An Overview of the Biological Processes of Mesenchymal Stem Cells and Their Response to an Inflammatory Milieu

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Abstract

There is continued interest in applying adult human mesenchymal stem cells (MSCs) in tissue regeneration, as well as mitigating overt inflammation such as graft versus host disease. MSCs are derived from different sources such as bone marrow, bone chips, dental pulp, adipose tissues, and placenta. MSCs appear to exert a memory for their tissue of origin. Interestingly, despite positive outcomes of MSCs *in vivo*, their survival in host tissues appears to be short-lived. To date, based on research and clinical literature, there is a need to understand how MSCs are maintained in a multipotent state. We discuss the role for the inflammatory milieu in which soluble and insoluble such as exosomes can determine the immune response of MSCs – suppressor versus enhancer. This article discusses a central role for the transcription factor NFκB in maintaining multipotency, and discusses how the inflammatory

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milieu influences the differentiation of MSCs. Lessons are drawn from the literature on MSCs in cancer to further describe the role of NFκB in maintaining the stem cell state. The findings outlined in this article could be important to future translational studies.

Keywords: Stem cells, cytokines, inflammation, NFκB, purinergic receptors, multipotency.

Mesenchymal Stem Cells (MSCs) – Brief Introduction

Stem cells hold great promise for treating a variety of pathological conditions, ranging from drug delivery, anti-inflammatory conditions, and regenerative medicine [1–4]. MSCs are multi-potent, non-hematopoietic adult stem cells with regenerative and unique immune properties. First discovered in the bone marrow by Alexander Friedenstein in the 1960s, MSCs have now been identified in multiple adult and fetal tissues. In adults, MSCs are found in tissues such as adipose, bone, bone marrow, dental pulp, and placenta [5–9].

Although derived from different tissues, MSCs share key characteristics including adherence to plastics, self-renewal, and multilineage differentiation (e.g. adipocytes, osteocytes, and chondrocytes). MSCs can home to areas of inflammation and can cross the blood–brain barrier. In an inflammatory milieu, MSCs are licensed or educated by the inflammatory mediators to be immune-suppressor cells. MSCs are generally characterized by specific cell surface proteins – $CD34^-$, $CD45^-$, HLA-DR^-, $CD44^+$, $CD73^+$, $CD90^+$, $CD105^+$, STRO-1^+ [2, 10, 11].

MSCs are functionally plastic due to their ability to generate cells of various tissues such as bone, fat, muscle, cartilage, myocytes and neurons [12, 13]. MSCs are also associated with multiple functions including angiogenesis, homing to areas of inflammation, and systemic modulation of immune responses – pro-anti-inflammatory. These inflammatory functions depend on the microenvironment that could be cytokines, neuropeptides and microvesicles [14–19].

MSCs can produce baseline and can be induced to produce cytokines. The types of cytokines produced by MSCs depend on the cues within the tissue niche [14–17]. MSCs can respond to the cytokines due to multiple cytokine and chemokine receptors. As third-party cells within an inflammatory milieu such as graft versus host disease (GvHD), MSCs can be licensed as immune suppressor cells to modulate the inflammation [14]. Minor differences in phenotype and function have been attributed to MSCs derived from different

tissue sources, but the key functions of MSCs as listed above are shared by MSCs derived from all sources [20, 21]. Critically, MSCs can cross allogeneic barriers, permitting MSCs derived from one individual to another, hence the potential to be used as an off-the-shelf stem cell source [1, 14].

The source of MSCs for expansion or direct use can be accomplished through minimally invasive procedures including bone marrow aspiration, abdominoplasty, lipoaspiration, and collecting of other discard tissues such as the placenta [18, 22]. The isolated tissues can be used in tissue regeneration using although this will result in the use of heterogeneous cells. Most applications use enriched MSCs that are achieved in culture. Together, the ease of isolation, capacity to cross allogeneic barrier, evidence of safety, and reduced ethical concerns explain MSCs' clinical appeal.

To date, MSCs are listed in over six thousand clinical trials (clinicaltrials.gov, July 1, 2023), capitalizing on the properties of MSCs described throughout this article – primarily their ability to home to areas of inflammation and to reduce inflammation locally and/or systemically [1, 3, 4, 14, 23–26]. Beyond these currently listed applications, MSCs are being studied as potential therapy in conditions such as cancer, diabetes mellitus, and end-stage liver disease [1–3, 26].

Homing of MSCs

Migration of MSCs from their microenvironmental niche or site of administration to the target tissue or organ is a fundamental characteristic of MSCs that facilitates their response to inflammation and tissue regeneration. MSC homing, which refers to MSCs migration towards a target, is facilitated by cytokines and chemokines released at the inflammatory site [18, 25]. To reiterate, MSCs express receptors that can interact with multiple cytokines and chemokines, which permits them to respond to an inflammatory microenvironment, including migration and response to rapidly changing microenvironments [27, 28]. Of note, MSCs express CXCR4 and CXCR7, which are receptors for CXCL12/SDF1α, which permits their chemoattraction to sites of inflammation [29]. Other chemokines have also been identified to serve as chemoattraction of MSCs [30–32]. An understanding of how MSCs are attracted to sites of inflammation is well-studied since insights into the mechanisms would allow for targeted therapy. Such treatment could be relevant to the case of immune regulation, and as a mechanism to deliver drugs [33]. Once MSCs migrate to sites of inflammation, they can be directly involved in tissue regeneration. However, the role of MSCs in tissue regeneration

has been predominantly due to their secretome [1, 34, 35]. The efficiency of exogenous MSC mobilization to the target tissue significantly impacts the efficacy of these cells to act as a possible therapy for diseases such as degenerative disorders and immune modulators [4].

Despite the promise of MSCs in medicine, their mobilization is inefficient ($<10\%$), leading to debate over optimal routes of administration to improve mobilization for different applications [35]. Local administration of MSCs to the target organ or tissue is one route that may enhance the efficacy of these stem cells. However, this mode of delivering MSC can be highly invasive, resulting in the probability of the MSCs escaping the [36]. Intravenous administration has also been suggested. However, most of the cells administered intravenously are entrapped in the lung due to the MSCs' large size and their expression of adhesion molecules such as VCAM1 and VLA-4, which can bind lung epithelial which can bind lung epithelial cells. It is estimated that only 1% of the cells reach the target organ [37–39]. The half-life of these entrapped MSCs is short – under four days – supporting a role for MSC secretome in the clinical effects of MSCs [40–42].

Different molecular engineering approaches have been employed to increase MSC homing to specific sites, including overexpression of cytokine receptors and downregulation of adhesion molecules [43–48]. Another approach shown to enhance MSC homing is magnetic guidance to the target tissue, whereby the MSCs are labeled with magnetic carbon nanotubules prior to administration [49]. Notably these studies have largely found decreased lung entrapment and increased homing of MSCs to the target tissues without significant effect on the viability of the cells or their capacity to differentiate [45, 49]. It is crucial to keep in mind that enhanced homing of MSCs and their response requires different approaches with the targeted organ or tissue as guide to the approach. Furthermore, the specific disease being treated, and the source and pre-treatment of the MSCs are also factors when designing treatment. Thus, understanding these nuances is key to developing effective treatments and improving patient outcomes.

MSCs – Source of Endocrine and Paracrine Mediators in Intercellular Communication

As discussed above, there is little evidence to support the basis of the clinical responses of MSCs, with respect to tissue engraftment. This statement is based on a small percentage of MSCs that reaches the target organ with

no strong evidence of long-term survival a mechanism by which MSCs facilitate tissue repair is likely due to released soluble factors, to released soluble factors, including cytokines and extracellular vesicles (EVs). Also, upon injection or engraftment. stem cells are deprived of their extracellular environment. This deprived the stem cells of soluble as well as physical, chemical, and biochemical factors that are needed for engraftment. In this context, soluble factors play a fundamental, but not exclusive to engraftment.

Among classes of EVs, exosomes are the most investigated. Exosomes are MVs of 30–150 nm in diameter, enriched in proteins, miRNA, lipids, and other regulatory molecules. They have been identified in a wide array of body fluids such as blood (including plasma and serum), urine, saliva, cerebrospinal fluid, pleural effusion, and ascites, and are considered representative of the cells from which they were derived (discussed in [50]). Due to their source-cell representation, circulating MVs are under investigation for diagnostic purposes, evaluating biomarkers for the presence and type of aberrant cells – including malignancy, injury, and other disorders [50–53]. It thus stands to reason that the MVs derived from MSCs of different source tissues, and different treatments and exposures *in vitro*, would differ from one another [54, 55]. Due to the similarity of MSCs and their derived exosomes (MSC-Exos), there are intense research investigations to determine how the MSC-Exos could be leverage for clinical applications [4, 56].

MSC-Exos have been associated with anti-inflammatory and reparative functions [55, 57–60]. Over 2000 proteins have been identified within MSC-Exos [54, 55]. These include cytokines (e.g. IL-10, IL-6, TGF-β, TNFα), chemokines (e.g. MCP1, CXCL14, MCP3, SDF-1α), and trophic factors (e.g. FGF, HGF, IGF1, VEGF) [55]. Like their parent cells, MSC-Exos can suppress effector T-cells, dendritic cell (DC) maturation, M1 macrophages, and natural killer cells (NKs), while enhancing regulatory T-cells and M2 macrophages [56, 61–63]. The exosome cargo of MSCs contribute to their regenerative capacity such as enhanced osteogenesis, chondrogenesis, and angiogenesis [60, 64–66]. It should be noted, however, that both direct and indirect forms of intercellular communication between MSCs and target cells have been reported; for example gap junctional intercellular communication (GJIC) for direct intercellular communication, and release of MVs for indirect intercellular communication [67–70]. It should be noted that both means of communication have the potential to transfer similar cargo, including proteins and miRNAs to target cells [71].

MSC Licensing

MSCs can be licensed or educated as anti-inflammatory cells in a tissue niche [14, 72]. While the process of MSC licensing is poorly defined, specific factors are known to be necessary – namely IFNγ, in the presence of other pro-inflammatory cytokines (e.g. TNFα, IL-1α, IL-1β) [73–75]. The immunomodulatory properties of MSCs were not well understood until recent studies showed that MSCs could impair the function of both innate and adaptive immune system cell proliferation [76, 77]. These studies paved the way for scientists to shift their focus from the MSCs multiple-lineage and regenerative properties towards understanding the immune regulator capacity of these cells. MSCs regulate the immune system response through the release of MVs and soluble factors that impact the ability of the innate and adaptive immune cells such as myeloid DC and T-cells to respond to an infection [73, 78, 79]. MSCs impair DC function by preventing their transition from immature to mature DCs, thus preventing presentation of antigen to naïve T-lymphocytes and decreased release of pro-inflammatory cytokines (e.g. TNFα) [79, 80]. MSCs also decreased NK cytotoxicity. This could occur by decreased IFNγ, leading to reduced NK proliferation, in part through downregulated expression of NKp30 and NKG2D on NK cells [73, 81]. MSCs further regulate the immune system by impairing the inflammatory response induced by the cells of the adaptive immune system. For example, MSCs inhibit T-lymphocytes differentiation by increasing IL-4 and decreasing IFNγ secretion [73]. The decrease of pro-inflammatory cytokines allows T-lymphocytes to differentiate towards anti-inflammatory T_h2 rather than pro-inflammatory T_h1 phenotype [40, 73, 82]. MSCs also act on macrophages by polarization from pro-inflammatory M1 to anti-inflammatory M2 phenotype [61, 83, 84]. These findings have relevance to MSC function in the uterus, as MSCs isolated from and menstrual fluid have immunomodulatory properties [85]. Thus, it has been postulated, although unproven, that similar interactions between MSCs and uterine immune cells (e.g. uterine NK (uNK) cells and macrophages) play a role in promoting the immune microenvironment required for endometrial regeneration [86].

Regenerative Potential of MSCs

MSCs, in addition to their crucial role in immune modulation, also play an essential role in maintaining the host tissues' homeostasis by replacing dead and dysfunctional tissue. The capacity of MSCs to sustain host

homeostasis through repair and replacement of dead and dysfunctional cells is predominantly attributed to their secretome and the microenvironment, as discussed above. The effectiveness of MSCs response to inflammation or injury is conditioned by their ability to home to the site of insult or injury. However, once MSCs are recruited to the site of inflammation, they can directly or indirectly interact with the affected tissue by GJIC or paracrine factors, as indicated above. Local inflammatory cytokines (e.g. TNFα, IFNγ) signal MSCs to release immunomodulatory, pro-angiogenic, regenerative, and neuroprotective factors including TGF-β1, VEGF, HGF, SDF-1, IGF-1, and angi-1 [40, 59, 87, 88]. These effects can be accomplished via the MSCs' endogenous cargo or can be engineered to enhance these effects [1, 2, 89, 90].

A key role for MSCs involves research studies to apply MSCs as a drug delivery tool such as gene therapy [70, 91–93]. The self-renewing capacity of MSCs permits these stem cells to act as self-maintaining drug delivery vehicles at a site of inflammation so long as the microenvironment remains permissive to the MSCs [40, 94, 95]. An advantage of using MSCs in drug delivery is their unique ability to be delivered across the immune barrier. This makes these cells available as off the shelf for immediate use to patients.

Although the research predominantly supports MSCs' effects on their secreted secretome rather than cellular replacement, the latter could be possible. MSCs have been found to generate osteocytes, adipocytes, chondrocytes, myocytes, and functional neurons *in vitro* [2, 12, 13, 96, 97]. Numerous groups are investigating ways to accomplish similar direct reprogramming of MSCs and other cells *in vivo*, for example differentiating fibroblasts into neurons [98]. In order to dissect these two options, it is required to understand the behavior of MSCs within different inflammatory milieu, which is addressed in this review. A key factor in understanding the different inflammatory milieu is the transcription factor nuclear factor κB (NFκB) due to is role in cytokine regulation as well as other inflammatory mediators.

Nuclear Factor κB (NFκB) Family and Activation

NFκB is a family of constitutively expressed, inducible transcription factors that regulate immune and inflammatory responses by controlling the expression of other genes [99, 100]. NFκB is found in the cytoplasm as a homodimer or heterodimer composed of combinations of the family's five subunits: NFκB1 (precursor: p105, mature: p50), NFκB2 (precursor: p100, mature: p52), RelA (p65), RelB, and c-Rel (Figure 1) [99, 100]. The NFκB dimers then bind the κB enhancer element on target genes to

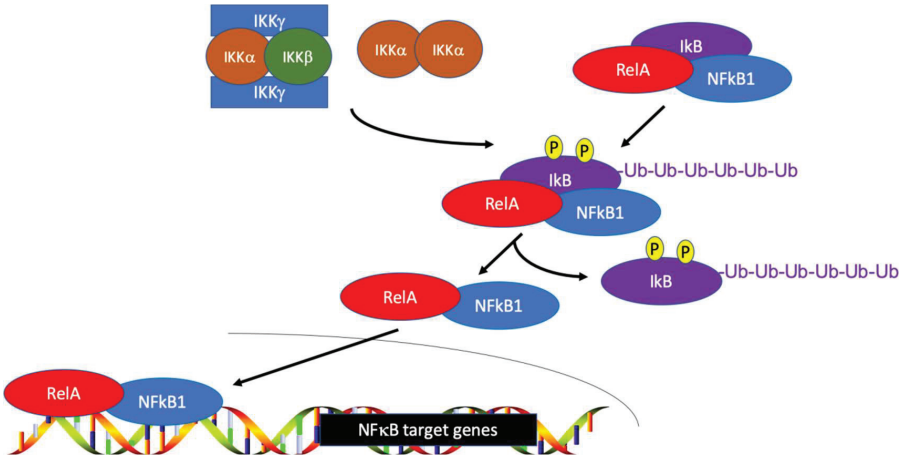

Figure 1 NFκB activation. NFκB dimers are inactive in the cytoplasm. This occurs by interaction with a IκB molecule (or otherwise include an elongated precursor NFκB1 or NFκB2 subunit). Upon activation, IκB (or NFκB1 or NFκB2) is phosphorylated, which signals ubiquitination, leading to release of the NFκB dimer. NFκB is then able to translocate to the nucleus, where it can bind its target genes for transcription.

mediate gene transcription for various cell processes [101]. Although the predominant binding sequence has been identified as GGRRNNYYCC, alternative, noncanonical binding sites have been identified [102–104]. Under baseline conditions, the NFκB proteins are sequestered in the cytoplasm by the ankyrin repeats region of either a member of the IκB family of inhibitory proteins (namely IκBα) or an elongated precursor form of NFκB1 or NFκB2 [105, 106].

The IκB family is composed of seven molecules (IκB-α, IκB-β, IκB-γ, IκBε, Bcl-3, NFκB1, and NFκB2), which bind the NFκB dimer in the cytosol to maintain NFκB inactivity (Figure 1). An additional IκK member, IκBδ, can bind the NFκB dimer in the nucleus. Each of these proteins contains ankyrin repeats, which interact with NFκB's RHD domain inactive [107, 108]. Upon receipt of an NFκB activation signal the IκB molecule dissociates from the NFκB dimer and degrades, permitting NFκB translocation to the nucleus. In the case of NFκB1 and NFκB2, there is cleavage from p105 to p50 and p100 to p52, respectively [107, 108]. Thus, NFκB activity can be linked to IκB transducing upstream cytoplasmic signals. However, it should also be noted that the IκB proteins can be regulated through NFκB synthesis, permitting an auto-regulatory NFκB feedback loop [109, 110].

NFκB activation can be divided into two major signaling pathways: canonical and noncanonical pathways (Figure 2). Although both signaling cascades play important roles in regulating immune and inflammatory responses, the signaling mechanisms have unique upstream activating receptors and signaling molecules [101, 105, 106]. Canonical NFκB signaling is initiated by diverse stimuli, including the ligands for various cytokines, pattern recognition receptors, TNF receptor superfamily members, T cell receptors, and B cell receptors; it is primarily activated by toll-like receptors, IL-1, and TNFα [99, 111–114]. Through various downstream pathways, these canonical signaling cascades predominantly converge at the inducible degradation of IκBα: a multi-subunit IκB kinase (IKK) phosphorylates IκBα as specific sites to release the NFκB dimer, permitting NFκB translocation to the nucleus [99]. The most common NFκB dimers observed in canonical NFκB signaling are the p50/RelA and p50/c-Rel dimers [99, 106, 115, 116].

IKK itself is composed of two catalytic subunits, IKKα and IKKβ, as a homodimer or heterodimer and its own regulatory subunit NFκB essential modulator (NEMO; IKKγ) [117–119]. IKK can be activated by different inflammatory stimuli, including cytokines, growth factors, mitogens, microbial components, and stress molecules [118, 119]. The activated IKK complex phosphorylates two serines on the N terminus of IκBα, triggering ubiquitin-dependent degradation of IκBα by the 26s proteasome and nuclear translocation of the NFκB dimer to the nucleus [99, 118].

In noncanonical NFκB signaling, activation predominantly occurs through B-cell activation factor, lymphotoxin β-receptor, CD40, receptor activator for nuclear factor kappa B (RANK), TNFR2, and fibroblast growth factor-inducible 14 (Fn14) and other ligands of the TNF receptor family [107, 120–123]. These alternative pathways are often associated with lymphoid organogenesis and B-cell function [124, 125]. Rather than inducible degradation of IκBα, the noncanonical pathways usually converge on processing the NFκB2 precursor protein p100 to the mature p52 [105, 121]. p100 undergoes phosphorylation, ubiquitination, and processing through an NFκB-inducing kinase (NIK)-IKKα complex [124, 126]. Like in the canonical signaling pathways, the ubiquitinated fragment of the protein is processed in the 26s proteasome [124, 126]. This processing yields the mature p52 NFκB2 subunit, allowing translocation of the NFκB dimer to the nucleus. The most prevalent dimer in non-canonical NFκB signaling is p52/RelB [99]. Although both the canonical and noncanonical NFκB pathways are involved in almost all aspects of immune responses, the canonical pathway is considered predominant in these functions, with the noncanonical pathways supplementing

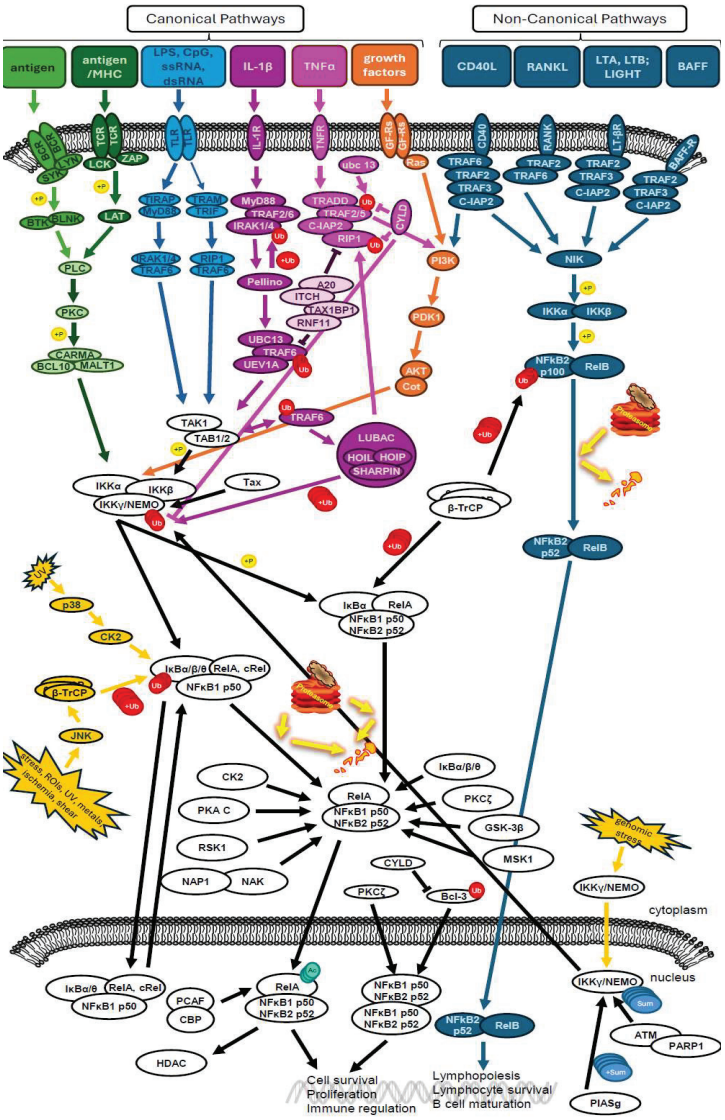

Figure 2 NFκB signaling occurs through a complex molecular network with canonical and noncanonical pathways. Shown are overlapping signaling molecules within the pathways such as changes in phosphorylation (p), ubiquitination (UB), sumoylation (Su), and acetylation (Ac). These changes demonstrate influence on downstream NFκB transcriptional activity. The figure represents a compilation of the pathways discussed in this article. Some of the components used images from Motifolio and others using PowerPoint.

the canonical pathways and regulating further aspects of adaptive immunity [105, 120].

Targeting NFκB in Inflammation and Cancer

NFκB is best known for its roles in inflammatory and anti-apoptotic responses [101, 106, 115–117, 120]. NFκB induces various pro-inflammatory genes, activates inflammasomes, and regulates the activation and maturation of various immune cells [122, 127, 128]. Depending on the NFκB dimer, different target genes, through slight differences in the binding site consensus sequence, are activated including genes linked to inflammation, such as IFNγ, IL-1α, IL-1β, IL-10, TNFα, TGF-β, as well as various growth factors and cell surface receptors [129–134]. The diversity of the NFκB binding sequences, in conjunction with the diversity of NFκB dimers, makes *in silico* identification of putative NFκB binding sites difficult [104, 135]. Regarding regulation of functions, NFκB contributes to a range of innate and adaptive immune functions including regulation of adhesion molecules and apoptotic genes, induction of proliferation genes, and involvement in cell specialization (i.e. Schwann cells myelination) and development [136–141]. Beyond these broad mechanisms, NFκB has been implicated in both pro- and anti-inflammation functions.

NFκB has been found to activate the expression of cytokines and chemokines, including the pro-inflammatory cytokines TNFα and IL-1α, which can in turn activate NFκB [112–114]. These chemokines activate NFκB at different points in time, for different lengths of time, after activating their respective pathways; this can result in biphasic NFκB activity [114]. Various chronic inflammatory conditions, in which TNFα is elevated, have shown that inhibition of NFκB abrogated the elevated TNFα with reduction in inflammation [142]. However, mechanisms of blocking NFκB have NFκB have also resulted in septic shock and inflammation [143–145], suggesting an anti-inflammatory role of NFκB as well. However, the full role of NFκB in inflammation is yet unclear (reviewed in [146, 147]).

NFκB dysregulation has been observed in various inflammatory diseases, including atherosclerosis, inflammatory bowel diseases, multiple sclerosis, and rheumatoid arthritis [99]. Targeting of NFκB has been investigated at the levels of IKK inhibition (e.g. aspirin, preventing phosphorylation of IκBα), proteasome inhibition (e.g. bortezomib, preventing IκBα degradation), inhibition of nuclear translocation (e.g. tacrolimus), and inhibition

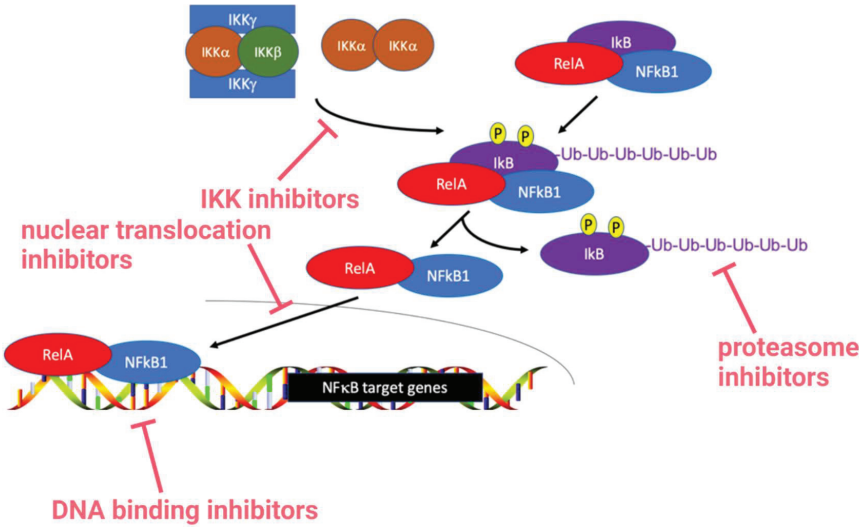

Figure 3 Clinical targeting of NFκB. Available pharmacological agents that inhibit NFκB at various points, including inhibiting IKK to prevent IκBα phosphorylation, inhibiting the proteasome to preventing IκBα degradation, inhibiting nuclear translocation, and inhibiting DNA-binding to prevent target gene transcription.

of DNA-binding (e.g. glucocorticoids, preventing target gene transcription) (Figure 3) [148–152].

NFκB is among the signaling cascades that are aberrantly regulated in cancer target genes include molecules that are retained intracellularly and extracellularly. This and extracellularly. This allows cancer cells to influence signaling of neighboring non-malignant cells in the microenvironment, resulting in the cancer cells regulating their own cellular support [153–156]. Aberrant NFκB signaling has been implicated in all cells of the tumor microenvironment, including tumor-associated macrophages (TAMs), DCs, myeloid-derived suppressor cells (MDSCs), neutrophils, mast cells, NK cells, T-cells, B-cells, cancer-associated fibroblasts (CAFs) and endothelial cells [157].

NFκB is involved with all stages of tumor progression: tumor initiation, tumor proliferation, and tumor metastasis [157]. During tumor initiation, NFκB can stimulate cell cycle entry of cells containing a single strand of damaged DNA, thus ensuring that a daughter cell has two copies of the damaged gene(s) [158, 159]. Further, NFκB can induce transcription of activation-induced cytidine deaminase (AID), a mutator enzyme, which

deaminates cytosine residues to cause cytosine-to-thymine transitions [160]. Within the tumor proliferation aspect of tumor progression, NFκB can promote cancer cell proliferation and survival through the production of inflammatory cytokines and growth factors [161, 162]. apoptosis that would otherwise be induced by oncogenes like Myc [163]. For tumor metastasis, NFκB can induce genes such as SLUG, TWIST, and TRAIL, whose protein products contribute to epithelial mesenchymal transition (EMT) [164, 165]. Additionally, NFκB can stimulate the expression of motility factors such as HGF and CXCL12, and HIF1α to enhance survival of the metastatic cells [166–168].

NFκB in Stem Cell Multipotency: Healthy and Malignant

Initial studies of NFκB in adult stem cells were done in hematopoietic stem cells (HSCs). There is increased NFκB activity in HSCs, specifically the RelA subunit that can increase hematopoietic cell proliferation, decreased numbers of long-term HSCs, and increased numbers of short-term HSCs [169–171]. Although increased NFκB (RelA) activity led to differentiation of HSCs, the short-term HSCs were unable to reconstitute the hematopoietic system, indicating that these short-term HSCs have lost multipotency [171]. However, further research in MSCs and HSCs have found that NFκB maintains multipotency, with NFκB inhibiting multilineage differentiation [172–175]. This correlated with a decrease in NFκB during differentiation. This was corroborated in studies in which inhibition of NFκB initiated MSC differentiation [176, 177]. It has been suggested that the loss of NFκB mitigates the proinflammatory microenvironment and thus triggers MSC differentiation [178, 179]. Variable effects on multipotency have been observed when exposing MSCs to NFκB-stimulating factors. Specifically, if NFκB signaling maintains multipotency of CSCs and MSCs. For example, stimulation with TNFα resulted in differentiation of the MSCs while TLR4 did not result in a loss of multipotency [180–182].

NFκB is constitutively active in CSCs, stimulating CSC maintenance, proliferation, and expansion [183–185]. Together with STAT3, NFκB promotes CSC maintenance through SLUG, TWIST, and SNAIL [183–186]. In breast cancer, NFκB has been shown to expand the CSC population by activating Notch signaling [187]. NFκB has also been implicated in CSCs from hematological malignancies, including increased NFκB activity in AML, CML, and multiple myeloma CSC [188–191]. This elevated NFκB

activity yields increased expression of stem cell associated genes such as CD44, Sox2, and Nanog within the CSCs [192].

Purinergic Receptors (Purinoceptors)

Purinergic receptors (purinoceptors) are a family of plasma membrane channels and receptors involved in import of adenosine-5′-triphosphate (ATP), adenosine-5′-diphosphate (ADP), adenosine-5′-monophosphate (AMP), and adenosine or their signals into the cell generally associated with inflammatory conditions while adenosine is generally associated with decreased inflammation [194]. This evolutionarily basal system has been evolutionarily basal system has been identified in nearly all mammalian tissues, with roles in embryonic development, the nervous system, and endocrine systems; pain, inflammation and immune repair; and cell proliferation, differentiation, and death, among others [195–198]. During the energy metabolism process, ATP is hydrolyzed into ADP and AMP, followed by adenosine by ectonucleosides [199–201]. In humans, these are predominantly CD39 and CD73; with CD39 among the ectonucleosides responsible for hydrolyzing ATP to ADP and AMP, and CD73 hydrolyzing AMP into adenosine (Figure 4) [199].

Purinoreceptors are divided into three main classes based on their ligand(s) and channel/receptor type: P1 (adenosine, **A**DORA) receptors, P2X receptors, and P2Y receptors [193, 202]. The P1 (ADORA1/A1R, ADORA2A/A2AR, ADORA2B/A2BR, ADORA3/A3R) receptors are G-protein coupled receptors (GPCRs) selective for adenosine [203]. The P2 receptors are selective for purines and pyrimidines and are divided into P2X and P2Y classes [193, 204]. The P2X receptors (P2X1-7) are ligand-gated ion channels of three homomultimers or heteromultimers selective for ATP [202, 204]. The P2Y receptors (P2Y1/2/4/6/11-14) are GPCRs selective for all nucleotides [202, 204]. The missing P2Y receptor numbers are due to non-human orthologs or non-functional receptors in humans [193].

Purine-related diseases are complex, involving aberrant purine genesis and metabolism [205–208]. For example, gout is associated with accumulation of urate crystals in joints secondary to a purine-rich diet [209]. Additionally, various tumor microenvironments have been reported to be rich in purinergic receptors. Their substrates, ATP and adenosine, are critical energy signals and storage modulators for tumor metabolism [205, 210–212]. Purine metabolism and purinoceptors have thus become clinical targets, with US Food and Drug Administration (FDA) approved drugs including

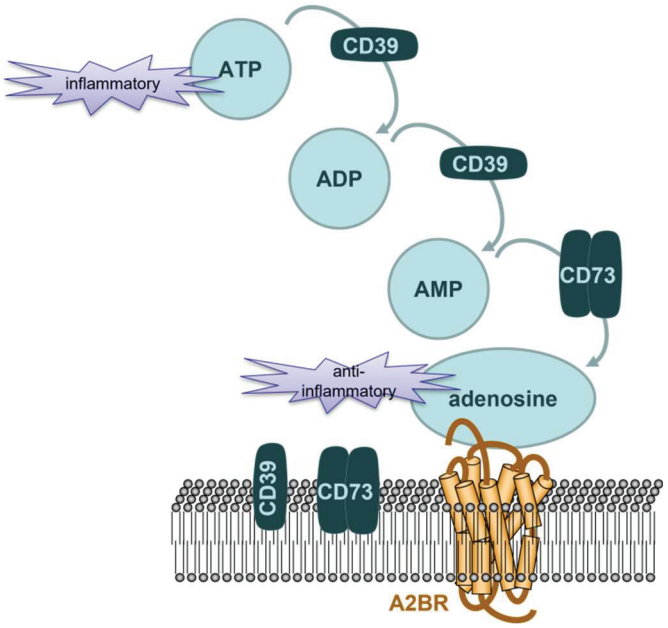

Figure 4 Conversion of ATP to adenosine. ATP is hydrolyzed to ADP, then AMP, by CD39. CD73 then hydrolyzes AMP to adenosine. These metabolic changes from ATP to adenosine can be completed by a cell autonomous method or with the signaling from a neighboring cell. MSCs express both CD39 and CD73 on the cell membrane, permitting them to complete all stages of ATP hydrolysis in a cell-autonomous manner.

regadenoson, istradefylline, dipyridamole, clopidogrel, prasugrel, cangrelor, and ticagrelor [205].

The immune system is rich in purinergic receptors and signaling, with almost all immune cells expressing multiple types of purinoceptors [205]. Additionally, CD39 and CD73 are widely expressed on these cells [213, 214]. ATP is generally associated with danger signals and activation of immune cells in which adenosine generally blunts immune responses (Figure 3) [194, 215]. Thus, the P2 receptors are generally considered to be more heavily involved in activation of the immune response while P1 receptors are generally considered more involved in diminishing immune responses [205, 216]. More broadly, purinergic signaling has also been linked to hematopoiesis, including hematopoietic stem cell development and trafficking [217, 218].

Among the P1 adenosine receptors, we focus on ADORA2B due to its association with CD73 through its ligand, adenosine. ADORA1 and ADORA2A have a higher affinity for adenosine than do ADORA2B and

ADORA3 [193]. However, ADORA1 and ADORA2A are more closely linked with the central nervous system, while ADORA2B and ADORA3 are more closely associated with immune [219]. Studies agree that ADORA2B is expressed on stem cells, while different groups have reported no or low expression of ADORA3 [220–222]. This variability is seen both for MSCs and for other stem cells, including CSCs. It is possible that this heterogeneity of expression is based on the heterogeneous nature of MSCs in culture, with different labs enhancing different MSC subpopulations as an artifact of culture [2].

ADORA2B is a low abundant protein expressed throughout the body (https://www.proteinatlas.org/ENSG00000170425-ADORA2B) [223]. Its stimulation requires a relatively high concentration of adenosine relative to other purinergic receptors [193]. ADORA2B is involved in various pro- and anti-inflammatory processes [224–226]. Further, changes in ADORA2B activation have been seen with various types of MSC differentiation, most notably increased activation during osteogenic differentiation [227–229]. However, it has also been reported that increased ADORA2B activation inhibits [230]. These differences in ADORA2B activation with respect to differentiation lead to questions regarding the receptor's role in stem cell multipotency. stem cell multipotency.

Conclusion and Discussion

Globally, there are over six thousand reported clinical trials with MSCs that are ongoing and completed (clinicaltrials.gov). These trials include but are not limited to treatment of immune mediated disorders such as autoimmunity and inflammation, infection, tissue repair and regeneration, and drug delivery [2, 3]. The outcome of these trials are mixed, with several positive outcomes and several positive results. The varied outcomes might be largely due to the combined analyses of results from different sources of MSCs [2, 231]. Specifically, differences in donor and tissue source, method of isolation and expansion, treatments to the MSCs *in vitro*, and method of delivery. Beyond these differences, much of MSC biology remains unresolved. Notably, the fate of MSCs *in vivo* is unclear. To date, it is unclear if MSCs can exert functional changes without engrafting long-term [1, 34, 67, 232]. It is clear, however, that MSCs can be engineered to transport drug cargo to target regions (e.g. bone marrow, brain) [2, 40, 70]. MSCs are functionally plastic with the expression of a wide array of cytokines and chemokines, and their

receptors, which permit the MSCs to respond rapidly to changing microenvironments [231, 233]. In the presence of an inflammatory milieu, the MSCs are licensed to be immune suppressor cells [72]. Beyond licensing, the fate of the MSCs *in vivo* is less clear. It is thus critical to understand the microenvironmental interactions to elucidate the fate of MSCs after they release their drug cargo and/or after the cells have mitigated pathologic inflammation.

We and others have reported the role of NFκB as a regulator of multipotency [175, 177]. However, it is unclear what NFκB pathway is active to maintain multipotency. NFκB can activate multiple pathways in MSCs, depending on the inflammatory milieu [234, 235]. There are several studies on the role of cytokines on multipotency of MSCs [236–241]. However, in cell culture the MSCs can maintain multipotency throughout cell passages. This indicated that there must be a cell autonomous method that has not been elucidated, which must be addressed in future studies. In contrast to the overwhelming number of studies on cytokines that can act in a cell-autonomous mechanism to maintain multipotency, there is a family of inflammatory mediators belonging to the purinergic family whose role in multipotency is less understood [242–244]. In this capacity, this review article has highlighted the gap in knowledge by addressing the purinergic signaling in multipotency. Specifically focusing on ADORA2B, a purinergic receptor for adenosine with both pro- and anti-inflammatory functions – a duality shared with MSCs [224–226]. Further, ADORA2B expression is known to change during MSC differentiation, and its expression has been linked with that of NFκB [226, 245–247].

The ligand for ADORA2B is adenosine, which requires conversion of ATP to ADP to AMP to adenosine in the extracellular space. The first two steps of this conversion are completed by the ectonucleotidase CD39 (ectonucleoside triphosphate diphosphohydrolase 1); the final conversion of AMP to adenosine is completed by the ectonucleotidases CD73 (5'-nucleotidase ecto) – both of which are expressed on MSCs, among other cells in the microenvironment [201]. CD73 is a constitutive marker for MSCs. However, its role in maintaining the stem cell state is poorly understood [248, 249]. In other cell systems, CD73 has been found to regulate both pro- and anti-inflammatory signaling [247, 250]. In MSCs, it has been suggested that CD73 may be linked to anti-inflammatory function, with $CD73^{high}$ anti-inflammatory function, relative to $CD73^{low}$ MSCs [251]. Additionally, CD73 is upregulated in many cancers, including an observed correlation with increased CD73 and observed correlation with increased CD73 and increased

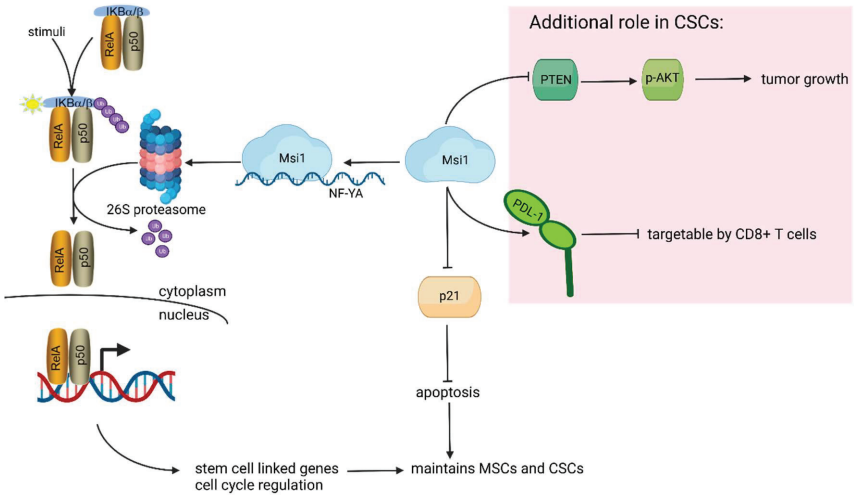

Figure 5 Summary: NFκB regulation in stem cell maintenance. RelA-ccontaining NFκB complex is sequestered in the cytoplasm by IkBα. Through a series of upstream stimuli, IKKα phosphorylates IkBα, which is subsequently ubiquitinated for degradation by the 26s proteasome. Upon phosphorylation and ubiquitination, IkBα releases NFκB, which translocates to the nucleus for transcription of stem cell-linked genes. Msi1 induces transcription of NF-YA, a subunit of the 26s proteasome. Msi1 also inhibits p21, thus blocking apoptosis for stem cell maintenance. Specifically in the context of CSCs, Msi1 has the additional functions of blocking PTEN to enhance tumor growth, and increased PD-L1 expression to exert immune suppression such as tumor- targeting $CD8^+$ T cells.

NFκB in MSCs derived from patients with myeloproliferative neoplasms [252, 253].

This article discusses a rationale to assign NFκB as key to maintaining multipotency of MSCs, partly maintained by cell autonomous process, and exogenously, by the inflammatory milieu. The cell-autonomous method involves the NFκB-purinergic axis, specifically the purinoceptor ADORA2B. IKKα phosphorylates IkBα, which releases the RelA subunit of NFκB, permitting nuclear translocation to activate NFκB targeted gene transcription (Figure 4). In this regard, inhibition of NFκB activity could lead to a loss of multipotency and increased cellular senescence. The experimental inflammatory milieu can activate NFκB, directly or indirectly through release of other cytokines such as IL-1α, IL-10, TGF-β TNFα. Activation of NFκB, in turn can sustain the high levels of the produced cytokines through autonomous regulation of the MSCs (Figure 4). Stemness discussed in this review is not limited to NFκB. In cancer stem cells (CSC), Musashi 1 (Msi1) was shown to

maintain CSCs. It appears that Msi1 might be linked to immune checkpoint since PD-L1 was co-expressed with Msi1 on CSCs. Possible mechanism of Msi 1 in CSC maintenance is summarized in Figure 5.

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