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REVIEW

Could cancer and infection be adverse effects of mesenchymal stromal cell therapy?

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Abstract

Multipotent mesenchymal stromal cells [also referred to as mesenchymal stem cells (MSCs)] are a heterogeneous subset of stromal cells. They can be isolated from bone marrow and many other types of tissue. MSCs are currently being tested for therapeutic purposes (*i.e.,* improving hematopoietic stem cell engraftment, managing inflammatory diseases and regenerating damaged organs). Their tropism for tumors and inflamed sites and their context-dependent potential for producing trophic and immunomodulatory factors raises the question as to whether MSCs promote cancer and/or infection. This article reviews the effect of MSCs on tumor establishment, growth and metastasis and also susceptibility to infection and its progression. Data published to date shows a paradoxical effect regarding MSCs, which seems to depend on isolation and expansion, cells source and dose and the route and timing of administration. Cancer and infection may thus be adverse or therapeutic effects arising form MSC administration.

Key words: Cancer; Infection; Mesenchymal stem cells; Therapy; Biosafety

Core tip: Mesenchymal stem cells (MSCs) derived from different origins have recently received much attention as potential therapeutic. However, such cells also appear to have essential functions in building and supporting tumor microenvironments. Here, we review the effect of MSCs on tumor establishment, as also susceptibility to infection and its progression. The literature reveals incongruity regarding the impact of MSCs on the development of cancer and infection; such paradoxical effect might be attributed to differences in isolation and expansion conditions, the source and dose of the cells, the administration route and its timing and host characteristics. MSCs immunomodulatory potential seems to be the leading mechanism responsible for such effects.

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INTRODUCTION

Multipotent mesenchymal stromal cells, also referred

to as mesenchymal stem cells (MSCs), were described for the first time half a century ago[1]. Such cells are distributed throughout the stroma of several organs *in vivo* whilst MSCs adhere to plastic *in vitro* and proliferate when stimulated by fetal bovine serum[1]. MSCs differentiate into mesodermal cells *in vitro* and *in vivo* (*i.e.*, adipocytes, chondrocytes, osteocytes and myocytes)[2]. They can also cross the germ line barrier and produce cells from endo- and ectodermal lineages, such property being known as cell plasticity[3].

MSCs are an ideal tool for cell therapy because they are easily procured from live donors[4] and can be efficiently expanded *ex vivo*[5]. The receptors do not need to have been conditioned before cell administration transplant[6], as in total bone marrow or hematopoietic stem cell transplant. Once administered intravenously, they are able to home onto and engraft into damaged tissue where they could become differentiated into tissue-specific cells, release trophic factors, promote neovascularization, manage oxidative stress and fibrosis, or trigger an anti-inflammatory response[7-11].

MSCs from the same individual (autologous) were administered into a human for the first time in 1995[12]; MSCs were safely allogeneically transplanted seven years later[13]. More than 350 clinical trials involving the use of MSCs are currently under way (www.clinicaltrials.gov) and no serious adverse events have been reported to date. Nevertheless, MSCs biosafety is still a major concern, particularly regarding the development of adverse event-related cancer and infection.

MSCs AND CANCER

MSCs might form tumors

Like any other cell, when MSCs are manipulated in the long-term they might have chromosomal aberrations and produce tumors in healthy animals[14]; this has mainly been reported regarding mouse cells, which require extensive cultures for producing a significant number of hematopoietic-free MSCs[14]. For instance, it has been shown that intravenously administered NOC/SCID bone marrow-derived MSCs embolize within the lung capillaries, expand and invade the lung parenchyma and form tumor nodules[15]. These lesions rarely contain lung epithelial cells but they have the characteristics of cartilage and immature bone resembling well-differentiated osteosarcoma.

No transformation has been proven so far for human MSCs when expanded properly *ex vivo* (*i.e.,* non-exhausted and not forced to cell crisis)[14]. The Canadian Critical Care Trials Group has recently published a meta-analysis of randomized, non-randomized, controlled and uncontrolled, phase Ⅰ and phase Ⅱ clinical trials[16]; no association between autologous or allogeneic MSCs administration and tumor formation was reported in the 36 studies reviewed by them. Nonetheless, longer follow-up is required to draw a final conclusion regarding human MSCs' tumorigenic potential.

MSCs may promote tumor growth

Human bone marrow-derived MSCs have increased the growth of ERAα positive breast cancer cell lines (T47D, BT474 and ZR-75-1) in an *in vitro* three-dimensional tumor environment, but have had no effect on an ERAα negative cell line (MDA-MB-231)[17]; however, the growth rate of another ERAα negative cell line (MDA-MB-468) was high in the presence of human MSCs. Another study has shown that both human fetal MSCs and human adipose-derived MSCs transplanted subcutaneously into BALB/c-nu/nu mice alone or together with tumor cell lines F6 or SW480 (ratio 1:1 or 1:10), favored the growth of these tumor cell lines[18].

Tumor cells obtained from primary breast cancer grown in the presence of human bone marrow-derived MSCs (ratio 1:1) and tested in secondary mice have been seen to have greater tumor-producing ability than cells obtained from primary tumors and grown in the absence of MSCs[19]. Besides, tumor incidence and/or size[18,20,21] as well as tumor vascularity[22] have all increased when breast, lung, colon or prostate tumor cells have been co-injected with human adipose-derived or bone marrow-derived MSCs. The same has been proven for osteosarcoma, melanoma and glioma tumor cells[23]. Another interesting observation concerned adipose tissue implant adjacent to lung cancer or Kaposi sarcoma xenografts resulting in a substantial increase in tumor size along with the appearance of stromal cells from the implant; adipose-derived MSCs can thus promote tumor growth[24].

MSCs' innate tropism for established tumors has been widely reported[24], yet the mechanism behind it still remains to be fully elucidated[25]. The explanation advanced to date is that tumors behave as unresolved wounds as their stroma closely resemble healing granulation tissue and they produce cytokines, chemokines and other chemoattractants[26] and MSCs chemotactic properties are similar to those of leukocytes[27,28]. MSCs tropism for tumors has been successfully exploited for the delivery of antitumor agents in animal models of lung and breast cancer and melanoma and glioma[25].

MSCs might promote metastasis

Breast cancer cells co-cultured with human bone marrow-derived MSCs (ratio 1:1) up-regulate the expression of oncogenes and proto-oncogenes associated with tissue invasion, angiogenesis and apoptosis (*i.e.,* N-cadherin, vimentin, Twist, Snail and E-cadherin)[29]. Such molecular changes have been accompanied by morphological and growth alterations, these being features of a more metastatic phenotype. It has been seen that 0.5×10^5 breast cancer cells co-injected subcutaneously with 1.3×10^6 human bone marrow-derived MSCs have significantly increased lung metastasis rate in NOD/SCID mice. This effect was lost when bone marrow-derived MSCs were injected

separately from tumor cells[20]. On the other hand, it has been shown that bone marrow-derived MSCs facilitate cancer cells [MCF-7, T47D low invasive cell lines and stromal cell-derived factor 1 (SDF-1)^{null} MDA-MB-231 highly aggressive ones] homing into bone marrow and have modified the metastatic niche through trophic factor secretion (SDF-1 and CXCR4) and improved neovasculogenesis in a xenogeneic mouse model[30].

MSCs might inhibit tumor growth

It has been shown that human bone marrow-derived MSCs interfere *in vitro* with small cell lung cancer (A549), esophageal cancer (Eca-109), Kaposi's sarcoma and leukemic cell line proliferation kinetics[31]. The foregoing was observed when 0.5 × 10^5 tumor cells were co-cultivated with 0.5 × 10^5 human bone marrow-derived MSCs but also when they were exposed to MSCs-conditioned medium; cells were arrested during the cell cycle G_1 phase in both cases by the downregulation of cyclin D2 and induction of apoptosis[32,33]. MSCs from other sources, including human fetal skin-derived MSCs and adipose-derived MSCs, have also inhibited the growth of human liver cancer cell lines[34], breast cancer (MCF-7)[35] and primary leukemia cells by reducing their proliferation, colony formation and oncogene expression[22]. The intravenous injection of 4 × 10^6 human bone marrow-derived MSCs into Kaposi's sarcoma-bearing nude mice has inhibited tumor cell growth[36]. A similar effect has been observed in an animal model of hepatocellular carcinoma and pancreatic tumors as altering cell cycle progression has led to decreased cell proliferation[22,37]; the same has happened with melanoma due to increased apoptosis of capillaries[38] and rat colon carcinoma growth has been inhibited when rat MSCs (the MPC1cE cell line) were co-implanted with tumor cells in a 1:1 or 1:10 ratio[39].

Human fetal skin-derived MSCs (Z3 cell line) have also delayed liver tumor growth and decreased tumor size when injected with the same number of cells from the H7402 cell line in SCID mice[34]. Injecting human adipose-derived MSCs (1 × 10^3 cells/mm^3) into established pancreatic cancer xenografts has led to apoptosis and the abrogation of tumor growth in female Swiss nude (athymic) mice[37].

The role of MSCs in cancer thus remains paradoxical. Evidence to date has suggested that they are pro- as well as anti-tumorigenic[40-42] such discrepancy seems to depend on isolation and expansion conditions, cell source and dose, the administration route and the tumor model used.

MSCs AND INFECTION

MSCs might increase infection

MSCs can be recruited into inflamed sites secondary to microbial infection where they promote potent immune-suppressive activity[43,44]. For instance, it has been shown that administering MSCs (1.25 × 10^5 cells/kg) to animals infected by *Trypanosoma cruzi* (*T. cruzi*, protozoa) or *Mycobacterium tuberculosis* (*Mtb,* bacteria) has worsened the natural course of infection. Activated macrophages play an essential role in host defense against *T. cruzi* as they can destroy intracellular parasites *via* interferon (INF)-γ- and tumor necrosis factor (TNF)-α-stimulated nitric oxide (NO) production[45]. It has been shown that mice bone marrow-derived MSCs switch macrophages to an anti-inflammatory profile, thereby suppressing inflammatory cytokine production and enhancing interleukin (IL)-10 production[46]. An immune response to *Mtb* depends on IFN-γ-producing T-lymphocytes activating macrophages to produce NO[47,48]. Bone marrow-derived MSCs (2.5 × 10^5/kg) infusion into animals, which are normally resistant to this infection [transforming growth factor β (TGF-β) RIIDN transgenic mice], has resulted in making them susceptible to disease. Furthermore, it has been observed that donor MSCs have been recruited to the periphery of live bacteria-containing granuloma and have induced regulatory T-cell differentiation, thus resulting in immunosuppression.

A recent study aimed to prove the safety and feasibility of autologous bone marrow-derived MSCs infusion (1 × 10^6 cells/kg, two doses) into kidney allograft recipients, showing that three out of six enrolled patients developed an opportunistic viral infection[49].

MSCs might decrease infection

Regarding fungal infection, the intravenous administration of an IL-17-producing sub-population of bone marrow derived-MSCs (1 × 10^6 cells) significantly reduced the fungal burden of kidneys in immunocompetent mice, which had suffered invasive candidiasis[50].

Both un-stimulated and IFN-γ stimulated human MSCs can inhibit the growth of Gram-negative bacteria such as *Escherichia coli* and *Pseudomonas aeruginosa*, as well as the growth of Gram-positive pathogens such as *Staphylococcus aureus*, *Staphylococcus epidermidis*, group B *Streptococci* and *Enterococcus faecium*[46,51]. MSCs' antimicrobial effect depends on whether they have been stimulated[51]; while cathelicidin LL-37 antimicrobial peptide is critical to un-stimulated human MSCs, tryptophan-catabolizing enzyme heme oxygenase-1 and indoleamine-2,3-dioxygenase (IDO) are needed in IFN-γ-stimulated human MSCs. Tryptophan depletion and toxic kynurenine accumulation leads to the inhibition of bacterial growth in the latter case. Differences between human and murine MSCs antibacterial activity have also been reported; murine MSCs do not produce cathelicidin LL-37 and cannot express IDO, even after stimulation with a combination of cytokines, but they do produce lipocalin 2 (an antimicrobial molecule)[52].

Little data has been published concerning the

impact of MSCs on viral pathogens. One study has reported that IFN-γ-stimulated human MSCs have reduced intracellular replication of cytomegalovirus and herpes simplex virus type 1 *in vitro*[46], such effect being attributed to IDO activity[46].

Together with MSCs' direct antimicrobial effect, it has been shown that they play an important role in the complex network of host immune response against pathogens, particularly regarding the dynamic coordination of the immune system's pro- and anti-inflammatory components[53].

MSCs' antimicrobial activity observed *in vitro* has been clearly supported by animal models of experimental infection, such as polymicrobial sepsis[42], lipopolysaccharide (LPS) administration[54] and pulmonary respiratory distress syndrome[55]. Regardless of MSCs source, administration route (intravenously *cf* intraperitoneally) or strategy (prophylaxis *cf* therapy), their administration leads to reduced pathogen burden and significantly improved survival rate[41,42,53,56].

It has been shown that administering 2.5×10^5 mouse bone marrow-derived MSCs led to decreased mortality, controlled multi-organ dysfunction/injury and reduced pulmonary and systemic inflammation in a clinically relevant model of polymicrobial sepsis where infection was settled after the inoculation of Gram-negative and Gram-positive organisms[42]. An endotoxemic rat model (involving intravenous LPS injection) has been used to demonstrate that administering 2.5×10^5 human adipose-derived MSCs decreased inflammatory cytokine level in serum and the lungs, reduced inflammatory changes in the lungs, prevented apoptosis in the kidneys and reduced multi-organ injury[54]. A pulmonary respiratory distress syndrome model (induced by intratracheal endotoxin administration) has been used to show that the intrapulmonary delivery of mouse bone marrow-derived MSCs has down-regulated an LPS-induced inflammatory response and reduced lung injury, while direct lung injury by toxins or pneumonitis led to severe pulmonary edema and inflammation[57,58].

MSCs' antimicrobial effect has also been demonstrated in the blood, peritoneum, liver and spleen, using a Gram-negative pneumonia model involving immunocompetent mice[42,44,56].

As MSCs might lessen the development of infection, they have been used recently in a clinical study aimed at treating patients suffering acute respiratory distress syndrome (NCT01902082); one intravenous dose of 1×10^6 cells/kg allogeneic adipose-derived MSCs proved to represent a safe and feasible therapeutic tool for this infection[59].

MSCs have been seen as an innovative therapeutic tool for preventing or treating graft-versus-host disease (GvHD) following allogeneic hematopoietic stem cell transplant (HSCT)[60,61] owing to their immunosuppressive properties, such as not eliciting immunological responses from alloreactive T-lymphocytes and/or other immunological effector cells. However, it is not known whether using immunosuppressive MSCs may inadvertently inhibit antimicrobial immune responses and ultimately result in an increased risk of infection in allogeneic HSCT recipients[62], considering that infection is one of the major complications following an HSCT contributing to high morbidity and mortality indexes[63,64]. One open randomized clinical trial has demonstrated that acute grade Ⅱ-Ⅳ and chronic GVHD incidence in 10 patients receiving a median 3.4×10^5/kg MSCs dose from a human leukocyte antigen-identical sibling donor was lower than in 15 patients who did not receive MSCs (11% *cf* 53% and 14% *cf* 29%, respectively)[65]. Unfortunately, this did not mean a lower risk for infectious complications. Early and mid-phase severe infection incidence was even higher in patients who had received a co-transplant of hematopoietic stem cells and MSCs compared to a control group, which did not receive MSCs, although differences were not statistically significant [4/10 (40%) *cf* 5/15 (33%)]. Patients receiving MSCs suffered from cytomegalovirus (CMV) interstitial pneumonia and bacterial and/or fungal infection whereas this was only seen in two of the patients who did not receive MSCs[65]; no patient treated with MSCs died because of infectious complications, whereas this happened in two control group patients who did not receive MSCs. This raises the question of whether infection severity is lower when MSCs are co-transplanted with a graft.

By contrast, another two non-randomized clinical trials, involving 20 patients[66] and 14 pediatric patients[67], showed that co-transplanting MSCs did not result in higher infection incidence and severity when compared to historical controls.

On the other hand, multivariate analysis regarding a retrospective cohort study of 691 HSCT patients showed that GVHD grade Ⅱ-Ⅳ, CMV infection and having received human bone marrow-derived MSCs were factors which were associated with overall pneumonia-related deaths[68].

Thus, the role of MSCs in infection is paradoxical. Evidence reported to date suggests that there may be pro- as well as anti-microbial effects[40-42] and this seems to depend on isolation and expansion conditions, cell origin and dose and administration route and timing.

MECHANISMS BEHIND MSCs CANCER-INDUCING EFFECT

MSCs modify cancer cells

Although the cancer stem cell (CSC) concept was first introduced in hematological malignancies (chronic and acute leukemia)[69], it has been identified during recent years in a variety of solid tumors such as glioblastomas, medulloblastomas and carcinomas[70]. It has been demonstrated that MSCs interact with CSC in human cancer and regulate their own self-renewal through cytokine networks involving IL-6 and *CXCL7*[19]. CSC-produced IL-6 interacts with IL6R/gp130 expressed on MSCs to produce *CXCL7*; this molecule

interacts with CSCs through the CXCR2 receptor where it induces the synthesis of others cytokines (*i.e.,* IL-8, IL-6, *CXCL6*, and *CXCL5*)[19]. These cytokines trigger CSC self-renewal and enhance their invasive properties while IL-6 mediates chemotaxis, which may facilitate MSCs homing to primary tumor growth sites. It has been shown that MSCs administered subcutaneously in mice having had a breast tumor xenograft became recruited to the tumors and produced IL-6 and IL-8, which accelerated their growth by regulating the CSC population[20].

MSCs might induce epithelial-to-mesenchymal transition

Most malignancies have an epithelial origin, and cancer progression is often associated with epithelial-to-mesenchymal transition (EMT)[71]; this is a physiological process, which is recognized as being crucial for embryogenesis and wound healing. It involves epithelial cell conversion to mesenchymal cells through the disruption of cell-cell junctions and the reorganization of the actin cytoskeleton; EMT has gained much attention recently due to its role in converting benign lesions into invasive and metastatic tumors[72]. It is governed by complex networks, which are influenced by signals from the neoplastic microenvironment, such as collagen, cytokines and TGFβ, epidermal growth factor, fibroblast growth factor (FGF), hepatocyte growth factor (HGF) and platelet-derived growth factor[71-73]. Interestingly, all the aforementioned factors are secreted by MSCs[9].

MSCs modify vasculogenesis

Vasculogenesis plays a critical role in tumor growth[74]; MSCs could contribute towards tumor vasculogenesis because they act as pericytes but may also differentiate into endothelial cells and secrete provasculogenic factors[75-77], thereby allowing blood vessel formation[75]. Vascular endothelial growth factor (VEGF) and FGF-2 are the two main MSCs-secreted vasculogenic factors involved in tumor neovascularization[76]. VEGF is known to regulate MSCs mobilization and recruitment to neovascularization sites and directs MSCs differentiation to vascular cell[78,79]. VEGF expression in MSCs can be enhanced by hypoxia, a common phenomenon in tumor tissue[80] whilst FGF-2 is a potent mitogen which is produced and secreted by endothelial cells and MSCs[81]. This factor has been implicated in cell proliferation and endothelial cell migration during tumor growth[81]; conversely, MSCs appear to reduce vascular density due to endothelial cell cytotoxicity in certain conditions[38].

MSCs modify anti-cancer immune response

MSCs suppress both innate and adaptive immune responses[82,83]; they inhibit $CD4^+$ and $CD8^+$ T-cell proliferation[84] by producing a wide range of mediators, including TGFβ1, HGF, insulin-like growth factor, prostaglandin E_2, NO, heme oxigenase-1 and IDO[85-89]. MSCs also inhibit monocyte and hematopoietic progenitor proliferation and differentiation into mature dendritic cells[32,90]. Other MSCs-induced effects regarding dendritic cells would be a loss of their ability to stimulate allo-responses[91], acquiring a regulatory phenotype due to the production of large amounts of IL-10[91] and changing dendritic cells' cytokine secretion profile by MSCs-derived PGE_2[91]. MSCs alter the natural killer (NK) cell phenotype besides suppressing their proliferation and cytokine secretion[92]; this requires cell-to-cell contact and soluble factors (TGFβ1 and PGE_2). Hence, MSCs could promote an anti-inflammatory response within a tumor, thereby allowing its enlargement[93]. Systemically administered MSCs have promoted immune-tolerance in damaged organs, irrespective of whether donor cells home into them[7,8,94]. It is expected that MSCs would worsen the immune-destruction of tumor cells and thus facilitate tumor growth and metastasis. Conversely, increased macrophage and granulocyte infiltration in MSCs-injected tumors has been shown, suggesting that allogeneic MSCs immunogenicity might contribute towards their antitumor effect[32,39].

Changes in MSCs microenvironment, together with changes in transformed cells, would also seem to contribute towards carcinogenesis[95].

MECHANISMS BEHIND MSCs INFECTION ADVERSE EFFECTS

MSCs modify bacterial growth inhibition and clearance

MSCs can participate in host defense through the secretion of antimicrobial peptides (cathelicidin LL-37[51] and lipocalin 2[52]), which can directly inhibit bacterial growth or kill the pathogens. The secretion of these soluble peptides improves resident phagocyte ability to clear bacteria through the up-regulation of pathways associated with monocyte/macrophage, phagocytosis, NK cell activity and antigen presentation[42] while MSCs antifungal activity means an increased amount of TH17 cells in the blood, thereby promoting TH1-type immune responses and restraining TH2-type ones[50].

MSCs modify anti-microorganism immune response

MSCs induce a marked decrease in Toll-like receptor 2 expression, which plays a fundamental role in pathogen recognition and activation of innate immunity[96]. MSCs induce a marked increase in macrophage susceptibility to infection by parasites and bacteria. The mechanisms so involved appear to be linked to the production of inflammatory cytokines TNF-α, IL-12p70 and IFN-γ which drive NO production[43]. MSCs switch activated macrophages into regulatory ones producing low levels of pro-inflammatory cytokines. MSCs could modify an immune response against microorganisms by inducing apoptosis and cell-cycle arrest of T-cells by producing NO, TGFβ or IDO[91]. MSCs can inhibit cellular immune responses and promote regulatory T-lymphocyte production, thereby establishing T-cell tolerance for microorganisms[97-100].

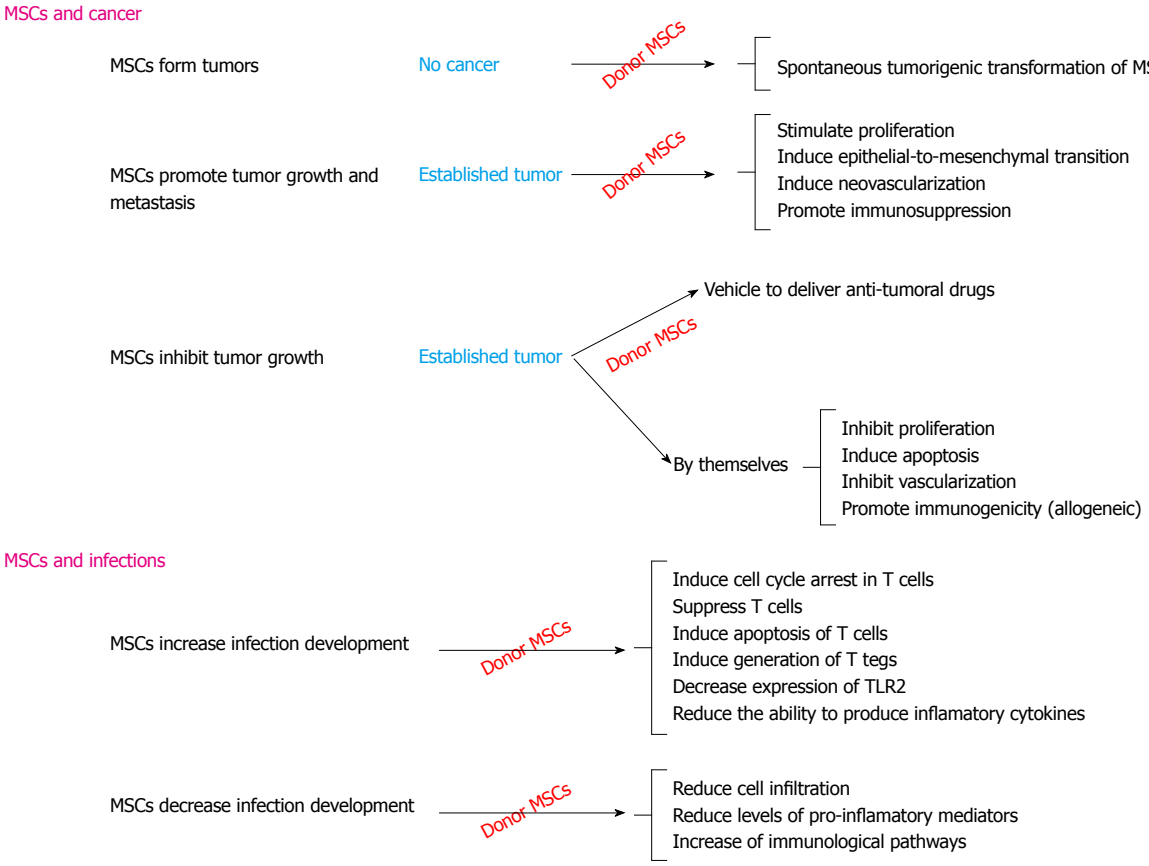

Figure 1 Paradoxical effect of donor mesenchymal stem cells in cancer and infection development. MSCs: Mesenchymal stem cells; TLR2: Toll-like receptor.

ARE CANCER AND INFECTION ADVERSE EFFECTS ARISING FROM USING MSCs IN THERAPY?

In vitro and *in vivo* studies have demonstrated MSCs' pro- and anti-cancer and pro- and anti-infection effects nevertheless, most clinical trials have reported that MSCs-based therapy appears safe and has not been associated with serve adverse events. Together, due to MSCs' context-dependent potential to produce immune-modulatory factors they seem to be an ideal therapeutic tool for both cancer and infections.

CONCLUSION

The pertinent literature reveals incongruity regarding the impact of MSCs on the development of cancer and infection (Figure 1); such paradoxical effect might be attributed to differences in isolation and expansion conditions, the source and dose of the cells being used, the administration route and its timing and host characteristics. MSCs immunomodulatory potential seems to be the leading mechanism responsible for such effects. Until conclusive data becomes available, cancer and infection will still be seen as adverse effects and therapeutic targets for using MSCs-based therapy.

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