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Review Article

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Mesenchymal Stem Cells Can Alleviate Tuberculosis Infection and Transmission

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Abstract

Mesenchymal stem cells are increasingly becoming a topic of interest for their breadth of treatment for a range of complications in the medical field. Their unique abilities to restore damaged tissue and modulate various aspects of the immune system are understood, and more studies continue to reveal other therapeutic aspects. Some studies have begun to focus on their potential as a treatment for Tuberculosis, a complex disease caused by a population of bacteria in host tissue environments. There is currently no cure for this disease, which has developed resistance to a range of drugs over the course of history, and a novel therapeutic is required in order to effectively treat and eventually eradicate the disease. In this paper, we discuss the potential immunomodulatory and tissue-repairing effects of mesenchymal stem cells that hint to their efficacy as a treatment for the disease. We also consider the reality of distributing this advanced therapeutic to regions of the world where Tuberculosis is most prevalent. Based on these countries' political and economic infrastructures and the emergence of other disease, mesenchymal stem cells may not be a treatment that can realized soon to treat those most affected by Tuberculosis.

Keywords: Tuberculosis, Stem Cells, Therapy, International Health

Introduction

The infectious disease Tuberculosis (TB) is caused by the bacteria *Mycobacterium tuberculosis* (Mtb), which primarily resides in and is transmitted through the respiratory tract. The World Health Organization reported that there were around 10 million infected with TB, including 7.1 million new cases and 1.2 million deaths in 2020 [1]. They also reported that around nearly 500,000 are infected with rifampin-resistant tuberculosis (RR-TB), a commonly used antibiotic to treat the infection.

After infection, Mtb enters a prolonged latent state that can last decades, and the patient shows no signs of symptoms. In some infected individuals, the bacteria enter an active state and causes clinical symptoms and can be spread through the respiratory tract [2]. Once it enters the new host, Mtb is believed to be phagocytized by host dendritic cells and macrophages then enters a state of intracellular replication [3]. It drains into the lymph node and enters the blood stream eventually repopulating another region of lung tissue. When this occurs, immune responses like the recruitment of monocytes and lymphocytes take place and surround the Mtb in a structure called a granuloma [4]. These granulomas (TGs) are characteristic of TB and allow the bacteria to persist in a slow or latent state of replication. If the structure of the granuloma is somehow disrupted cellular necrosis will occur and the nutrient rich area becomes available to the bacteria [5]. This event not only creates lesions in the lung tissue of the patient, but also releases thousands of bacteria that can form infectious aerosols and allow Mtb to transmit to a new host and complete its lifecycle [6].

A recurring issue with treating this infection is the persistence of multidrug-resistant Mtb (MDR-Mtb). Alternative approaches have been attempted to either treat Mtb or understand potential therapeutics against them like using reactive oxygen species (ROS) like H2O2 and NO [7]. Recently in the medical field, there has been an increasing interest and success in treating a range of illnesses and injuries using mesenchymal stem cells (MSCs). MSCs are pluripotent stem cells that exist in skin, fat, bone marrow, gingival, umbilical cord tissue, and many more [8]. They can differentiate into neuron cells, adipocytes, osteoblasts and chondroblasts, and have been shown to migrate to injury sites in the body [9]. There, they can promote anti-inflammatory regulation and tissue regeneration, and thus have been used to treat a range of immune and inflammatory diseases. Based on the understanding of the mechanisms of infection of Mtb and the capabilities of MSCs, there has been

interest in using MSCs to treat Mtb and MDR-Mtb. In this paper We will discuss the current understandings of the effect of MSCs on Mtb, and whether implicating this novel therapeutic to irradiate the disease is at all possible.

Mesenchymal Stem Cells (MSCs) Play a Complicated Role in Tuberculosis (TB)

The aggregate of cells that make up TG can consist of infected or uninfected macrophages and T lymphocytes. Here, Mtb can lie dormant and persist in the carrier's lungs for long periods of time [10]. In order to understand the role of MSCs in Mtb, it is important to understand their role in TG. In a mouse study by Raghuvanshi *et. al,* MSCs with CD29 markers were injected into mice infected with Mtb and they found that MSCs were distributed throughout the TGs [10]. They also measured the interaction between the MSCs in the TG with the immune system and dormant Mtb. They found that the MSCs produce nitric oxide (NO) in a similar manner to T cells, which can limit the immune response to target and kill Mtb [10]. This same NO response, however, seems to also inhibit the growth of Mtb in the granuloma. MSCs seem to play a complicated role in these structures, and other studies have come to similar conclusions. Some patients that overcome their infection have been found to harbor dormant Mtb in CD271+ bone marrow MSCs [11]. A study by Garhyan *et. al* looked closely at this interaction. In the study they labeled an Mtb strain with a green fluorescence protein, infected mice with the modified bacteria, and recovered the MSCs where the bacteria localized: the hypoxic niche of the CD271+ MSCs [11]. When they injected these cells into healthy mice, they found that the mice became infected with Mtb, indicating that the hypoxic environment induced by these MSCs can harbor dormant Mtb. Even worse, MSCs have been shown to play a role in promoting antibiotic resistance in Mtb [12]. Singh *et. al* found that Mtb could, like Garhyan *et. al* survives in bone marrow MSCs, but they also found that the pathogen does not induce any noticeable cell death [11, 12]. Throughout the *in vitro* study, they found that the Mtb living in these MSCs increased their expression of HspX, which is known to be a marker for tolerance to the drugs that treat TB: Rifampin and isoniazid [12].

The relationship between MSCs and TG is also not very well understood. One common understanding in the formation of TG is that fibrin deposition is an important step [13]. Fibrin deposition is also a critical pathway in the body that can heal wounds, stimulate muscle fibers, and support granulation tissue formation. MSCs are known to activate these pathways (which is why there has been so much interest in their use for regenerative medicine), but this points to the fact that they may contribute to the formation of granulomas in TB [13]. Another speculative role that MSCs play in TG formation comes from a study by Chen *et. al* [14]. They monitored the blood plasma of untreated TB patients and found that lysophosphatidic acid (LPA) was abnormally high and, as treatment progressed, these levels fell [14]. LPA is known to be an activator of the transcription factor proliferator-activated receptor-λ (PPAR-λ), which causes the accumulation of lipid droplets in macrophages, but also has been known to induce the differentiation of MSCs into adipocytes [14]. There may be some interaction between MSCs, macrophages, and Mtb that change the expression of this pathway, and likely many more. This study seemed to raise more questions about these interactions. One explanation may come from a study by Beigier-Bompadre *et. al* that found adipose tissue to be another niche for Mtb [15]. Thus, the high plasma levels of LPA may induce adipogenesis in MSCs and provide another environment for Mtb growth.

Some studies also look at the location in TGs that MSCs reside to better understand the relationship between the two. TGs have a well-defined structure consisting of an acellular core surrounded by macrophages of several varieties, and this layer is covered by B cells and T cells [16]. It is not currently known if MSCs have a specific position or location in this structure, but they have been found to surround the structure and inhibit T cell activation [16]. This, as was found by Raghuvanshi *et. al* is a result of NO production which can restrict Mtb growth [10]. It is not clear whether either of these interactions influence the dormant TB. The lymphocyte-rich area of TG may interfere with the interaction of T cells and the Mtb inside the granuloma, so the effects of peripheral MSCs would be negated [16]. MSCs play many roles in immunomodulation, so the understanding of their role in TG formation and location in the structure will be important in understanding their capacity to serve as a therapeutic for TB.

Mycobacterium Tuberculosis (Mtb)- Mesenchymal Stem Cells (MSCs) Interactions

The direct interactions between MSCs and Mtb have also been studied to understand the mechanisms in which MSCs can eliminate Mtb. One study by Khan *et. al* reported that MSCs can behave as phagocytic cells and have potential to be used to treat MDR-Mtb [17]. MSCs express a scavenger receptor that can internalize lipids. Two of the scavenger receptors examined in this study were MARCO and SR-B1. Through siRNA knockdown, they observed that the phagocytic uptake of Mtb by MSCs decreased without expression of the scavenger receptors [17]. They also reported that the MSCs that endocytosed Mtb behaved similarly to the studies previously mentioned by producing nitric oxide [17]. However, they were able to induce intrinsic autophagy by treating the Mtb-containing MSCs with rapamycin and found that the rapamycin treatment increased the killing of Mtb in the cell [17]. This highlights interactions between MSCs and Mtb that are essentially for their intracellular dormancy. It also suggests that there may be ways to influence MSC behavior to eliminate intracellular Mtb through certain treatments.

Some studies look at independent organelles called lipid droplets (LD) to understand Mtb-MSC interaction. LDs are lipid ester nuclei with a phospholipid monolayer on the surface and involved in cellular functions [18]. One study by Fatima *et. al* found that Mtb can induce lipid synthesis when it infects MSCs [19]. These peripheral particles would further impede the immune system from not only detecting the infection in the cell, but also prevent action against the bacteria. This understanding agrees with other studies including one by Knight *et. al* they found that during infection of macrophages, LD formation increases through the IFN-γ and HIF-1α signaling pathways that are normally activated as an immune defense mechanism [20]. They also report that Mtb is capable of acquiring other host lipids as a nutrient source in the absence of LDs. However, Mtb could not acquire host lipids in the presence of IFN-γ induced LDs [20]. This signaling pathway may not be present in the formation of LDs in MSCs, but it may have future clinical importance. There needs to be an understanding of the lipid-formation pathways in MSCs to understand which types of LDs are essential for Mtb survival. By effectively activating a defense mechanism while simultaneously eliminating the energy supply of

Mtb, there may be a way to genetically engineer MSCs that resist infection or kill phagocytized bacteria.

Immune Cell Modulation

With an increase in drug resistant in Mtb, ineffective therapeutics, and the combination of immune disfunction in patients, there is even more of a need to develop a new and effective treatment [21]. Interestingly, the infection, or even the reinfection, of Mtb has not been shown to depend on the health of a patient's immune system. Instead, Shamputa *et. al* report that the activation of latent Mtb is a result of a deficient immune system [22]. Therefore, the treatment for Mtb and even MDR-Mtb may be the use of techniques to improve the immune response to Mtb infection. Recently, host-directed therapy has become an interest in several areas of infection treatment, including Mtb. Host-directed therapy is the improvement of infection control and reduction of inflammation through the modulation of the host immune response [23]. This is particularly relevant to this topic because MSCs have immunomodulation capabilities that are known to repair and replace damaged tissue, thus pointing to their potential role in modulating the immune response against TB and restoring tissue damage [24].

MSCs affect the immune system through the production of enzymes and soluble cytokines which indicates their direct interaction with cells, rather than inducing downstream effects. They can regulate the response of T cells through expression of 2,3-dioxygenase (IDO), which activates the CD39-CD37-adenosine signaling pathway [25,26]. This has also been shown to promote the conversion of M1 to M2 macrophages. IDO has also been found to be involved with the function of Tregs and Th1, which are involved with the regulation of PGE2, an inflammatory marker common in rheumatoid arthritis and osteoarthritis [27]. MSCs can also inhibit the activation of B cells and the maturation of dendritic cells [28]. The list goes on, and new effects and pathways are being discovered, as well as the wide range of effects of these changes.

Immunomodulatory effects induced by MSCs is also a result of cell-to-cell signaling through the use of extracellular vesicles (EVs). EVs are either classified as exosomes, micro vesicles, or apoptotic bodies, and display antigens to bind target cells and deliver functional or regulatory substances like DNA and mRNA [29]. MSC EVs can inhibit immunoglobulin secretion in B cells, which can affect B cell lineage function and regulated inflammatory response [30]. MSC EVs have also been shown to increase levels of transforming growth factor-β (TGF-β) in Th17 cells, indicating a shift to an anti-inflammatory response in T helper cells [31]. The MSC EVs can also be delivered to macrophages and induce a M0 to M2 polarization, they have been shown to reduce the expression of CCR7 in dendritic cells and weaken their overall function [31, 32]. In summary MSCs have mechanisms of immunomodulation that need to be understood to realize their potential role in TB treatment.

A key player in the immune system are neutrophils, that are involved with innate responses to infection. They not only target and phagocytize pathogens and release bactericides, but also play an important role in promotion of immune response [33]. The progression of TB in mice has been found to relate to the inflammatory response of neutrophils and their localization to lung tissue [33]. A study by Brandau *et. al* found MSCs can interact with neutrophils by releasing inflammatory cytokines when exposed to a bacterial endotoxin [34]. The release of these cytokines recruited neutrophils that were activated and showed a prolonged lifespan. The activated neutrophils also showed increased inflammatory cytokine secretion as well as an enhanced response to LPS challenge [34]. This activation induced by MSCs may be able to improve the response of neutrophils when infection first occurs to prevent Mtb dormancy in granulomas.

Another important player in the Mtb immune response are T cells. They can control long-term Mtb and can help prevent the development of TB [35]. A strong T cell response is not entirely beneficial since there needs to be balance between the activation of the immune system and tolerance, which can be characterized by the levels of Th1 and Th2 cytokines [35]. In a healthy individual, the cytokines remain in equilibrium, but in Mtb patients this balance is not observed. Th1/Th2 cytokine imbalance has been shown to be directly related to TB infection in a study by Li *et. al* [35]. They found this imbalance in TB patients and found that by treating peripheral blood mononuclear cells (PBMCs) *in vitro* to reduce Notch signaling, they were able to restore the balance of Th1/Th2 cytokines [35]. MSCs, as previously mentioned, have immunomodulatory effects that regulate Th1 and Th2 activations. Thus, this may be another possible use for MSCs in Tb treatment.

Macrophages have bene found to play an important role in the immune response to any infection, but a study by Upadhyay *et. al* found that Mtb does not undergo the same phagocytic response to macrophages as other microbes [36]. Normally, the ingested microbe is digested by reactive oxygen and nitrogen species, but Mtb has been found to resist these and many other immune responses [36]. They can interfere with immune recognition, cell signaling, prevent phagosome acidification, delay antigen expression and even modify epigenetic responses in cells [36, 37]. A recent study by Huang *et. al* examined the role of macrophage polarization in TG in lung tissue of patients and *in vitro* [38]. They observed that upon *in vitro* infection, M1 to M2 polarization increased and they found that M2 macrophages predominated the lungs in TG of patients [38]. They also noticed that when the polarization of M1 to M2 macrophages was prevented or reduced, the formation of TG increases *in vitro* indicating some mechanism in which M2 macrophages play a role in TG prevention [38]. M2 macrophages may be important in preventing tuberculosis progression, and a study by Hyvärinen *et. al* found that bone marrow derived MSCs can modulate their polarization [39]. MSCs were cultured with regulatory macrophages and found that MSC EVs induced the polarization of M2, which were expressed in greater amounts than M1 regulatory macrophages [39]. These data would suggest MSCs may be able to modulate an immune response that has inhibitory effects on the development of TGs.

Tissue Survival and Repair

The infection of Mtb into alveolar epithelial cells leads to the development of TGs, where the bacteria live in an isolated environment suitable for replication [3]. Cell apoptosis occurs in the TG and thousands of bacteria are released, which spread the disease but also damage alveolar tissue [3]. This infection and spread are well understood, but one study by Vir *et. al*. has looked at an underlying mechanism of the apoptosis that occurs [40]. Phosphatidylinositol mannosides, lipids produced by Mtb after infection into

macrophages, were exposed to *in vitro* alveolar epithelial cells, and found that cells treated with these lipids underwent apoptosis, which was explained by the increased production of reactive oxygen species [40]. The phosphatidylinositol mannosides seem to contribute to apoptosis in alveolar cells by creating a hypoxic environment through the accumulation of reactive oxygen species. A study by Bernard *et. al* in 2018 looked specifically at the interactions between alveolar epithelial cells and MSCs [41]. Mice alveolar epithelial cells were exposed to hypoxic conditions that mimic the effect of reactive oxygen species and were treated with MSCs. They found that the MSCs had a protective effect on the epithelial cells with a reduction in apoptosis compared to the untreated control [41]. They explained this by the increase in antioxidant enzyme activities induced by MSCs that regulated the effect of reactive oxygen species. The authors noted that these protective effects may be partially dependent on the secretion of keratinocyte and hepatocyte growth factors [41]. This protective mechanism of MSCs indicates that they can help prevent the spread of disease in latent TB patients but can also protect lung tissue from damage.

When there are no protective mechanisms in place and the patient's infection is released through apoptosis of alveolar tissue cells, the lungs become scarred and pulmonary function is impaired [42]. Even treatment, lung damage has been shown to persist with clear effects including airflow obstruction and increased risk for chronic obstructive pulmonary disease [42, 43]. MSCs have been shown to play important roles in tissue repair, and specifically in lung tissue for several diseases. One study by Aslam *et. al* mimicked the effects of neonatal chronic lung disease (bronchopulmonary dysplasia) in neonatal mice through the exposure of hyperoxia [44]. By day 14, the untreated mice saw major reductions in alveolar cells, increased inflammation and pulmonary hypertension [44]. Mice injected with MSCs on day 4 showed reductions in all these symptoms, including some that had normal levels of alveolar epithelial tissue and macrophage stimulating factor 1, indicating immunomodulatory effects of MSCs in their role of tissue repair [44]. Another mouse model study by Gupta *et. al* found that MSCs isolated from normal mice were able to clear
E. coli infections from lung tissue as early as 48 hours after treatment [45]. MSCs can also decrease the dysfunction of lung tissue induced by *E. coli* infections by reducing overall tissue damage [46]. MSCs may not only be a preventative treatment for tissue damage but could be a mechanism of repair after harmful conditions from bacterial infection.

Who Benefits the Most from TB Treatment?

The immunomodulatory effects of MSCs show some promise as a potential therapeutic for TB and MDR-TB patients. It may not necessarily be a cure or completely effective method of preventative treatment, but as research continues there is some hope for a solution. However, in dealing with a pathogen as prevalent and persistent as Mtb, the ease of facilitation of care must be considered when evaluating a novel therapeutic. If a treatment method exists but cannot be made accessible for those who need it, then all efforts from research to application may be completely nullified.
The WHO estimates that 10 million people fell ill with TB in 2020, with 1.5 million deaths globally [47]. The global distribution of this disease, however, is not even. Eight countries make up two thirds of these infections including, but not limited to Pakistan, India, Nigeria, and Indonesia [47]. Some of these countries with higher rates of TB are have low gross national income (GNI) per capita below $4,095 per year in the 2022 fiscal year [48]. These are considered low- and middle-income countries (LMICs) and are often a focus of global health efforts. These countries experience greater rates of malnutrition, live in closer quarters, and have a lower or no standard public hygiene practices [49]. These factors facilitate the spread and contraction of many diseases while also increasing the risk of death for those that fall ill. LMICs have higher rates of diseases ranging from viral, like Human Immunodeficiency Virus (HIV), to bacterial like TB [49]. For example, the reported incidence rate of TB in African Regions ranged between 200 and 300 cases per 100,000 people from 2000 to 2020, while the reported TB cases per 100,000 people in the Americas and Europe remained around 30 for that time [50].

These are reported values, so must be considered rough estimates, but the entire order of magnitude difference between these regions makes the point clear. LMICs, like many in African and Asian countries, exhibit certain conditions that mitigate the spread and increased instances of TB in their populations. These LMICs poor conditions also lead to an increase in TB deaths when compared to other countries with higher GDI per capita like the Americas and European countries, according to WHO [51]. Countries in the African region reported over 30 deaths per 100,000 at the end of 2020 while European countries and the Americas reported less than 3 deaths per 100,000 at the end of 2020 [51]. Again, there is an order of magnitude difference in the effects of TB in these LMICs. Countries that have higher standards of hygiene, nutrition, and overall better medical care are not the most at risk for infection of and death from TB. In order to develop a therapeutic that can help the optimal number of patients with the hopes of eradicating this disease, efforts must go toward a treatment that can be distributed and provided to those in greatest need.

Stem Cell Delivery and Distribution

To consider MSCs as a potential therapeutic for TB, the distribution of the treatment to LMICs must be considered. Unfortunately, these living cells require certain environments for growth and maintenance that must be regulated by certain equipment and conditions. One limitation is that MSCs require *ex vivo* replication [52]. Several studies have been conducted to determine which substances and protocols are required for *ex vivo* expansion. One study by Tamama *et. al* found that using epidermal growth factor (EGF) in combination with bone marrow MSCs that were engineered to express epidermal growth factor receptor (EDFR) induced proliferation [53]. They noted that these cells expressed robust levels of certain protein kinases indicative of successful proliferation. Another study noted that the use of certain signaling molecules in combination with expression for receptors of that kind also induced proliferation, and many agree that the use of platelet-derived growth factor (PDGF) promotes stem cell proliferation *ex vivo* [53-55]. Unfortunately, even these methods are not entirely successful. With increased time in cell cultures, some cells will undergo altered cell cycles which can result in undesired genetic changes, rendering the MSCs unable to fulfill their role for the experiment or treatment [56]. Regardless of the technique used to preserve and allow the replication of MSCs, they require laboratory-standard monitoring and substances that are not readily available nor inexpensive. When considering the use of MSCs as a therapeutic for TB in LMICs that need it most, a massive effort

would be required. This would include, but not be limited to, scientists that understand the technology and how to monitor them, proper storage conditions that can be remain outside of a culture setting for long periods of time, volunteers and doctors to administer the treatment, and enough funds to cover the expenses for all of this.

Fortunately, international health teams and organizations have made attempts to distribute advanced forms of medicine to regions of low income in the past, and some are currently working to reduce endemic diseases. One disease of interest is poliomyelitis. In 1988 the World Health Assembly aimed to eradicate polio by the year 2000, and began developing strategies, mobilizing resources, and implementing strategies to make rapid progress [57]. They began vaccination campaigns in countries with good health infrastructure and found success in raising immunity to the threshold of herd immunity [58]. With these vaccination efforts and other means of interrupting transmission, the number of countries considered polio-endemic remained at 20 by the year 2000 (compared to the over 125 at the start of the effort) [59]. The beginning of 2000 marked the second phase of polio eradication efforts. Focus and efforts became more aimed to difficult countries that either had difficult-to-access populations for security reasons, and poor participation in vaccine campaigns [60]. They noticed that most of these countries had already reached relatively high levels of immunity since polio had been endemic in their country for long periods of time. Because of this, most of the efforts to interrupt communication of the disease relied heavily on vaccinations [60]. By 2011, the third phase of the efforts had begun, and 4 countries remained. Real progress was made in India, which was predicted to be near impossible with the population density and remote number of remote areas [61]. Things became less promising in the three remaining countries: Pakistan, Afghanistan, and Nigeria. When these efforts of the third phase began, Pakistan was riddled with political instability and terrorist organizations interfered with health care workers. Between the years of 2012 and 2016, over 100 polio health care workers attempting to distribute the vaccine were killed by terrorist organizations [62]. In Nigeria efforts were successful and polio remained undetected until 2016 when a case of type 1 wild poliovirus emerged [63]. A plan was made to distribute over 800,000 vaccines to the children in Borno State (a part of north eastern Nigeria where the disease emerged) but were unsuccessful because that area was controlled by an extremist group which would not allow the distribution of medical care to anyone living in their territory [63].

These barriers of political instability cannot be overcome by any amount of money or research. It is unfortunate that innocent citizens of these countries fall under control of groups that will not allow health care from groups, but it is a reality that must be faced. When attempting to translate polio eradication efforts to the distribution of any medicine or therapeutic for treatment of TB, all these factors must be considered when a novel therapeutic arises for such a widespread disease. The polio efforts were backed by large organizations with lots of funding like the Bill & Melinda Gates Foundation, WHO, and UK Medical Research Council [64]. Even with unlimited funds would these efforts still be futile? Is it worth putting more healthcare workers at risk? There have already been reports of TB health care workers returning from trips with latent TB. In a survey of healthcare workers that traveled to 26 LMICs where TB incidence was over 300 per 100 000, they found that around 17% of the workers returned with latent TB [65]. The lives of the workers are at risk not only from terrorist organizations, but also risk their health. They are constantly surrounded by the sick, and for disease like TB that has no vaccination, it cannot be guaranteed that they return from the trip without illness. Generally implementing the care for these patients is not only dangerous in terms of safety from extremist groups, but also in terms of risk of falling ill to the disease they are trying to treat. This is yet another barrier in any type of international health effort and must be taken into account when considering the practical application and distribution of MSCs as a TB therapeutic.

Fighting TB During Other Pandemics

In August of 2015 the WHO released a plan called the "End TB strategy", with the vision to end the TB epidemic and specifically reduce the rate of TB by 90% by 2035 [66]. In the report they outline principles and pillars that are required to keep in place for ending the epidemic. This includes certain milestones each year like a 10% reduction in new cases each year [66]. However, TB is an opportunistic infection and can take advantage of a host with battling another infection. This becomes a problem as other diseases become endemic in certain areas, especially LMICs where TB is prevalent. One obstacle the WHO had to overcome in their TB efforts was the HIV epidemic. In Iran, for example, 14% of the population was diagnosed with HIV/TB coinfection [67]. The meta-analysis by Pourakbari *et. al* explained that risk factors like intravenous drug use and age<40 years contributed to this number [67]. Another survey in South Tongu district of Ghana found that 32% of the 344 HIV-positive patients were positive for TB infection [68]. The proportion of HIV/TB coinfection globally is somewhat debated. Some African countries have populations of TB patients where up to 80% are infected with HIV, and a metanalysis by Gao *et. al* estimates that the rate of global HIV/TB coinfection is as high as 23.51% [69, 70]. Meanwhile the WHO, which samples a broader range of countries, reports around 13% prevalence globally [71]. Nonetheless, HIV and TB are not only prevalent together, but also contribute to high rates of death. It is estimated that around one in four deaths of HIV-positive patients is associated with TB infection [72]. This is a clear demonstration that any attempts to eradicate TB will be slowed or halted by other emerging disease. When considering the reality of distributing treatment to reduce TB transmission by 90%, the type of therapeutic, means of delivery, and rates of other diseases must be considered.

"The COVID pandemic further demonstrates the impact that other diseases have had on efforts to distribute treatment for TB patients".The WHO reported that 1.4 million fewer people received treatment for TB when compared to 2019, a 21% reduction [73]. Even worse, they reported that the 10 most "high-burden" countries received the greatest impact of these shortfalls where distribution of treatment was reduced by 28% when compared to 2019 [73]. Other reports show that groups like the Global Fund, which distribute care to LMICs, saw a 19% reduction in distribution of care to countries where MDR-TB is most prevalent [74]. This disease has placed many stressors on health care systems across the globe, demonstrating the impact that other diseases have on TB treatment not just because of coinfection and morbidity, but also

due to thinning of resources and efforts.

Abbreviations

EDRF: Epidermal Growth Factor Receptor
EGF: Epidermal Growth Factor
EV: Extracellular Vesicle
GNI: Gross National Index
HIV: Human Immunodeficiency Virus
IDO: 2,3-dioxygenase
LD: Lipid Droplets
LMICs: Low- and Middle-Income Countries
LPA: Lysophosphatidic Acid
MDR-Mtb: Multidrug-Resistant Mtb
MSCs: Mesenchymal Stem Cells
Mtb: Mycobacterium tuberculosis
NO: Nitric Oxide
PGE2: Prostaglandin E2
PPAR-λ: Proliferator-Activated Receptor-λ
ROS: Reactive Oxygen Species
RR-TB: Rifampin-Resistant Tuberculosis
siRNA: Short Interfering RNA
TB: Tuberculosis
TG: Tuberculosis Granuloma
TGF-β: Transforming growth factor-β

Conclusion

The immunomodulatory tissue repairing effects of MSCs revealed in various studies hint that this could be a treatment used for the prevention of TB prognosis, transmission, and damage to pulmonary tissue. In a field of medicine that continues to be explored, more evidence and data are necessary to understand the effects and implication of MSCs as a treatment. However, when considering such an advanced form of medicine to treat a disease as widespread as TB, the practical distribution and facilitation of care must be considered. TB is a disease that disproportionately affects LMICs where health care standards and living conditions are worse than countries of higher GDI per capita. These populations are in most need of care and efforts to find a treatment for TB and MDR-TB must consider the possibility of getting treatment to these regions. In the past this has not been necessarily easy. Some of these countries suffer from political instability and extremist groups control certain areas which make it near impossible to get treatment to members of the population. A type of medicine as advanced as MSCs, which requires highly specific conditions, may not be possible to distribute to LMICs, especially those where there is political unrest. The emergence of other diseases also plays a role in the rates of TB. Some, like HIV, increase the morbidity rates of TB-infected individuals, while others like the novel coronavirus thin resources and put stress on the health care system resulting in the reduction of global treatment. This is yet another obstacle in the efforts of reducing TB transmission and morbidity. The reality is that TB might be disease that humans live with for the rest of our time on this planet. The constantly adapting bacterium that develops resistance to a range of antibiotics may not ever be eradicated, even if some advanced technology is developed. Keeping this in mind, MSCs may not be the answer to global eradication of TB, but maybe it can be used as an alternative form of medicine in countries with health care systems that can facilitate its use. There is real promise and hope in this type of treatment, but it may only be available to a select group of individuals.

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