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The mechanisms of cellular crosstalk between mesenchymal stem cells and natural killer cells: Therapeutic implications

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Abstract

Mesenchymal stem cells (MSCs) are mesenchymal precursors of various origins, with well-known immunomodulatory effects. Natural killer (NK) cells, the major cells of the innate immune system, are critical for the antitumor and antiviral defenses; however, in certain cases, they may be the main culprits in the pathogenesis of some NK-related conditions such as autoimmunities and hematological malignancies. On the other hand, these cells seem to be the major responders in beneficial phenomena like graft versus leukemia. Substantial data suggest that MSCs can variably affect NK cells and can be affected by these cells. Accordingly, acquiring a profound understanding of the crosstalk between MSCs and NK cells and the involved mechanisms seems to be a necessity to develop therapeutic approaches based on such interactions. Therefore, in this study, we made a thorough review of the existing literature on the interactions between MSCs and NK cells with a focus on the underlying mechanisms. The current knowledge herein suggests that MSCs possess a great potential to be used as tools for therapeutic targeting of NK cells in disease context and that preconditioning of MSCs, as well as their genetic manipulation before administration, may provide a wider variety of options in terms of eliciting more specific and desirable therapeutic outcomes. Nevertheless, our knowledge regarding the effects of MSCs on NK cells is still in its infancy, and further studies with well-defined conditions are warranted herein.

KEYWORDS

autoimmunity, cancer, immunomodulation, NK, stem cell

1 | INTRODUCTION

More than 5 decades ago, Friedenstein found a group of stem cells in the bone marrow (BM), which could differentiate into multiple cell lineages like osteoblasts, chondrocytes, and adipocytes, in vitro (Afanasyev, Elstner, & Zander, 2009). Since these cells possessed some stem cell-like characteristics such as self-renewal and differentiation potential and at the same time proved to be the precursors for mesenchymal tissues, they were since then recognized as mesenchymal stem cells (MSCs; Barry & Murphy, 2004). MSCs are nonhematopoietic stem cells (HSCs; Pittenger, Mosca, & McIntosh, 2000) with plastic-adhering properties. They can be isolated from the lungs (Cruz, Lopez-Giraldo, Agusti, & Faner, 2016), placenta (Park, Kim, Kim, & Lew, 2018), BM (H. Lin, Sohn, Shen, Langhans, & Tuan, 2019), skin (Saulite et al., 2017), adipose (Kohli et al., 2019), and dental tissues (Sharpe, 2016), as well as the peripheral (Yang et al., 2019) and cord blood (Xie, Liu, Chen, & Liu, 2019). Several surface markers, including CD73, CD105, and CD90, have been frequently

used to identify these cells (C.-S. Lin, Xin, Dai, & Lue, 2013). Studies have shown that MSCs play supportive roles for other cell types (Bielby, Jones, & McGonagle, 2007; Maltman, Hardy, & Przyborski, 2011). Promotion of tissue damage repair, organelle and protein transfer to other cells via nanotube tunnel formation, and hemostasis adjustment of the living microenvironment through their production of exosomes and other soluble mediators are only some among many critical roles of MSCs concerning their physiological environment (Spees, Lee, & Gregory, 2016).

Moreover, MSCs act as double-edged swords, playing roles as major culprits in the pathogenesis of many conditions like cancer (Goldstein, Reagan, Anderson, Kaplan, & Rosenblatt, 2010), metabolic disorders (D. Gao et al., 2014), and hepatic failure (Baertschiger et al., 2009). Recent studies have shed light on the immunomodulatory functions of MSCs, as well. A substantial amount of data suggests that MSCs and immune cells are involved in an important mutual cross-talk and the alteration of such an interplay is responsible for some diseases, as mentioned earlier.

Natural killer (NK) cells are important cells of the innate immune system (Cerwenka & Lanier, 2016) for which, based on their expression of the CD56 marker, two subpopulations have been identified (Jacobs et al., 2001): (a) $CD56^{dim}$ cells, the major cells with significant cytotoxic activities (Moretta, 2010) and (b) $CD56^{bright}$ NK cells, which are known to be major producers of cytokines such as interferon-γ (IFN-γ; Michel et al., 2016). It is important to note that NK cells mainly exert their cytotoxic functions via their release of granzymes and perforin (Vivier et al., 2011). On the other hand, MSCs exert their modulatory effects in several ways, mainly including direct cell-to-cell contact (Menge et al., 2013) as well as their production and release of their soluble factors such as exosomes (Lai et al., 2010). Depending on the way through which MSCs choose to interact with their target cells, they may exert variable effects. There is a great deal of evidence indicating that MSCs can be powerful therapeutic tools for many immune-related disorders due to their immune system-regulating effects (F. Gao et al., 2016). Acknowledging the fact that NK cells play pivotal roles in antitumor immunity (Böttcher et al., 2018), transplantation (López-Botet et al., 2017), autoimmunity (Gianchecchi, Delfino, & Fierabracci, 2018), and many other immune system-related disorders, it seems necessary to acquire a deep understanding of the possible crosstalk(s) between MSCs and NK cells. On such a basis in the present study, we have reviewed the MSC–NK cell crosstalk mechanisms and the various contexts through which MSCs can change the activity of NK cells. Moreover, the therapeutic importance of such interactions has been outlined.

2 | MECHANISMS OF MSC–NK CELL INTERACTIONS

MSCs have unique properties that make them promising therapeutic tools to be potentially utilized in many medical areas like regenerative medicine (Bunpetch et al., 2019) and for the treatment of immune system-mediated disorders (Gomzikova, James, & Rizvanov, 2019). They can differentiate into several cell lineages and have been shown to interact with diverse immune cells, including T cells (Kiernan et al., 2020), B cells (Carreras-Planella, Monguió-Tortajada, Borràs, & Franquesa, 2019), dendritic cells (DCs; Shahir et al., 2020), monocytes (Mansouri et al., 2019), and NK cells (Yan et al., 2019). In this regard, NK cells as imperative arms of the innate immune system, which play major roles in many immunopathological conditions like autoimmunity (Hudspeth et al., 2019), tumor (X. Zheng et al., 2019), transplantation (Ashraf et al., 2019), graft versus host disease (Arvindam, Aguilar, Felices, Murphy, & Miller, 2019; Ullrich et al., 2016), graft versus leukemia (Arvindam et al., 2019), and immune system-mediated abortion (X. Zhao et al., 2018), have particularly attracted the attention of scientists to explore their crosstalk with MSCs. Although there is a great deal of evidence supporting the immunosuppressive effects of MSCs on NK cells (De Miguel et al., 2012), there are interestingly several studies with conflicting results revealing a stimulatory role for these cells in terms of their effects on different NK cell functions, such as cytotoxicity, proliferation, and cytokine secretion (Abumaree et al., 2019; Boissel, Tuncer, Betancur, Wolfberg, & Klingemann, 2008; Thomas et al., 2014). These controversial findings may be the result of variations in the sources from which MSCs have been obtained (Ribeiro et al., 2013), the different MSC:NK ratios used in each study (H. F. Wang, Shi, & Ren, 2012), and variations in vitro culture conditions (Abdelrazik, Spaggiari, Chiossone, & Moretta, 2011). In addition to the NK-cell directed effects of MSCs, NK cells have been shown to exert cytotoxic effects on MSCs (Spaggiari, Capobianco, Becchetti, Mingari, & Moretta, 2006). Such a cytotoxic effect can take place in an inflammatory site like in a BM transplant in which inflammatory cytokines are predominant. The complex nature of such reciprocal interactions between MSCs and NK cells has prompted researchers to look for the responsible mechanisms in hopes of findings ways to therapeutically exploit the knowledge herein. This has been to the point that a number of clinical trials have been carried out to investigate the efficacy of stem cell therapy, taking advantage of the modulatory effects of MSCs. Therefore, a deeper understanding of MSC:NK cell interactions will be an inevitable requirement to exploit the findings for therapeutic purposes. The following section summarizes the different mechanisms through which MSCs can inhibit or stimulate NK cell functions (Figure 1).

2.1 | NK inhibition by MSCs

Studies on the role of MSCs in immune cell interactions commenced during the first years of the present century. Rasmuson Ringdén, Sundberg, and Le Blanc (2003) reported that MSCs are responsible for inhibiting the function of cytotoxic T lymphocytes but not NK cells. Nevertheless, in the next years, researchers revealed some NK cell-modifying effects of MSCs. It was soon revealed that MSCs could affect NK cells and their functions at least via two primary mechanisms: (a) direct cell-to-cell contact, and (b) secretion of soluble

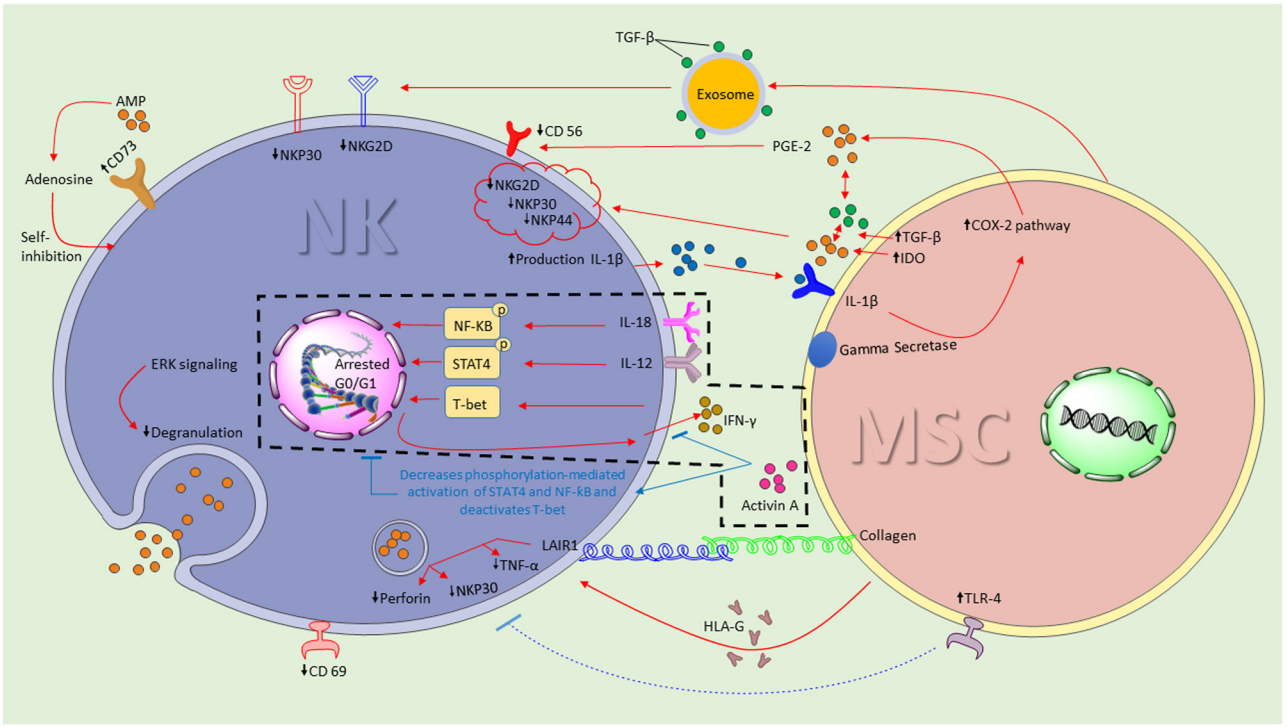

FIGURE 1 The mechanisms of MSC–NK cell crosstalk. The interactions between MSCs and NK cells consist of three primary mechanisms: (1) direct cell-to-cell contact between these cells; (2) release of soluble factors like exosomes, cytokines (IFN-γ, TGF-β, IL-1, etc.), and activin A; (3) indirect effects via modulation of other cells such as regulatory T cells (not included in the figure). Some of the MSC-mediated mechanisms of NK modulation are initiated by NK cells themselves, giving rise to a negative feedback regulatory mechanism for these cells. AMP, adenosine monophosphate; CD, cluster of differentiation; COX2, cyclooxygenase 2; ERK, extracellular-signal-regulated kinase; HLA-G, human leukocyte antigen G; IDO, indoleamine 2,3-dioxygenase; IFN-γ, interferon-γ; IL-1, interleukin 1; LAIR-1, leukocyte-associated immunoglobulin-like receptor 1; MSC, mesenchymal stem cell; NF-κB, nuclear factor-κB; NK, natural killer; PGE2, prostaglandin E2; STAT4, signal transducer and activator of transcription 4; TGF-β, transforming growth factor β; TLR-4, Toll-like receptor 4

factors (Spaggiari & Moretta, 2012). In vitro studies implied that the addition of cell culture medium of MSCs to NK cells could exert the same effects as those seen following the direct coculture of MSCs with NK cells (Fan et al., 2019; Spaggiari et al., 2008). However, it is essential to note that the extent of the observed effects, regardless of their inhibitory or stimulatory nature, was higher in the case of direct cell-to-cell contact than sole treatment with the soluble factors of MSCs. Direct contact of MSCs with NK cells results in the downregulation of 2B4 (CD244) and natural killer group 2-member D (NKG2D), two critical activating receptors on NK cells, which mainly mediate cytokine production and the cytotoxic function of NK cells (Sotiropoulou, Perez, Gritzapis, Baxevanis, & Papamichail, 2006). Soluble factors secreted by MSCs serve in an additive manner making MSCs more powerful in altering the function of NK cells. Prostaglandin E_2 (PGE2), an end-product of the cyclooxygenase 2 (COX2) pathway, is one of the most studied of these soluble agents. This molecule exerts its inhibitory effects through decreasing the expression of CD56 and γc-chain as well as via impairing the proliferation and cytotoxicity of NK cells (Sotiropoulou et al., 2006). Chatterjee, Marquardt, Tufa, Beauclair et al. (2014) showed that the inhibition of the COX2 pathway in umbilical cord-derived MSCs (UC-MSCs) could restore the function of NK cells, confirming the role of the COX2 pathway in PGE_2-mediated inhibition of NK cells by MSCs.

Interestingly, when NK cells were treated with the conditioned medium from MSC:NK coculture, NK cytotoxicity was suppressed more potently compared to the experiments in which the conditioned medium of sole MSC cultures was used for NK treatment. It was then pointed out that although soluble PGE2 was a potent agent responsible for NK inhibition by MSCs, its effect on NK cells was more pronounced when MSCs and NK cells were in direct cell-to-cell contact. The reason for these observations is that when MSCs and NK cells are brought in close contact, the production of higher amounts of PGE2 is stimulated, which consequently results in a more potent inhibitory effect (Chatterjee, Marquardt, Tufa, Beauclair et al., 2014). Another interesting finding was that the interleukin 1β (IL-1β), produced by NK cells per se, serves as an activator of the COX2 pathway, giving rise to the possibility that NK cells themselves are the first cells that communicate the initial orders to MSCs to form their inhibitory effects (a possible negative feedback mechanism). Gamma-secretase, a downstream mediator of IL-1β receptor, helps in the downstream signaling of such IL-1β-mediated COX activation. In other words, it seems that NK cells give some sort of permission to MSCs to be inhibited by these cells (Chatterjee, Marquardt, Tufa, Beauclair et al., 2014). Transforming growth factor β (TGF-β) is another major soluble factor produced by MSCs. This cytokine impairs NK cell proliferation and cytotoxicity and downregulates the expression of activating

receptors on the surface of NK cells. Indispensable cooperation has been shown to exist between PGE2 and TGF-β, which accounts for the complete impairment of NK cell activity (Sotiropoulou et al., 2006). It is also important to note that these two soluble factors are of particular importance in tumor microenvironment playing roles in tumor growth (Joshi, Zhou, Cuchens, & Jones, 2001) and metastasis (Villalba, Evans, Vidal-Vanaclocha, & Calvo, 2017); this reinforces the importance of MSC:NK interactions with regard to tumors and their progression. Activin A, another member of TGF-β superfamily produced by MSCs, has also been shown to suppress the function of NK cells through inhibiting IFN-γ production. This inhibition is dependent upon interruptions in IL-12 and IL-18 receptors' (IL-12R and IL-18R, respectively) downstream signaling; however, the downregulation of these receptors has not been reported in this case. Activin A also impairs the phosphorylation of several transcription factors like signal transducer and activator of transcription 4, nuclear factor-κB, and the DNA binding activity of T-bet, which have been shown to play pivotal roles in the production of IFN-γ by NK cells (Figure 1; Chatterjee, Marquardt, Tufa, Hatlapatka et al., 2014).

HLA-G, the non-classic class I human leukocyte antigen (HLA), is another soluble mediator of MSC-mediated NK inhibition. It has been revealed that MSCs express MHC-I molecules at low levels, while they do not express MHC-II molecules. In this regard, MSCs may secrete HLA-G as an inhibitory molecule. HLA-G production of MSCs not only can impair NK function in general but also protect MSCs from NK cell cytotoxic effects. It has been shown that the release of HLA-G by MSCs can diminish the cytotoxicity of NK cells against other neighboring cells via reducing their IFN-γ production and that neutralizing antibodies against HLA-G can reinvigorate the cytotoxicity of NK cells by 70%. The inhibitory role of HLA-G became even more pronounced when it was discovered out that this molecule in its secreted form can mediate the suppression of allogeneic T-cells as well as the induction of regulatory T cells. These findings are particularly important in transplantation to be potentially recruited to pacify the mediators of graft rejection (Selmani et al., 2008). Indoleamine 2,3-dioxygenase (IDO) is another soluble agent, which acts in synergism with both PGE2 and TGF-β to reduce the expression of the stimulatory receptors NKp30, NKp44, and NKG2D on NK cells. Importantly, similar to PGE2, the production of IDO in MSCs also depends on the assistance of NK cells. In this regard, it has been observed that the—cytokines produced by NK cells, mainly TNF-α and IFN-γ, can help MSCs to produce IDO (Spaggiari et al., 2008).

Later studies revealed novel interaction mechanisms between NK cells and MSCs obtained from other less conventional sources. For instance, in 2017, a novel cell-to-cell contact mechanism was found between MSCs and NK cells isolated from human decidua. This interaction was between collagen, produced by decidual mesenchymal stem cells (DMSCs) and its ligand, leukocyte-associated immunoglobulin-like receptor 1, on NK cells. Such an interaction between DMSCs and NK cells results in decreased expression of TNF-α and NKp30 and reduces perforin secretion by NK cells. This MSC-mediated suppressive effect is among the basic mechanisms behind a safe pregnancy (Fu et al., 2017).

In 2019, in pursuit of an alternative tool to therapeutically exploit the desirable effects of MSCs more safely, a study was conducted in which exosomes released by MSCs were used to see whether or not MSC-like effects could be elicited independently of their cells of origin. Exosomes are membranous structures of nano size (30–90 nm) and have recently attracted a great deal of attention as intercellular mediators carrying bioactive contents, such as microRNAs (miRNAs), cytokines, and growth factors. These nanosized vesicles, being shed from almost every cell type in the human body, play major roles in a variety of physiological and pathological processes (Moloudizargari et al., 2019; Moloudizargari, Asghari, & Abdollahi, 2018). Exosomes isolated from fetal liver-derived MSCs have been shown to diminish NK cell proliferation, activation, and differentiation mostly via their surface-associated TGF-β. In fact, the exosomal TGF-β downregulated the stimulatory receptors NKG2D and NKp30 on the surface of NK cells. It is suggested that MSC-derived exosomes are even better alternatives to MSCs since they possess the capability to inhibit NK cell functions without the need for their cells of origin. In spite of attractive perspectives into the MSC therapy of many medical conditions, there are important safety concerns regarding their use in clinical practice. Stem cells can potentially form teratomas, chimeras, tumors, and may also exert immunogenicity inside the human body under certain circumstances. As a result, cell-free alternatives like MSC exosomes are, in some ways, advantageous to MSCs as potential therapeutic tools in clinical practice (Fan et al., 2019).

Other subtypes of MSCs, such as tumor-associated MSCs, exert their effects through other distinct mechanisms. For instance, MSCs isolated from acute myeloid leukemia patients and lung cancer tissues showed overexpression of Toll-like receptor 4 (TLR-4) compared to normal BM-derived MSCs. Such an overexpression could help tumor-MSCs induce an immunosuppressive microenvironment (Lu et al., 2015). There are other less commonly confirmed mechanisms through which MSCs can diminish NK cell cytotoxicity and inflammatory function. MSCs induce the overexpression of CD73, an enzyme on the surface of NK cells capable of suppressing NK cell activity via converting ATP to adenosine. Through such a mechanism and as a result of being affected by MSCs, $CD73^+$ NK cells can inhibit either themselves or other adjacent NK cells in autocrine and paracrine manners, respectively (Chatterjee, Tufa et al., 2014). It has also been shown that MSCs can downregulate the expression of CD69, an activation marker on the surface of NK cells. Moreover, MSC-treated NK cells display an apoptotic characteristic defined by an arrest in their G0/G1 phase of growth (Li et al., 2015).

In addition to NK cell functions, which are suppressed following exposure to MSCs, the function of other immune cells like $CD8^+$ T cells also do not remain unaffected by MSCs. Parallel results show that MSCs impair the activation of $CD8^+$ T cells in the same manner as has been stated for NK cells, such as PGE2, IDO, and TGF-β production. Moreover, the NKG2D receptor on the surface of these cells is mainly affected by alterations in the expression of major histocompatibility complex class 1-related chain A/B (MICA/B) on MSCs, which is supposed to be the main mechanism of inhibition in

these cell types (M. Li et al., 2014). Other studies have revealed that MSCs can also interfere with intracellular signaling of NK cells, such as the extracellular-signal-regulated protein kinases 1 and 2 pathway, which is necessary for the cytolytic degranulation of NK cells (Giuliani et al., 2011).

In addition to the aforementioned mechanisms, the results of other in vitro studies indicate that MSCs can suppress NK cell activity through interacting with other immune cells. For example, in an interesting study, it was observed that the percentage of $CD4^{+}CD25^{+}$ regulatory T cells in an MSC–NK coculture and, consequently, the extent of NK cell inhibition increased as they elevated the ratio of MSCs to NK cells. This indicated that the induction of regulatory T cells might be another mechanism involved in the inhibition of NK cell function by MSCs. It can also be concluded that there are additional mechanisms of NK cell inhibition by MSCs other than direct cell-to-cell contact and soluble factors, which can only be uncovered in vivo, calling for further *animal* studies to precisely study these mechanisms (Li et al., 2009).

2.2 | NK stimulation by MSCs

Putting aside the widely studies inhibitory effects of MSCs on NK cell functions, there still exist a few conflicting studies reporting completely opposite findings. These studies indicate that MSCs, under certain conditions, can potentially invigorate NK cell functions and increase their expansion (Boissel et al., 2008). Experimental conditions such as the MSC:NK ratio in culture, cell concentrations used, the quality of prestimulated NK cells, and coculture incubation time can affect the direction and quality of the interactions between MSCs and NK cells. Moreover, the methods by which NK cells are stimulated before their coculture with MSCs are another determining factor. The results of a study indicated that MSCs can induce secretion of IFN-γ by NK cells in the presence of IL-12 and IL-18. These conflicting findings show that whether or not MSCs stimulate the cytotoxic function of NK cells depends largely on the MSC:NK ratios used (Thomas et al., 2014). In line with this, MSCs can increase the antitumor function of NK cells at low doses, while these cells tend to suppress the activity NK cells at high doses (H. F. Wang et al., 2012). The sources from which the MSCs and NK cells are isolated are also among other important factors that determine what types of responses to expect. For instance, DCs exposed to UC-MSCs were found to upregulate ligands for NK cell stimulatory receptors and, therefore, can be killed by NK cells (Y. Zhao, Cao, & Chen, 2013). The inhibitory power of MSCs can even vary among different sources. For instance, UC-MSCs, BM-MSCs, and adipose tissue (AT)-MSCs were found in a study to inhibit $CD56^{dim}$ NK cells, while only BM-MSCs and AT-MSCs could affect the function of $CD56^{bright}$ NK cells. It has been proven that amongst these cells, AT-MSCs possess the highest ability to inhibit NK cells (Ribeiro et al., 2013). These conflicting results warrant further studies to be carried out considering various influencing factors too, more precisely, determine the direction and quality of MSC-mediated effects on NK cells and vice versa.

2.3 | NK cytotoxicity on MSCs

MSCs can not only alter the cytotoxic effects of NK cells on other cell types, they can, per se, be the targets of NK cells. Whether an MSC remains unaffected or is killed by an NK cell can be fate determining, since it determines whether or not the MSC can survive to induce its likely modulatory effect on NK cells. It is also particularly important when MSCs are used as therapeutic tools, in which case they are expected to exhibit certain effects of interest rather than simply being killed by the NK cells that they may encounter in the body. Spaggiari et al. (2006) demonstrated that the stimulatory receptors on NK cells can recognize several types of ligands on the surface of MSCs such as poliovirus receptor and Nectin2, ligands for DNAM and ULBP, an NKG2D ligand. Moreover, axillary molecules like NKp30 and NKp46 were shown to cooperate with other activating receptors of NK cells during the process of MSC killing. In addition, it has been found that activated NK cells have the power of killing MSCs, while resting NK cells do not possess such a potential. Moreover, preconditioning of MSCs with IFN-γ could protect MSCs from being killed by NK cells, suggesting the role of IFN-γ in increasing the expression of HLA-I on MSCs. These results show that IFN-γ treatment of MSCs before their infusion to patients could be a desirable option in the context of transplantation (Spaggiari et al., 2006). It was then observed that activated NK cells can kill both allogenic and autologous MSCs, giving rise to the notion that the inhibitory effect of HLA-I is not adequate to protect MSCs from NK cytotoxicity and that autologous MSCs are as prone as allogenic MSCs to NK cytotoxicity. In this view, there seems to be no difference in using autologous or allogenic MSCs in transplantation since they are similarly immunogenic for NK cells (Crop et al., 2011). However, there still exists a puzzling open question, which remains to be addressed: why are not MSCs always killed by NK cells in vivo anyway? The answer to this question is that MSCs can employ mechanisms to protect themselves from being killed by NK cells both in vivo and in vitro. For instance, the study of Giuliani et al. (2014) showed that TLR can be one of these molecules. Their results showed that TLR-3-primed MSCs are not susceptible to NK killing, revealing that these MSCs can activate matrix metalloproteinases, which result in decreased expression of MICA on their surfaces (Giuliani et al., 2014). MSCs can also receive protection from other immune cells like monocytes to survive against NK cells. Monocytes can produce several cytokines such as TNF-α, IL-6, and vascular endothelial growth factor, which can support the differentiation of MSCs. Moreover, they can protect MSCs against NK cytotoxicity via inducing the production of IFN-γ by NK cells and diminishing their cytotoxic functions (Jewett et al., 2010). Another possibility is the difference between in vitro and in vivo experimental conditions. It is likely that either NK cells cannot reach the threshold of activation or MSCs may highly express HLAs on their surfaces in vivo. Acknowledging these findings, due to the promising prospects into MSC-based therapies in many clinical trials of transplantation or tumor immunotherapy, more studies are required to uncover more aspects of the complex crosstalk between NK cells and MSCs.

3 | MSC–NK INTERACTIONS IN DIFFERENT PATHOLOGIES

3.1 | MSC–NK interactions in malignancies

In addition to their well-known properties, such as regeneration ability, MSCs possess some other exceptional properties, which make them excellent tools to be used in a wide variety of medical areas. The inability of MSCs to stimulate an intense immune response (Lee et al., 2014), their potential to differentiate into diverse cell lineages (Mackenzie & Flake, 2001), and their pivotal roles in the pathogenesis of different conditions like tumors (Suzuki et al., 2011) as well as in the success of organ transplantation (Casiraghi, Perico, & Remuzzi, 2018) has made these cells exciting tools to be utilized in immunotherapy. The tumor microenvironment is full of MSC-derived cells capable of suppressing the antitumor immune response in those specific sites (Studeny et al., 2004). An excellent example of these cells is tumor stromal cells (TSCs), which share functional and morphological characteristics with MSCs. This gives rise to the possibility that MSCs may most probably be the source of these stromal cells (Wülling, Delling, & Kaiser, 2003). TSCs have been shown to negatively affect the critical antitumor immune cells like NK cells by downregulating their surface expression of NKp44 and NKp46 (Johann et al., 2010). In parallel to these findings, it was revealed that these MSC-derived suppressor cells are responsible for the immune evasion of pediatric tumors like neuroblastoma (Johann et al., 2010). Neuroblastoma cells are considered to be good targets of NK cells in view of the fact that they express low levels of HLA molecules (Cantoni et al., 2016). Nevertheless, they have a significant immune system suppressing properties due to the abundance of immunosuppressive cells like TSCs within their microenvironment (Pelizzo et al., 2018).

On one hand, it is known that the adoptive infusion of specific immune cells like cytokine-activated NK cells to patients with cancer following HSC transplantation is a promising approach to eliminate any residual tumor cells and to achieve a better therapeutic outcome (Hontscha, Borck, Zhou, Messmer, & Schmidt-Wolf, 2011). On the other hand, it has been previously revealed that BM transplants contain MSCs, which have been shown to survive long term in the host. Hence, it would be quite logical to postulate that these surviving MSCs in the body of the transplant recipient may confer suppressive effects on the NK cells subsequently transferred to the patient to eliminate the residual disease. Accrediting these interesting findings in mind, Li et al. (2011) carried out a study to uncover the possible modulatory effects of these MSCs on the cytokine-activated killer cells infused to patients. Their results were interesting indicating that the simultaneous injection of MSCs and cytokine-induced killer (CIK)/NK cells in their experimental setting could enhance the MSCs-mediated suppression of NK cells due to a prolonged interaction, which may have most probably taken place between MSCs and NK cells in the liver and lungs (Table 1; Li et al., 2011). Just a year before this study, the same team had shown that coinfusion of BM-derived MSCs with CIK/NK cells resulted in their interaction within the reticuloendothelial tissues of lungs and liver, confirming the possibility of the abovementioned suppressive crosstalk between NK and MSCs, which limited the therapeutic efficacy of the experimental adoptive NK transfer (Li et al., 2010).

Studies have revealed that in the context of tumors, tumor-associated MSCs (T-MSCs) are among the principal cells responsible for immunosuppression via their production of PGE2 (Lazennec & Lam, 2016). It has also been proven that T-MSCs, via direct cell-to-cell contact with NK cells, induce a significant inhibitory activity by downregulating the expression of NKG2D, DNAM-I, and NKG2A on NK cells. In this context, Galland et al. (2017) performed a comparative study on T-MSCs directly derived from lung squamous cell carcinoma tissues, MSCs from adjacent normal tissues, and BM-MSCs to conduct a thorough investigation of the suppressive capabilities of these MSCs of different origins (Galland et al., 2017). It was shown that unlike the BM-MSCs, which possessed strong immunosuppressive effects on NK cells, those isolated from normal tissues were less suppressive. This is while their results showed that the T-MSC of the tumor-bearing tissues close to the normal sites from which normal MSCs were obtained, demonstrated more potent suppressive features similar to the BM-MSCs. It was then pointed out that the inflammatory microenvironment of the tumor site induced by tumor cells (Valenti et al., 2007), stromal cells (Pistoia & Raffaghello, 2014), and even immune cells (Han, Shi, & Liu, 2016) had driven the MSCs of the tumor tissues towards regaining potent BM-MSC-like suppressive functions.

It has also been shown that T-MSCs possess the ability to change the phenotype of NK cells. Moreover, they are able to increase the ratio of $NK^{CD56dim}$:$NK^{CD56bright}$ cells, serving in favor of the tumor via skewing the advantage from $NK^{CD56bright}$ cells, which are well-known to be better producers of IFN-γ (a critical cytokine utilized by immune cells to defeat tumors; Michel et al., 2016), towards $NK^{CD56dim}$ cells, which are less protective against tumors. In parallel with these findings, MSCs just like macrophages, can be subdivided into two groups each demonstrating distinct activities; the first class, MSC1, which tend to produce proinflammatory cytokines and the second class, MSC2, that exhibit suppressing effects on the immune cells (Waterman, Tomchuck, Henkle, & Betancourt, 2010).

The dual immunostimulatory and immunosuppressive effects of MSCs on NK cells have been an attractive issue to researchers who have made efforts to clarify the roles of MSCs in the context of malignancies. On the basis of results of a study by Entrena et al. (2015), MSCs isolated from low-/intermediate-risk acute lymphoblastic leukemia (ALL) patients not only do not suppress NK cells, but also stimulate the cytotoxicity of these cells. On the other hand, in high-risk ALL patients, the results were entirely opposite revealing that the MSCs of these patients can inhibit antitumor functions of NK cells similar to BM-derived MSCs. Interestingly, it has been shown that the stimulatory function of MSCs is gained after exposure to malignant cells, being affected by the particular tumor microenvironment (Entrena et al., 2015). As a conclusion, MSCs do not necessarily play deleterious roles in tumors, a finding that calls for a deeper understanding of these important role players before

TABLE 1 The mechanisms of MSC–NK cell interactions and their importance in various contexts

Context/intervention	Effector cell/ source	Mediator(s)/mechanism(s)	Target cell/ source	Net outcome(s)	Therapeutic importance	Reference
Expansion of MSCs in human platelet lysate (FBS alternative) for clinical application	MSCs/NS	• ↓ NK-activating ligands on MSCs: DNAM-1 ligands, PVR and Nectin-2; NKG2D ligand, ULBP3 • ↓ Expression of adhesion molecules: CD49d and αvβ3 • ↓ Expression of fibroblast-associated protein • ↓ PGE_2 production • ↑ IL-8, IL-6, and RANTES secretion	NK cells/NS	↓ The inhibitory capacity of MSCs on NK proliferation and cytotoxicity	Limiting the immunomodulatory efficacy of MSCs for clinical use	Abdelrazik et al. (2011)
Preconditioning NK cells with MSCs	MSCs/human placenta	• ↑ Expression of inflammatory and antitumor molecules	NK cells/NS	• ↑ Cytotoxic efficacy of NK cells against cancer cells	The potential application of placental MSCs to boost antitumor efficacy of NK cells	Abumaree et al. (2019)
Activation of NK cells with IL-2	NK cells/NS	• Via a mechanism involving CD69	MSCs/human placenta	Lysis of MSCs	–	
Expansion of NK cells in the presence of UC-derived MSCs	MSCs/human Wharton's jelly	• Cytokine-mediated stimulation[a]	NK cells/human cord blood	↑ Ex vivo expansion of NK cells	Increasing expansion of NK cells with desired characteristics for adoptive immunotherapy of tumors	Boissel et al. (2008)
Studying NK inhibition mechanisms by MSCs	MSCs/human UC	• Via production of soluble factors by MSCs: – PGE2 – Activin A: ↓ IFN-γ production • ↑ CD73 expression on NK cells by MSCs: Promotion of adenosine production	NK cells/ Human PBMC	↓ NK cell cytotoxicity	• A potential application of MSCs for GVHD prevention and graft rejection • Exploiting the immunomodulatory potential of MSCs for the alleviation of inflammation	Chatterjee, Marquardt, Tufa, Beauclair et al. (2014); Chatterjee, Marquardt, Tufa, Hatlapatka et al. (2014); Chatterjee, Tufa et al. (2014)
MSC lysis by NK cells	NK cells/ Human PBMC	• Inverse correlation of HLA-I expression on MSCs with their susceptibility to NK killing	MSCs/AT	Lysis of MSCs	Optimizing the efficacy of MSC therapy in organ transplantation via helping their survival against NK cytotoxicity	Crop et al. (2011).

(Continues)

TABLE 1 (Continued)

Context/intervention	Effector cell/ source	Mediator(s)/mechanism(s)	Target cell/ source	Net outcome(s)	Therapeutic importance	Reference
Effect of MSCs on the antifibrotic function of NK cells	MSCs/rat BM	• Recruitment of NK cell population	NK cells/ intrahepatic	↑ Expansion of intrahepatic NK cells	The potential use of MSCs for the treatment hepatic fibrosis	Duman et al. (2019)
Cancer: ALL	MSCs/low/ intermediate-risk ALL patients	• High expression of costimulatory molecules like CD40 or CD86 on ALL-MSCs	NK cells/human blood	↑ Cytotoxicity of NK cells	The potential use of tumor MSCs to boost antitumor NK response	Entrena et al. (2015)
Using MSC exosomes for NK inhibition	MSCs/fetal liver	• Exosome-associated TGF-β	NK cells/Human PBMCs	↓ Proliferation, activation, and cytotoxicity of NK cells	The potential use of MSC exosomes as tools of immunosuppression	Fan et al. (2019)
Studying NK inhibition mechanisms by MSCs	MSCs/human decidua	• Collagen-mediated increase in the expression of KIR2DL1 and IL-4 • ↓ NKp30 expression and TNF-α production of NK cells	NK cells/decidual NK cells	↓ Cytotoxicity of NK cells	Potential use/targeting of MSCs in immune-mediated pregnancy disorders	Fu et al. (2017)
Cancer: Lung cancer	MSCs/human lung tumor	• PGE2-mediated inhibition	NK cells/human PBMCs	↑ Ratio of $CD56^{dim}$/ $CD56^{bright}$ NK cells ↓ IFN-γ production	Targeting tumor MSCs to diminish immunosuppressive microenvironment of tumors	Galland et al. (2017)
MSCs protection against NK cell killing	NK cells/human blood PBMC	• Increasing MICA shedding by MSCs to survive against NK cells	MSCs/Human BM and H1 and H9 embryonic stem cell lines	↓ Cytotoxicity of NK cells against MSCs and other target cells	NS	Giuliani et al. (2014)
Studying NK inhibition mechanisms by iPS-derived MSCs	MSCs/H9 and SA-01-ES cell lines	• Via the inhibition of the ERK1/2 signaling pathway • ↓ Activation markers on NK cells	NK cells/Human PBMCs	↓ Cytotoxicity, proliferation, and activation of NK cells	Using iPS-derived MSCs in therapeutics such as prevention of allograft rejection	Giuliani et al. (2011)
Studying NK inhibition mechanisms by preactivated MSCs	MSCs/C57BL/ 6 BM	• Via PGE2 production	NK cells/mouse portal vein-isolated NK cells	Preactivated but not naïve MSCs inhibit NK cell ↑ Graft survival	Potential cotransplantation of preactivated MSCs for graft survival	Ishida et al. (2019).
Survival of MSCs against NK cytotoxicity by monocytes	NK cells/human PBMCs	• Monocyte mediated inhibition in NK cell killing abilities via: ↓ Cytotoxic function	MSCs/NS	Protection of MSCs against NK killing by monocytes	NS	Jewett et al. (2010)

TABLE 1 (Continued)

Context/intervention	Effector cell/ source	Mediator(s)/mechanism(s)	Target cell/ source	Net outcome(s)	Therapeutic importance	Reference
		↑ IFN-γ production				
Studying the effect of MSC: NK ratio variations on NK function	MSCs/human BM	– Inhibition mechanisms: • ↓ CD69 on NK cells • ↑ NK apoptosis • Cell cycle arrest • ↑ Regulatory T cell ratio in the coculture system – Activation mechanisms: NS	CIK/NK cells/ cord blood	↑ NK cell activation at low MSC: NK cell ratios ↓ NK cell activation at high MSC: NK cell ratios	Highlighting the importance of proper dosing of MSCs for different therapeutic purposes	Li et al. (2009)
The effects of time and site of MSC injection on injected NK/CIK cells	MSCs/human BM	NS	CIK/NK cells/ Cord blood	↑ NK cell inhibition following preinfusion of MSCs ↓ NK cell inhibition following separate injection of MSCs and NK cells	Adjusting MSC and NK/CIK infusion parameters to optimize the GVL effect of NK cells	Li et al. (2010)
Studying NK inhibition mechanisms by MSCs of various origins	MSCs/AML patients, normal BM, and Lung tumor	• TLR-4 upregulation by MSCs • Downregulation of the NKG2D receptor on NK cells	NK cells/human PBMCs	Stronger NK inhibition by MSCs with upregulated TLR-4 in the tumor microenvironment	Potential TLR-4 modification of MSCs for the elicitation of desired inhibitory outcomes	Lu et al. (2015)
Addition of dexamethasone to MSC: NK coculture	MSCs/BM	• ↓CD69 expression • Inhibition of STAT5 phosphorylation • Inhibition of IFN-γ and perforin production	NK cells/human PBMCs	Augmentation of NK cell inhibition power of MSCs	Potential pharmacotherapies to alter MSC: NK interactions	Michelo et al. (2016)
Effect of MSCs on NK cell recruitment	MSCs/human and mouse BM	• ↓ NK cell activation • ↓ Expression of sphingosine-1-phosphate receptor type 5 in vivo and in vitro • ↓ NK cell accumulation • ↓ Chemotaxis of NK cells	NK cells/human NK cell line YTs and mouse liver	↓ NK cell recruitment ↓ Poly I:C-induced liver injury	Therapeutic potential of MSCs in the treatment of NK-cell mediated disorders	Qu et al. (2015)
Effect of MSCs on NK cell cytotoxicity	MSCs/human BM	–	NK cells/human	No efficient inhibition on NK cell cytotoxicity	NS	Rasmusson et al. (2003)

(Continues)

TABLE 1 (Continued)

Context/intervention	Effector cell/ source	Mediator(s)/mechanism(s)	Target cell/ source	Net outcome(s)	Therapeutic importance	Reference
Studying NK inhibition mechanisms by MSCs	MSCs/human BM, AT, and Wharton's jelly	• ↓ Production of TNF-α and perforin	NK cells/ Human BM	• Potent inhibition of $CD56^{dim}$ cells by BM-MSC, AT-MSC, and UC-MSCs • ↓ activation of $CD56^{bright}$ cells by BM- and AT-MSCs	Clarifying the differences between different MSC sources for clinical use and helping to choose the best source of MSCs for therapeutic approaches	Ribeiro et al. (2013)
Studying NK inhibition mechanisms by MSCs	MSCs/human BM	• HLA-G mediated suppression of cytolysis and interferon-γ secretion	NK cells/human PBMCs	Suppression of NK cell activity	The potential use of MSCs to prevent GVHD	Selmani et al. (2008).
Studying NK inhibition mechanisms by MSCs	MSCs/human BM	• PGE2-mediated downexpression of NKp30, NKp44, and NKG2D	NK cells/human PBMCs	• Inhibition of the cytokine-induced proliferation of freshly isolated NK cells • Inhibition of cytotoxic activity and cytokine production	NS	Spaggiari et al. (2008)
IL-2 mediated activation of NK cells	NK cells/human PBMCs	• Via NKp30, NKG2D, and DNAM-1	MSCs/human BM	MSC lysis by activated NK cells (but not fresh NK cells)	NS	Spaggiari et al. (2006)
Mechanisms of NK activation by MSCs	MSCs/human PBMCs	• ↑ Expression of IL-12Rβ • ↑ Phosphorylation of STAT4 • ↑ IFN-γ production by NK cells	NK cells/NK92 cell line	NK activation by MSCs (dose-dependent)	Exploiting the NK stimulation potential of MSCs for infectious diseases	Thomas et al. (2014)
Mechanisms of NK activation by MSCs	MSCs/human PBMCs	• ↑ Formation of NK cells • ↑ Activation of NK cells	NK cells/NS	• NK cell activation by MSCs at low concentrations of MSCs • Inhibition of NK cells at high numbers of MSCs	The potential use of MSCs in tumor therapy	H. F. Wang et al. (2012)
Sirt1-overexpressed MSCs	MSCs/mouse BM	• ↑ Recruitment of NK cells and macrophages into the tumor site • ↑ CXCL10 and IFN-γ production	NK cells/Mouse	Suppressing tumor growth of prostate and breast cancer partly via increasing NK recruitment	Inducing unique genes in MSCs to boost NK response in tumors	Yu, Liu et al. (2016); Yu, Zhang et al. (2016)

TABLE 1 (Continued)

Context/intervention	Effector cell/ source	Mediator(s)/mechanism(s)	Target cell/ source	Net outcome(s)	Therapeutic importance	Reference
Activation of NK cells against DC	MSCs/UC	• Inhibiting of DC maturation by MSCs • Upregulating ligands for NK cell activatory receptors on DCs	NK cells/NS	NK activation following exposure to UC-MSC-modified DCs	NS	Y. Zhao et al. (2013)

Abbreviations: ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; AT, adipose tissue; BM, bone marrow; CD, cluster of differentiation; CIK, cytokine-induced killer; DC, dendritic cell; ERK1/2, extracellular-signal-regulated protein kinases 1 and 2; FBS, fetal bovine serum; GVHD, graft versus host disease; GVL, graft versus leukemia; HLA-I, human leukocyte antigen-I; IFN-γ, interferon-γ; IL-2, interleukin 2; IL-4, interleukin 4; IL-6, interleukin 6; IL-8, interleukin 8; iPS, induced pluripotent stem cell; MICA, major histocompatibility complex class 1-related chain A; MSC, mesenchymal stem cell; NK, natural killer; NKG2D, natural killer group 2-member D; NS, not specified; PBMC, peripheral blood mononuclear cells; PGE2, prostaglandin E2; RANTES, regulated upon activation, normal T cell expressed and presumably secreted; TLR-4, Toll-like receptor 4; UC, umbilical cord.

[a]Not tested/hypotheses.

any therapeutic intervention targeting MSCs. Acknowledging the various modulatory effects of MSCs, many researchers have shown interest in finding other sources of MSCs with stimulatory properties for NK cells. In this context, it has been demonstrated that placenta MSCs will enhance the cytotoxic lysis of cancer MCF-7 cells by NK cells. Results indicate that although some stimulatory receptors of NK cells such as NKG2D, NKp30, and NKp46 are downregulated by these cells, another stimulatory receptor called DNAM, which can boost NK cytotoxicity against cancer cells, is upregulated (Widowati et al., 2019). Besides the efforts to find sources of MSCs with stimulatory effects on NK cells, researchers have also endeavored to engineer MSCs to elicit modulatory effects of interest on NK cells. Studies have shown that genetically engineered MSCs can be used as effective therapeutic tools in tumor therapy and even for drug delivery due to the infiltrating potential of these cells into the tumor-bearing sites (Ye et al., 2020). It was shown in two separate studies by the same team that the overexpression of SIRT-1 gene in MSCs can induce recruitment of NK cells in the tumor site of breast cancer and prostate cancer in vivo. Moreover, preconditioning of NK cells with SIRT-1-overexpressed MSCs can promote their antitumor activities via enhancing their IFN-γ secretion (Yu, Liu et al., 2016; Yu, Zhang et al., 2016).

In view of the fact that NK cells are essential tools frequently used in cancer immunotherapy (Geller & Miller, 2011), any effort to find precursors capable of differentiating into NK cells can be of great importance. MSCs, due to their broad differentiation potential, have been studied to check if they can be differentiated into NK cells. It has been shown in this regard that transfecting special miRNAs in MSCs can skew NK cell differentiation. Considering the previous findings that Mir-150 is upregulated in NK cells and can promote the cytotoxicity of NK cells, Karlitepe et al. (2017) showed in his study that transfecting mir-150 to adipocyte-derived MSCs can induce their commitment to NK lineage. The advantage of such a method is the availability of adipose tissue to be used as a source of MSCs isolation.

3.2 | MSC–NK interactions in hepatic disorders

The liver is also among the organs from which MSCs have been isolated (Y. Wang, Yu, Chen, & Li, 2016). Due to the role of MSCs in hepatic tissue repair, they have attracted attention to be used as tissue-repairing tools for hepatic disorders (Lou, Chen, Zheng, & Liu, 2017). MSCs contribute to hepatocyte differentiation via producing matrix metalloproteases, hepatocyte growth factor, and stem cell factor-1 (Wu & Tao, 2012). Moreover, there several reports on the intrahepatic interactions of MSCs and NK cells, both of which play key roles in the progression of liver diseases like cirrhosis or hepatic fibrosis (Volarevic, Nurkovic, Arsenijevic, & Stojkovic, 2014). Studies have shown that grafting BM-MSCs can be a potential and promising alternative for liver transplantation, which comes with various limitations (Leung, Chan, & Cheung, 2006). These MSCs possess a unique function, which can alleviate the progression of liver fibrosis via interacting with NK cells in the liver microenvironment (Duman et al., 2019).

It is also shown that BM-MSCs, following their interaction with NK cells, can downregulate their expression of sphingosine-1-phosphate receptor type 5, which is a crucial molecule for NK trafficking into the inflammatory sites (Qu et al., 2015). BM-derived MSCs can, therefore, accelerate the recovery of the injured liver. Besides the effect of MSCs on NK cells, these cells can also revive acute liver injury through inhibiting natural kill T (NKT) cells, which have been shown to aggravate the acute liver injury via producing IL-17 (Bandyopadhyay, Marrero, & Kumar, 2016). A study by Milosavljevic et al. (2017) showed that the administration of the medium from BM-derived MSC cultures could decrease the activity of NKT cells in an IDO-dependent manner. In parallel, another study showed that MSCs can suppress the function of NKT cells via a mechanism involving iNOS production, revealing a novel intermediate for the beneficial effects of MSCs in the liver (Gazdic et al., 2018). Given the important role of MSC in inhibiting NK and NKT cells, scientists look hopefully toward MSCs as novel therapeutic tools for the treatment of liver disorders.

3.3 | MSC–NK interactions in renal disorders

Renal ischemia–reperfusion injury is an inflammatory disorder, known as the main cause of acute kidney injury (Devarajan, 2006). NK cells have been shown to be among the cells that promote renal disease progression (Zhang et al., 2008). These cells can directly lyse the epithelial cells within the kidneys, making; therefore, their elimination/targeting seems to be a necessary measure toward a successful alleviation of clinical signs (L. Zheng, Gao, Hu, Yang, & Rong, 2019). It has been shown that the administration extracellular vesicles isolated from MSCs can reduce the percentage of NK cells in an ischemic kidney and can, this way, ameliorate the injury of the tubules. Such an effect is due to the downregulation of molecules responsible for NK trafficking into the injured kidney sites (Zou et al., 2016). These findings support the beneficiary role of MSCs and their soluble factors to be used for regenerative purposes in kidneys.

3.4 | MSC–NK interactions in organ transplantation

Besides their potential to be used in the treatment of various pathologies, MSCs can also be potentially used in transplantation due to their role in hindering allograft rejection via preventing apoptosis and inhibiting the harmful effects of NK cells (Nasr et al., 2015). Recent findings suggest that preactivated MSCs, but not naïve cells, can prolong the transplantation survival time of pancreatic islet grafts (Ishida, Ishiyama, Saeki, Tanaka, & Ohdan, 2019). On such a basis, it can be implied that the preconditioning of MSCs before the administration can augment the efficiency of their use in transplantation. It has also been shown that the administration of certain drugs such as dexamethasone can complement the function of grafted MSCs in transplantation (Michelo et al., 2016). Indeed, more studies are required to clearly uncover the effects of preconditioning MSCs or their combinations with novel drugs to improve their immunomodulatory effects with regard to NK cells.

3.5 | MSC–NK interactions in coronavirus disease 2019

As of August 10, 2020, it is now months that the world has been facing a rapidly spreading viral infection caused by a severe acute respiratory syndrome (SARS)-like virus of the coronavirus family designated as SARS-CoV-2 (novel coronavirus 2019 or coronavirus disease 2019 [COVID-19]). The emergency has raised the requirement to look for prompt therapeutic options to tackle the problem (Demaria et al., 2020). Given the fate-determining importance of the inflammatory cytokine-mediated pulmonary pathology, therapeutic interventions targeting the exaggerated cytokine storm has been among the options (Market et al., 2020). In this regard, NK cells, based on their immunophenotype, have been shown to possess dual roles in the context of COVID-19: an early protective antiviral role and a deteriorative inflammation-promoting role induced by certain subsets (Alrubayyi, 2020). It has also been shown that the protective subsets of NK cells are markedly decreased in patients with moderate or severe COVID-19, which is compensated by the increased cytotoxic activity of the existing NK cells and T lymphocytes (Jiang et al., 2020). In light is these findings, several studies were designed to boost the beneficial antiviral NK responses either via NK-stimulating therapies or adaptive NK transfer to the patients, a protocol resembling that of cancer immunotherapy (NCT04324996, NCT04280224, etc.). On the other side, however, several trials have made efforts to fight the COVID-19 immunopathology via MSC-based therapies to target the cytokine-producing cell populations including NK cells. Among them are two, phase 2 and phase 1 clinical trials in which UC-MSCs alone or in combination with oseltamivir and azithromycin are used, respectively, to fight the cytokine-mediated immunopathology of critically ill COVID-19 patients (NCT04457609 and NCT04269525). It is important to note that NK cells are among the cell populations which have been considered as targets of the therapy in these studies and that measuring the changes in NK cell counts are among the secondary endpoints. These studies are currently ongoing and the results are not available yet. Considering the dual role of NK cells in COVID-19, it is extremely important to determine the efficacy and possible risks of such NK-modulating interventions since they might deteriorate the dampened antiviral response of NK cells. In this regard, an early phase 1 trial is underway to determine the safety and effectiveness of MSC-based therapies for COVID-19 (NCT04371601).

4 | CONCLUSION AND FUTURE DIRECTIONS

MSCs and NK cells participate in a complex network of reciprocal interactions, crucial for maintaining their optimal functioning under physiological conditions. Modulation of NK cell function by MSCs as a

mechanism for the physiologic regulation of these cells is a good example of such beneficial interactions. Nonetheless, this mutual entanglement of MSCs and NK cells can be negatively affected by certain pathologies like malignancies in which the tumor microenvironment educates MSCs to elicit tumor-promoting effects. On the other hand, given the important roles of MSCs in modulating the NK-mediated responses in various organs, it seems quite logical to use MSCs as targeting tools for therapeutic purposes. Accordingly, a substantial understanding of the interactions between MSCs and NK cells under both physiological and pathological conditions and the underlying mechanisms can provide us the opportunity to exploit this knowledge in the treatment of a variety of malignancies and autoimmune and inflammatory disorders as well as in organ transplantation. In this context, we now know that MSCs and NK cells may interact via three major routes: (a) direct cell-to-cell contact, (b) via soluble mediators, and (c) indirectly through modulating the function of other regulatory immune cells like regulatory T cells. MSCs or their soluble factors can be administered exogenously to elicit the outcomes of interest; however, it is important to note that the conditions under which MSCs are prepared can largely affect their properties. For instance, preconditioning of MSCs with multiple agents before administration or their genetic manipulation with miRNAs can skew their functions towards our therapeutic aims. Therefore, the following minimal factors seem to be necessary to be taken into consideration in any study that aims to attribute any therapeutic effect(s) to erogenous MSCs: the source of MSCs, their culture conditions, and any genetic or pharmacological manipulation. Moreover, since some of the beneficial effects of MSCs are the results of their indirect interactions with other cell populations, it is recommended that animal studies be carried out rather than in vitro experiments in which only a limited fraction, the complex intercellular network can be mimicked. Finally, our knowledge of the fate-determining factors that influence the quality of MSC-mediated effects on NK cells is still in its infancy and further studies using well-defined conditions are warranted herein.

CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

AUTHOR CONTRIBUTIONS

Milad Moloudizargari conceived the idea and wrote the manuscript. Ali Govahi wrote the manuscript. Marjan Fallah edited and commented on the manuscript. Mohammad A. Rezvanfar provided technical assistance. Mohammad H. Asghari edited and supervised the manuscript. Mohammad Abdollahi edited and supervised the manuscript.

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