and those that don't.

b) The choice to either interact with the agent or disregard their requests.

c) It is necessary for it to "regulate" the cells that have been recruited and activated.

Cytokines are responsible for regulating the maturation and differentiation of dendritic cells, as well as the activation and differentiation of T cells, the modification of connective tissue structures, and the control of blood vessel growth. Cytokines are also responsible for the communication that occurs between immune system cells and systemic mediators or the host response.

The maintenance of a healthy equilibrium between the proinflammatory cytokines tumour necrosis factor (TNF), interleukin (IL-1, IL-6, and IL-8), and the anti-inflammatory cytokines IL-10 is essential for the regulation of the immune system as well as the inflammatory response (**Park et al.,2001).**

Pro-inflammatory cytokines such as tumour necrosis factor alpha (TNF-α), interleukin-1 (IL-1), and interleukin-6 (IL-6) are important in the early phases of inflammation. It has been shown that these cytokines are higher in ventilated patients who have ARDS (**Suter et al.,1992).**

MIF was found to influence the production of other cytokines, including IL-1, IL-6, IL-8,

and TNF-α, in infants who had lung problems (**Calandra et al.,2000).**

The macrophage migratory inhibitory factor, often known as MIF

Macrophage migration inhibitory factor (MIF) is a crucial upstream regulator of both innate and acquired immunity, in addition to cellular redox signaling. Other names for this protein include glycosylation-inhibiting factor (GIF), L-dopachrome isomerase, and phenylpyruvate tautomerase (**Lu et al.,2016**). It regulates inflammatory response through extracellular and intracellular processes, and the MIF characteristics of cell activation and proinflammatory action make this molecule a constituent element of immunity and stress responses. This molecule significantly contributes to several immunopathologies brought on by excessive inflammation and autoimmunity (**Donnelly and Bucala.,1997; Stosic-Grujicic et al.,2009**), including septic shock (**Bernhagen et al.,1994**), arthritis (**Morand and Leech.,2005**) , diabetes (**Sánchez and Rodriguez.,2014; Sánchez et al.,2016**) , other inflammatory autoimmune conditions (**Denkinger et al.,2004;Morand., 2005; Santos and Morand.,2009**).

A brief history of the MIF

The discovery of macrophage migration inhibitory factor (MIF), previously considered as a T cell-derived cytokine, occurred more than forty years ago as a result of research into the delayed-type hypersensitivity reaction. MIF is considered to be one of the first and most significant cytokine activities of all time (**Bloom et al.,1966; David ,1966**) Prior to the finding of a human MIF complementary DNA (**Weiser et al.,1989**) and its subsequent rediscovery in 1991 as a pituitary-derived peptide generated in response to endotoxin exposure, there was no evidence that MIF had a role in the immune response (**Bernhagen.,1993; Calandra et al.,**

1995; Calandra et al.,1998), However, MIF had been a cytokine that had been shrouded in mystery up until this moment.

The structure of MIF

MIF is a highly conserved protein that is 12.5 kDa in size, 115 amino acids long, and a polypeptide. The protein is composed of three monomers that are identical to one another in terms of their three-dimensional structure. Each of these monomers consists of two antiparallel -helices, designated α 1 and α 2 in addition to six β strands (numbered 1-6).

The folding of each monomer results in the formation of two antiparallel -helices, which then pack against a 4 stranded β sheets (**Trivedi-Parmar and Jorgensen.,2018**). The contact between monomers in a MIF trimer is formed by the two remaining β strands (β sheets of adjacent MIF subunits), which are numbers 3 and 6. A solvent-accessible channel is generated by the three beta-sheets

and runs along a molecular 3-fold axis. This channel travels through the middle of the protein and provides access to the solvent.

The Action of MIF

Several metabolic and inflammatory processes are dependent on the cytokine human macrophage migration inhibitory factor (MIF), which was discovered and is currently being studied in the last decades (**Fig.3**). MIF are responsible for immune system regulation through acting as :

A. As a proinflammatory cytokine, it promotes the development of other inflammatory cytokines and inhibits the effects of glucocorticoids (**Calandra and Bucala.,1997**).

B. Acts as a chemokine, causing chemotaxis and the arrest of neutrophils, T lymphocytes, and macrophages (**Tillmann et al.,2013; Alampour-Rajabi et al.,2015**).
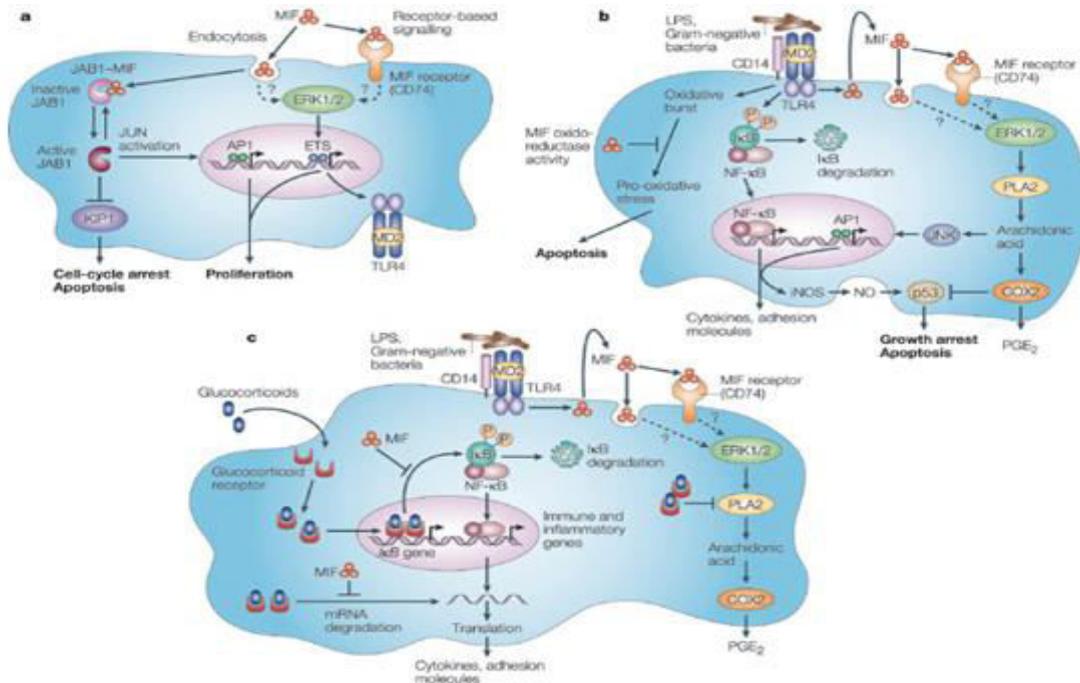

Figure 3 : Mode of action of MIF. (Calandra and Roger 2003)
a | Macrophage migration inhibitory factor (MIF) might mediate its biological activities either through a classical receptor-mediated pathway or through a non-classical endocytic pathway.
b | The induction and regulation of inflammatory responses of innate immune cells by MIF.
c | MIF counter-regulates the immunosuppressive effects of glucocorticoids at transcriptional and post-transcriptional levels.

MIF and Lung development

During the stage of development in which human infants are most vulnerable to RDS, the MIF play an essential role in the maturation of the lungs. **(Kevill et al.,2008)** In 2008, Kevill and his colleagues make public for the very first time the significant part that MIF plays in both the development of the lungs and the prevention of lung diseases. It was found, through the use of a mouse model of neonatal respiratory distress syndrome (RDS), that there was a decline in the levels of the hormones corticosterone and vascular endothelial growth factor, both of which are essential for the maturation of the fetal lungs. Additionally, there was a decrease in the maturation of the lungs of mice that were genetically deficient in MIF. According to research that was carried out in vitro, MIF is an essential component in the production of surfactant by pulmonary epithelial cells.

Recent findings using a model of preterm lambs have led researchers to speculate that the macrophage migration inhibitory factor (MIF) may play a significant role in the protection and maturation of infant lungs **(Dani et al.,2011)**.

It was hypothesized that increasing MIF activity in the developing lung without elevating it above physiological levels could help newborns at risk of poor outcomes due to Hyperoxia-Induced lung Injury by improving defective alveolarization. This would be possible if the MIF activity could be increased in the developing lung without exceeding physiological levels **(Sun et al .,2013)**. Recognizing MIF as an intracellular and extracellular mediator that combats adenosine and PGE2-mediated inhibition of TNF production and helps newborn monocytes' innate immune responses.. These findings provide evidence in support of the hypothesis

advanced by **(Roger et al.,2016),** which states that competing regulatory mechanisms work to control the immunological responses of newborns. The levels of MIF in the cord blood were found to be significantly higher in caesarean deliveries compared to vaginal deliveries in preterm newborns (**Bayraktar et al.,2021**), and also the MIF cord blood levels were found to be significantly higher than mother serum levels in vaginal deliveries in term newborns **(Ietta et al.,2002)**. Both of these findings are consistent with the hypothesis that MIF may have an effect on the development of the lung of infants. At birth, there is a significant increase in the amount of MIF in circulation. After being elevated for at least the first four postnatal days of a infant's life, MIF levels begin to normalize during the first few months of that infant's life. This coincides with the postnatal fall in the levels of cortisol, placental hormones, prostaglandins, and adenosine in the blood, all of which are significant inhibitors of the innate immune responses of the baby. **(Giannoni et al.,2011).** The expression pattern of MIF is distinctive in neonates because it reaches blood levels that are at least ten times greater than those reported in healthy children and adults. This is an observation for which there is no known proinflammatory cytokine or mediator that may provide an explanation **(Belderbos et al.,2013)**. In point of fact, the levels of circulating MIF in healthy babies who have reached their full gestation are analogous to the levels found in children and adults who are experiencing septic shock. **(Emonts et al.,2007)**.

The link between MIF and pulmonary diseases:

In cases of inflammatory lung injury, such as ARDS, it was discovered that MIF expression was greatly elevated in the lung tissue,

including the endothelium of the alveolar capillaries. There was a significant reduction in the likelihood of bronchopulmonary dysplasia, which is a consequence of RDS, when the intrapulmonary MIF was increased (**Lai et al.,2003).** Prencipe and his colleague research provides the first demonstration of a role for MIF in human lung development and provides some support for the idea that MIF may play a protective role in baby lung disease. (**Prencipe et al.,2011**).

The MIF Gene and Polymorphisms There is only one MIF gene in the human genome, and it can be found on chromosome 22q11.2 (**Fig.4**). However, there are many different types of polymorphisms (**Paralkar and Wistow.,1994; Budarf et al.,1997).**

Since its discovery, the human MIF gene has been found to include four different types of polymorphisms:

(**1**) A variant known as 794 CATT(5-8) that is characterized by a 5-8-CATT tetranucleotide repeat.

(**2**) 173 (173*G/C) variants MIF rs755622 G>C single nucleotide polymorphism .

(**3**) + 254 variant (+254*T/C).

(**4**) +656 variant (+656*C/G).

Given that they are located in introns, the +254 and +656 SNPs do not have any effect on the coding sequence of the MIF gene. The 173*G/C polymorphism as well as the 794 CATT(5-8) microsatellite have been the primary focuses of research on MIF genotyping (**Donn et al.,2002; Baugh et al.,2002; Hizawa et al.,2004**).

Specifically, the G/C SNP that is found in the MIF promoter sequence at position -173 (rs755622), which is the variant in this gene that has been researched the most frequently. Because it is located on the CpG island of the MIF, this variant plays a very important role in the gene promoter, where the G > C change generates an additional CpG motif and binding site for the transcription factor activator protein 4 (AP4) (**Donn et al.,2001**) which in turn increases the levels of both transcripts and protein (**Matia-García et al., 2015; Ramayani et al.,2016; Bae and Lee.,2017**).
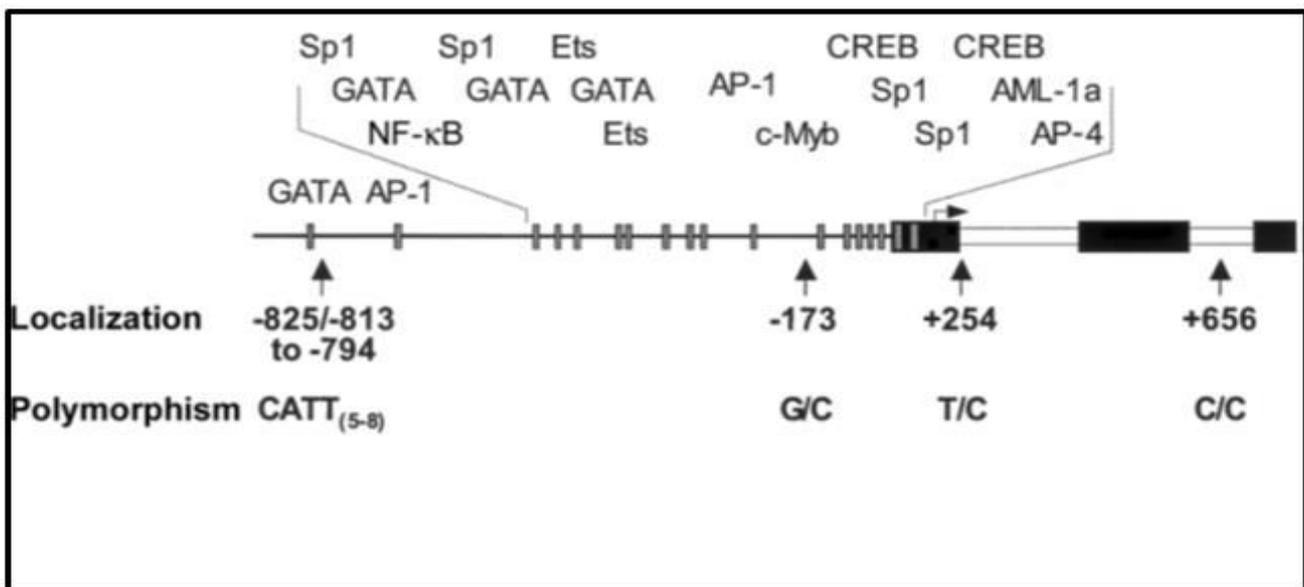
MIF-173G/C SNP polymorphism is connected to:

Figure 4:Structure of the human macrophage migration inhibitory factor (MIF) gene.(Renner et al., 2005)

a) Cancer **(Tong et al.,2015b; Wang et al., 2015; Zhang et al.,2015).**

b) Inflammatory bowel disease (**Zhang et al., 2013).**

c) Rheumatoid arthritis **(Bae and Lee.,2017).**

d) Kidney disease **(Tong et al.,2015a).**

To better comprehend complicated illnesses, it's important to study genes like MIF.

Conclusion

Neonatal RDs is the leading cause of morbidity and mortality in preterm newborns. Cytokines' role in causing and sustaining lung inflammation is essential ,The important MIF's role in neonatal lung diseases and lung development, and its impact on neonatal RDS progress.

Therefore, additional research is required to clarify more about the role of MIF in the development and progress of neonatal RDS, the significance of using it as a biomarker in diagnosis and differentiation of severity, the role of MIF gene polymorphism in neonatal RDS, and even search role in treatment of neonatal RDS. All of these questions need to be answered.

Abbreviations

- **AM:** Alveolar macrophages.
- **AP4:** Activator protein 4.
- **ARDS:** Acute respiratory distress syndrome.
- **CAP:** Caffeine for apnea of prematurity.
- **CPAP:** Continuous positive airway pressure.
- **DNA:** Deoxyribonucleic acid.
- **FRC:** Functional residual capacity.
- **GIF:** Glycosylation-inhibiting factor.
- **IL-1:** Interleukin 1.
- **kDa:** Kilo Daltons.
- **MAS:** Meconium aspiration syndrome.
- **MCP:** Monocyte chemoattractant protein.

- **MIF:** Macrophage migration inhibitory factor.
- **MV:** Mechanical ventilation.
- **NEC:** Necrotizing enterocolitis.
- **O2:** Oxygen.
- **PaCo2:** Partial pressure of carbon dioxide.
- **PaO2:** Partial pressure of oxygen.
- **PEEP:** Positive end-expiratory pressure.
- **PGE2:** Prostaglandin E2.
- **PMNs:** Polymorphnuclear neutrophils
- **RDS:** Respiratory distress syndrome.
- **SpO2:** Oxygen saturation.
- **TNF:** Tumour necrosis factor.
- **TTN:** Transient tachypnea of newborn.

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