


# Prospective Application of Mesenchymal Stem Cell-Derived Exosomes in the Treatment of Disseminated Intravascular Coagulation

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**Abstract:** Disseminated intravascular coagulation (DIC) is an acquired disorder characterized by systemic activation of blood coagulation, which can arise from various causes. Owing to its abrupt onset, rapid progression, and high mortality rate, DIC presents a major clinical challenge. Anticoagulant drugs, such as heparin or low-molecular-weight heparin, are the current gold standard of treatment; however, these interventions pose considerable bleeding risks. Thus, safer and more effective therapeutic strategies are urgently required. Owing to their strong anti-inflammatory and tissue repair capabilities, mesenchymal stem cell-derived exosomes (MSC-Exos) have gained considerable attention as novel therapeutic options for numerous disorders, including DIC. Their stability in diverse pathological states highlights their potential as promising candidates for DIC therapy. This review presents the latest insights on the pathogenesis of DIC and anti-inflammatory and anticoagulant properties of MSC-Exos. We aimed to elucidate the potential mechanisms by which MSC-Exos influence DIC pathogenesis. We speculate that MSC-Exos offer a multifaceted approach to DIC treatment by attenuating neutrophil extracellular trap formation, modulating M1/M2 macrophage polarization, altering Nrf2/NF- $\kappa$ B signalling pathway to downregulate pro-inflammatory factors, and correcting imbalances in the coagulation-fibrinolysis system through anticoagulant routes. This suggests that MSC-Exos are a potential paradigm in DIC therapy, offering novel targets and treatment modalities for DIC management.

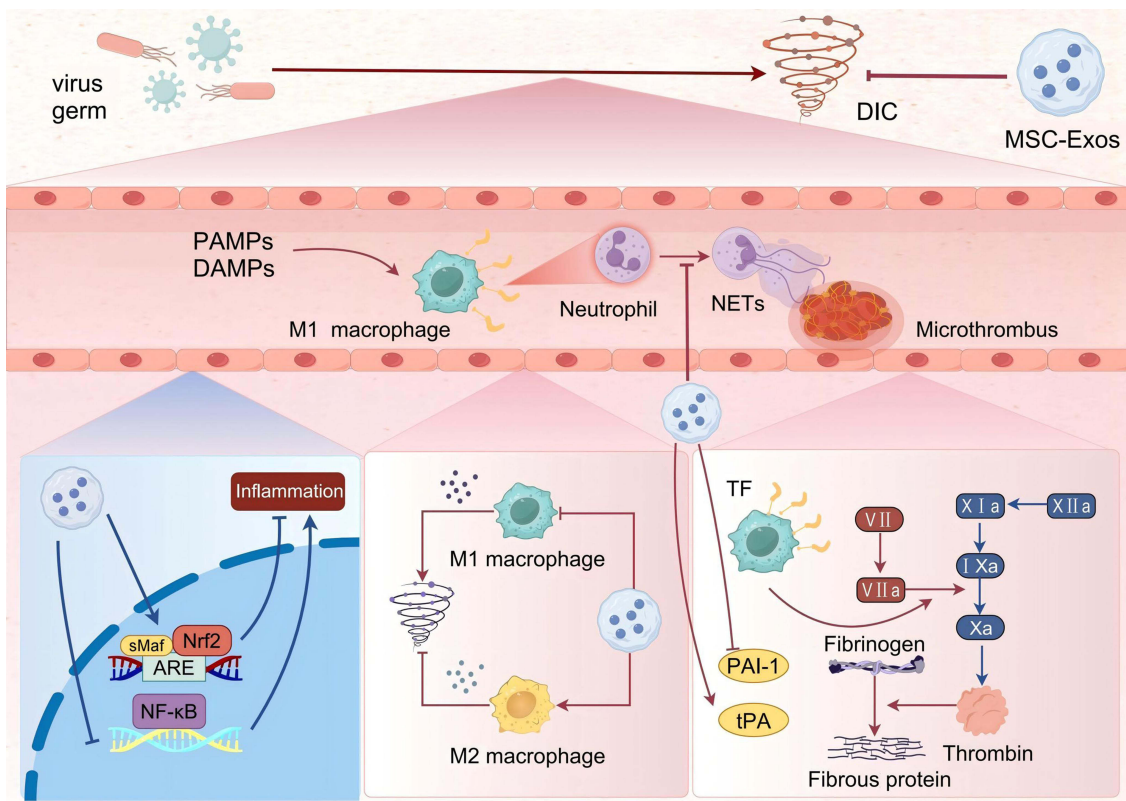
**Keywords:** disseminated intravascular coagulation, mesenchymal stem cell-derived exosomes, anticoagulant therapy, neutrophil extracellular traps, macrophage polarization

## Introduction

Disseminated intravascular coagulation (DIC), a life-threatening systemic condition characterized by widespread activation of the coagulation cascade, is associated with high morbidity and mortality rates. DIC is caused by a number of factors, including infections, trauma, and obstetric complications.<sup>1-3</sup> The pathogenesis of DIC is multifaceted, involving disruption of the balance between coagulation and fibrinolysis by neutrophil extracellular traps (NETs), mononuclear macrophage system abnormalities, and systemic inflammation.

Recent advances in the understanding of DIC and stem cell-derived exosomes have paved the way for the development of promising therapeutic strategies. Mesenchymal stem cell (MSC)-derived exosomes (MSC-Exos) are extracellular vesicles rich in micro RNAs, lipids, and proteins.<sup>4</sup> MSCs are involved in the regulation of inflammation, apoptosis, antigen presentation, and immune responses.<sup>5</sup> Wang et al<sup>6</sup> highlighted the potential of bone marrow MSCs (BMSCs) to indirectly modulate coagulation dynamics in DIC through the regulation of pro-inflammatory cytokines, such as tumour necrosis factor- $\alpha$  (TNF- $\alpha$ ), interferon- $\gamma$ , and interleukin (IL)-1 $\beta$ . MSC-Exos share the therapeutic capabilities of MSCs,

## Graphical Abstract



exerting anti-inflammatory and immunomodulatory effects with enhanced safety and efficacy. Therefore, we speculate that MSC-Exos are a potential therapeutic tool for the treatment of DIC.

This review aims to discuss the potential mechanisms by which MSC-Exos influence DIC treatment. Herein, we explore four key areas: (1) the role of NETs in DIC, (2) the role of the mononuclear macrophage system in DIC, (3) the anti-inflammatory effects mediated by the Nrf2/NF-κB signalling pathway, and (4) the promotion of thrombus dissolution, with the aim of providing fresh insights into DIC management (Graphical abstract).

## Definition and Clinical Importance of DIC

DIC is characterized by an imbalance between coagulation and fibrinolysis, along with systemic activation of the intravascular coagulation system,<sup>7</sup> which presents as a life-threatening condition. DIC is a secondary syndrome that is triggered by various clinical conditions (Table 1). Infection is the predominant trigger of DIC, accounting for 30–51% of all cases.<sup>8</sup> Notably, DIC was observed in 71.4% of coronavirus disease 2019 (COVID-19)-associated fatalities. Al-Samkari et al<sup>9</sup> reported that critically ill patients with COVID-19 frequently exhibited elevated D-dimer levels, indicating significant coagulopathy. Consequently, the prevention and management of DIC are of substantial clinical importance.

Based various hypercoagulable and fibrinolytic markers, DIC is categorized into four types: bleeding (prevalent in patients with leukaemia, primarily manifesting as haemorrhage), organ failure (characterized by hypercoagulability, often observed in patients with infections), consumptive (occurs in obstetric conditions, typically in patients experiencing severe haemorrhage), and non-symptomatic (both hypercoagulation and hyperfibrinolysis markers are relatively mild, resulting in no or mild clinical symptoms).<sup>7</sup>

**Table 1** Diseases Complicated with Disseminated Intravascular Coagulation (DIC)

Disease complicated with DIC	Reference
Severe infections (sepsis, COVID-19, varicella-zoster virus secondary to anaphylactoid purpura)	[1,10,11]
Severe tissue damage (trauma, burns)	[2,12]
Sunstroke	[13]
Severe allergic and toxic reactions	[14]
Severe immune reaction	[14]
Malignant tumour, solid tumour, blood cancer	[15,16]
Obstetric diseases (amniotic fluid embolism, placental abruption)	[3]
Haemolysis, elevated liver enzymes, low platelet (HELLP) syndrome	[17]
Severe hypotension of any aetiology (shock)	[18]
Kasabach–Merritt syndrome	[19]
Iatrogenic disease (transfusion reaction, infusion reaction caused by blood type mismatch)	[109]

**Abbreviations:** COVID-19, coronavirus disease 2019; DIC, disseminated intravascular coagulation.

As mentioned previously, the pathogenesis of DIC is multifaceted and involves intricate feedback mechanisms of the coagulation, immune, and inflammatory pathways.<sup>12</sup> A shared characteristic is the synergistic effect of coagulation and inflammation, leading to widespread microvascular thrombosis, which impairs blood supply, causing organ failure and potentially death.<sup>14</sup> Key players in the imbalance of coagulation and fibrinolysis in DIC include NETs, the mononuclear macrophage system, and the systemic inflammatory response.

Given its nature as an acquired thrombo-haemorrhagic syndrome with diverse types and complex causes, the clinical diagnosis and management of DIC are challenging. The cornerstone of DIC treatment is the treatment of the underlying conditions and anticoagulant therapy.<sup>7</sup> For anticoagulant therapy, the International Society on Thrombosis and Haemostasis guidelines recommend the use of heparin/low-molecular-weight heparin, antithrombin, recombinant human activated protein C, recombinant human thrombomodulin (TM), and tissue factor (TF) pathway inhibitors (TFPI).<sup>7–9</sup> However, anticoagulants are considered high risk medications (Table 2), associated with several risks, including bleeding, necessitating the need for safe and effective therapeutic options.

## Basic Properties and Therapeutic Potential of MSC-Exos

MSCs exhibit promising application prospects in the treatment of DIC. It can be derived from a variety of sources, including the bone marrow, adipose tissue, umbilical cord, amniotic fluid, placenta, dental tissue, endometrium, peripheral blood, and Wharton's jelly.<sup>41–47</sup> They exhibit various capabilities, such as self-renewal, multi-lineage differentiation, anti-inflammatory properties, and immunomodulatory effects.<sup>41,48–50</sup> MSC-Exos are less than 200 nm in diameter<sup>5</sup> and present in all bodily fluids (blood, saliva, urine, plasma, and amniotic fluid).<sup>51</sup> They are rich in bioactive molecules, such as mRNA, micro RNAs, long non-coding RNAs, lipids, and proteins,<sup>4</sup> and play a role in regulating inflammation, apoptosis, antigen presentation, and immune responses.<sup>4,5,52</sup>

Owing to infusion toxicity, immunogenicity, tumorigenic potential, and ethical issues, the application of stem cells in clinical applications is limited.<sup>51</sup> In contrast, exosome therapy offers advantages, such as reduced immunogenicity, absence of infusion toxicity, and excellent biocompatibility, making it a safer and promising approach for therapeutic applications.<sup>5,51,53</sup> MSC-Exos modulate NETs, the mononuclear macrophage system, the Nrf2/NF-κB signalling pathway, and coagulation and fibrinolysis systems in vivo. (Table 3) These mechanisms play a critical role in the onset and progression of DIC, which will be elaborated upon in the following sections. The prevailing clinical approach to the treatment of DIC predominantly focuses on the anticoagulation pathway,<sup>7</sup> and the therapeutic options are relatively constrained, while exosomes exhibit relative safety and possess a diverse range of biological functions. Consequently, the

**Table 2** Summary of Drugs Currently Used to Treat DIC

Medicine	Function	Disadvantages/side effects	Reference
Heparin/low-molecular-weight heparin	<p>Anticoagulant effect</p> <ol style="list-style-type: none"> <li>1)Conformational activation of antithrombin to promote the combination of antithrombin and thrombin.</li> <li>2)Binds to heparin cofactor (HC-II) to inhibit thrombin.</li> <li>3)Stimulates the release of tissue factor pathway inhibitors from the endothelium and inhibits the release of tissue factor, thus inhibiting the coagulation cascade</li> <li>4)Inhibits the coagulation of leukocyte and promotes fibrinolysis</li> <li>5)Inhibits plasminogen activator inhibitor-I and increases fibrinolysis</li> </ol> <p>Antithrombotic effect</p> <ol style="list-style-type: none"> <li>6)Inhibition of coagulation factors FXa, IXa, XIa and XII, and inhibition of vWF release, thereby playing an antithrombotic role.</li> </ol> <p>Anti-inflammatory effect</p> <ol style="list-style-type: none"> <li>7) Competitive displacement of interferon-<math>\gamma</math> for IL-6 binding, altering IL-6 activity.</li> </ol>	<p>Bleeding</p> <p>Heparin-thrombocytopenia-thrombotic syndrome</p> <p>Short duration</p>	[21–24]
RHAPC	<p>Anticoagulant effect</p> <ol style="list-style-type: none"> <li>1)Inactivates coagulation factors, FVa and FVIIIa, to inhibit the production of thrombin.</li> <li>2)Inhibits the release of tissue factors by endothelial cells and monocytes.</li> <li>3)Regulates the survival and apoptosis of endothelial cells and affects coagulation response</li> </ol> <p>Anti-inflammatory effect</p> <ol style="list-style-type: none"> <li>4)Inhibits the release of inflammatory factors by neutrophils and monocytes.</li> <li>5)Regulates NF-<math>\kappa</math>B in endothelial cells and monocytes.</li> </ol>	<p>Bleeding</p> <p>Ineffective treatment</p>	[25–29]
AT	<p>Anticoagulant and anti-inflammatory effects</p> <ol style="list-style-type: none"> <li>1)Binds to thrombin to form a thrombin-antithrombin complex, inactivating thrombin</li> <li>2)Inhibits coagulation factors FIXa, FXa, FXI a, and FXII a, reduces inflammatory infiltration and endothelial injury</li> <li>3)Through the cell signal transduction pathway, pro-inflammatory and pro-coagulant factors are down-regulated and anticoagulant factors are up-regulated</li> </ol>	<p>Bleeding</p> <p>Low certainty of efficacy</p>	[18,30–32]
RHTM	<p>Anticoagulation effect</p> <ol style="list-style-type: none"> <li>1)Binds to thrombin to promote the activation of protein C into APC, directly inactivating coagulation factors, FV and FVIII, inhibiting the expansion of the coagulation system.</li> </ol> <p>Anti-inflammatory effects</p> <ol style="list-style-type: none"> <li>2)Thrombin activation (also exerting an antifibrinolytic effect).</li> <li>3)Inhibits the interaction between thrombin and PAR-I, reduces the proinflammatory effect of thrombin, and inhibits the increase of inflammatory cytokines.</li> <li>4)Inhibits the activation of monocytes and macrophages, inhibits the release of inflammatory cytokines (TNF-<math>\alpha</math>, IL-1, IL-6), restricts the rolling of monocytes and neutrophils on damaged endothelial cells.</li> <li>5)Prevents the formation of NETs, reducing the level of inflammatory cytokines in sepsis, isolates and inhibits HMGB1, inhibiting the HMGB1/ TLR4/ NF-<math>\kappa</math>B inflammatory signalling pathway.</li> <li>6)Binds specifically to lipopolysaccharide (LPS) to reduce LPS-induced inflammation.</li> </ol>	<p>Only in patients with sepsis associated DIC</p>	[33–36]
TFPI	<p>Anticoagulant and anti-inflammatory effects</p> <ol style="list-style-type: none"> <li>1)Combined with TF-VII, it inhibits inflammation and exogenous clotting pathways.</li> <li>2)Direct inhibition of FXa and TF-FVIIa in an FXA-dependent manner.</li> <li>3)Binds to endotoxin to inhibit endotoxin/cell membrane binding and thus endotoxin target cell information transmission, inhibiting the onset of shock and DIC.</li> </ol>	<p>Bleeding</p> <p>Ineffective treatment</p>	[37–40]

**Abbreviations:** AT, antithrombin; rhAPC, recombinant human activated protein C; vWF, von Willebrand Factor; HMGB1, high mobility group protein B1; TLR4, toll-like receptor 4; rhTM, recombinant human thrombomodulin; TNF, tumour necrosis factor; IL, interleukin; NET, neutrophil extracellular traps; TFPI, tissue factor pathway inhibitor; PAI-1, plasminogen activator inhibitor type 1.

**Table 3** Anti-Inflammatory and Anticoagulant Effects of MSCs-Exos via Interaction with NETs, Macrophages, Nrf2/NF- $\kappa$ B Signalling Pathway, and Anticoagulation Pathway

Therapeutic method	Mechanism of action	Therapeutic effect	A treatable disease	Reference
Exosomal miR-127-5p from BMSCs	Target CD64 and act synergistically with anti-CD64 monoclonal antibodies	Reduces tissue damage, inhibits the release of inflammatory factors, and inhibits the formation of NETs	Acute lung injury associated with sepsis	[54]
MSC-EVs	Switch neutrophil death from NETosis to apoptosis	Reduces NET release in angiotensin II-induced mouse models of abdominal aortic aneurysm	Abdominal aortic aneurysm	[55]
hUC-MSCs-EVs contain functional mitochondria of neutrophils	Trigger mitochondrial fusion and restores mitochondrial status and function in neutrophils	Reduces NET formation	Ischemia reperfusion injury	[56]
MSC-Exos	Decrease IL-6 levels and increase IL-10 levels	Decreases M1 macrophage marker in myocardial tissue, and increases M2 macrophage marker	—	[57]
Exosome-shuttled miR-216a-5p from hypoxic preconditioned mesenchymal stem cells	Changes the M1/M2 polarization balance of microglia	Repairs damage	Traumatic spinal cord injury	[58]
MSC-Exos	Promoting M2 macrophage polarization via miR-let7/HMGA2/NF- $\kappa$ B pathway and suppressing its infiltration via miR-let7/IGF2BP1/PTEN pathway in the plaque.	Decreases macrophages infiltration and M1/M2 macrophage ratio	Atherosclerosis	[59]
IL-1 $\beta$ pretreats secreted MSC-Exos	miR-21 transfers to macrophages and down-regulates programmed cell death 4	Induces M2 macrophage polarization, relieves inflammation	sepsis	[60]
Exosome-shuttled miR-150-5p from LPS-preconditioned MSCs	Targets Irs1 in macrophages and down-regulating the PI3K/Akt/mTOR pathway.	Promote the polarization of M2 macrophages	Sepsis	[61]
HUC-MSC-EXOS	Increases the Nrf2 levels and inhibited the LPS-induced NF- $\kappa$ B p65 phosphorylation and NLRP3 inflammasome activation.	Ameliorates LPS/H <sub>2</sub> O <sub>2</sub> -induced neuroinflammation and oxidative stress	Neuroinflammation	[62]
MSC-Exos	Decreases activation of the NF- $\kappa$ B/NLRP3 signalling pathway	Reduces lung inflammation and fibrosis	Cytomegalovirus-Infected Pneumonia	[63]
Adipose-derived stem cell exosomes	Regulate Nrf2/ HO-1 expression	Relieves LPS-induced inflammation	Sepsis	[64]
MicroRNA-342-3p loaded by hUC-MSCs-Exos	Down-regulation of endothelin A receptor	Reduces deep vein thrombosis	Deep venous thrombosis	[65]
MSC-EVs	Auxiliary tPA	Promotes thrombolysis and reduces bleeding complications	Ischemic stroke	[53]

**Abbreviations:** MSC-EVs, mesenchymal stem cell-derived extracellular vesicles; hUC-MSC, umbilical cord mesenchymal stem cell; hUC-MSC-Exo, exosomes derived from umbilical cord mesenchymal stem cell; MSC-Exos, mesenchymal stem cell-derived exosomes; BMSC, bone marrow mesenchymal stem cell; tPA, tissue plasminogen activator.

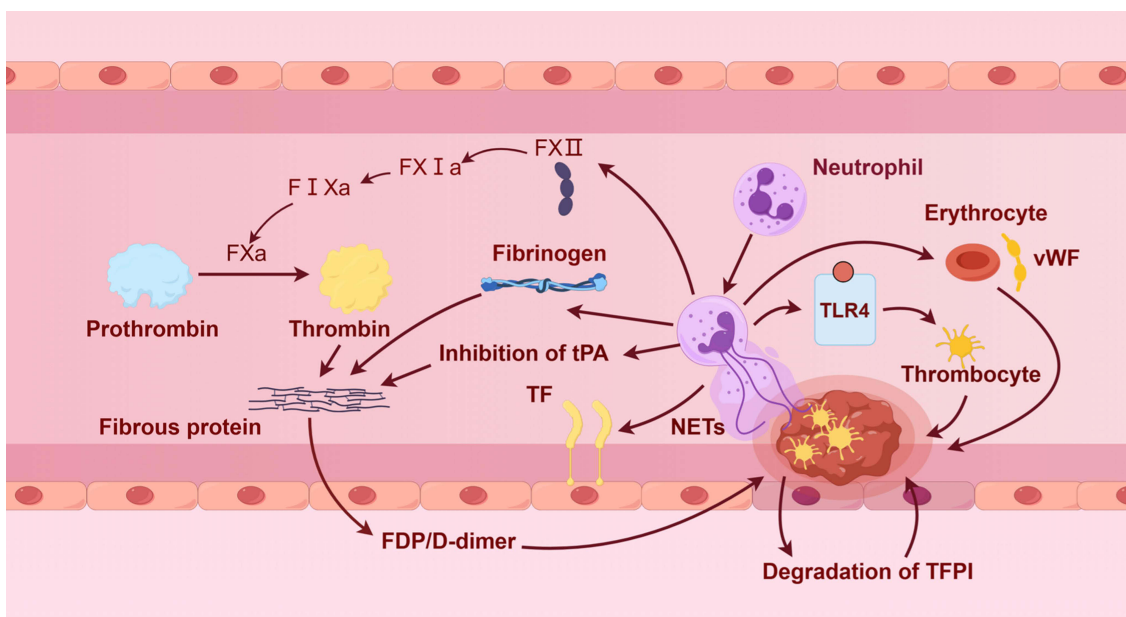
application of MSC-Exos in the treatment of DIC presents promising prospects and may offer a novel and effective therapeutic approach for this condition.

## MSC-Exos Inhibit NET Formation

In response to danger signals, neutrophils produce NETs via a specialized form of cell death.<sup>66</sup> These NETs include depolymerized chromatin, histones, neutrophil elastase, defensin, cathepsin G, myeloperoxidase, and other granular proteins.<sup>66,67</sup> NETs are crucial in inflammation and clotting, acting as a double-edged sword in human physiology. On the positive aspect, the formation of NETs facilitates the neutrophil-mediated eradication of pathogens and limits the spread of infection.<sup>68</sup> On the other hand, excessive NETs production leads to tissue damage. McDonald et al<sup>69</sup> demonstrated that NETs contribute to intravascular coagulation and microvascular dysfunction in sepsis. Aldabbous et al<sup>70</sup> displayed that NETs can induce pro-inflammatory and pro-angiogenic responses in human pulmonary artery endothelial cells via the MPO/H pathway. Additionally, excessive NETs formation is closely associated with organ damage, cancer progression, autoimmune disorders, and other pathological conditions.<sup>71–73</sup>

Recent researches suggest that NETs are involved in the initiation and progression of DIC. Stiel et al<sup>74</sup> pioneered the use of cellular fluorescence to observe circulating NETs in cases of septic shock-induced DIC. Zhang et al<sup>13</sup> identified a correlation between NET release and DIC in the context of heat stroke, proposing that the overexpression of NETs in heat stroke mouse models increases the risk of developing DIC. Furthermore, the fluctuation in NET levels exhibits a correlation with biomarker concentrations in the hypercoagulable state DIC. Zhang et al<sup>13</sup> identified a positive or negative association between NETs and several coagulation-related markers of DIC in a murine model of heat stroke. They observed that upon NETs degradation, DIC-related indices such as prothrombin time, D-dimer, and TM decreased, whereas platelet counts increased. Mao et al<sup>75</sup> demonstrated through statistical analysis that the formation of NETs is independently associated with both the incidence and mortality of DIC in the context of sepsis.

NET-induced DIC occurs through several mechanisms (Figure 1). (1) The interaction between neutrophils and endothelial cells leads to the release of adhesion factors and TFs by endothelial cells, causing endothelial damage. This in turn promotes thrombosis and NET formation,<sup>75</sup> activating the coagulation cascade and contributing to the



**Figure 1** Schematic diagram of NET-induced DIC. NETs stimulate endothelial cells to release TF and activate platelet TLR4, leading to increased vWF and D-dimer levels. Consequently, fibrinogen-to-fibrin conversion, Factor XII activation, and the coagulation cascade are triggered, while tPA is inhibited and TFPI is degraded, resulting in thrombosis and DIC onset.

**Abbreviations:** NET, neutrophil extracellular trap; TF, tissue factor; TFPI, tissue factor pathway inhibitor; TLR4, Toll-like receptor 4; vWF, von Willebrand factor; tPA, tissue plasminogen activator; FDP, fibrin degradation product.

hypercoagulable state observed in the early stages of DIC. (2) Histone proteins in NETs interact with Toll-like receptor 4 (TLR4) on platelets, initiating prothrombotic responses and thrombocytopenia,<sup>76</sup> resulting in positive clotting feedback and widespread microvascular occlusions. (3) NETs act as scaffolds for red blood cells, facilitating the deposition of von Willebrand factor (vWF), fibrinogen, and fibrin, increasing D-dimer levels,<sup>75</sup> thereby inducing thrombosis. (4) NETs activate coagulation factor XII<sup>77</sup> and induce TFPI degradation,<sup>78</sup> enhancing the intrinsic coagulation cascade and promoting thrombosis. (5) NETs block the activity of tissue plasminogen activator (tPA),<sup>79</sup> inhibiting fibrinolysis.

MSC-Exos can effectively inhibit NET formation. Exosomal miR-127-5p from BMSCs can reduce NET formation and alleviate acute lung injury in sepsis by CD64 targeting to induce monoclonal synergies with anti-CD64 and mitigate tissue damage and inflammatory factor release.<sup>54</sup> MSC-derived extracellular vesicles (EVs) can transform NETosis into apoptosis, decreasing NET release, in models of angiotensin II-induced abdominal aortic aneurysm, and reducing the incidence of aneurysms.<sup>55</sup> Furthermore, EVs from umbilical cord mesenchymal stem cells (hUC-MSCs) contain functional mitochondria that can fuse with the mitochondria of neutrophils, improving their function and reducing NET formation, thereby alleviating ischemia-reperfusion injury.<sup>56</sup> Through these NET inhibiting mechanisms, MSC-Exos offer potential therapeutic benefits in DIC treatment.

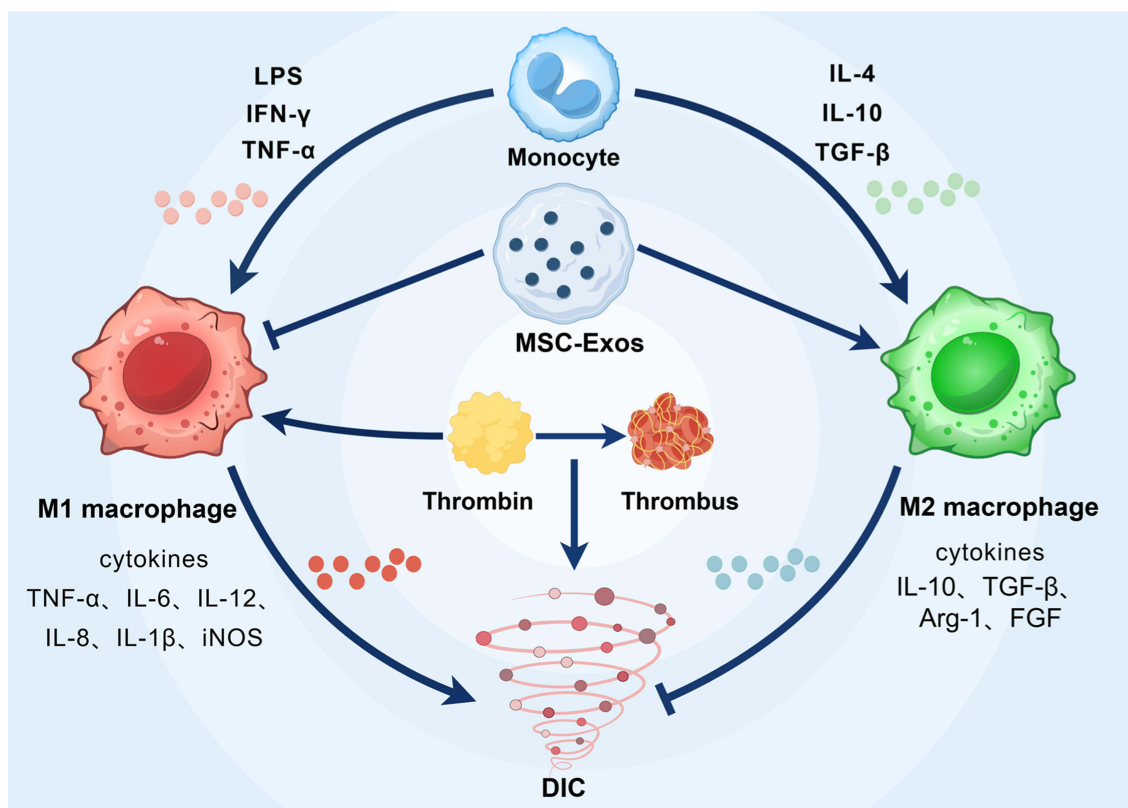
## MSC-Exos Regulate the Polarization Balance of M1/M2 Macrophages

Macrophages play key roles in the development of DIC, and therefore in therapeutic approaches for DIC. Normally, the mononuclear macrophage system plays a pivotal role in clearing coagulation and fibrinolysis products, such as thrombin, plasminogen, fibrin, and fibrin degradation products from the bloodstream, thereby maintaining equilibrium between coagulation and fibrinolysis.<sup>80,81</sup> In the context of infection, pattern-recognition receptors, specifically TLR4, located on the surface of macrophages, can bind to pathogen-associated molecular patterns (PAMPs) and/or damage-associated molecular patterns (DAMPs),<sup>82,83</sup> leading to the release of TF that activates endogenous coagulation pathways.<sup>84</sup> Furthermore, polarization dysfunction in macrophages impairs their capacity to clear coagulative agents,<sup>85</sup> which may contribute to the development of DIC.<sup>86,87</sup>

Within the inflammatory milieu, macrophages exhibit remarkable plasticity, transitioning between M1 (classically activated) and M2 (alternatively activated or inflammation-resolving) phenotypes.<sup>65</sup> The dynamic balance between M1 (pro-inflammatory) and M2 (anti-inflammatory) macrophages is crucial for modulating inflammation, thrombogenesis and its subsequent resolution.<sup>85</sup> M1 macrophages can express a series of pro-inflammatory cytokines (IL-1 $\beta$ , IL-6, IL-12, TNF- $\alpha$ , inducible nitric oxide synthase etc).<sup>88</sup> to initiate inflammatory responses. Excessive M1-driven inflammation may lead to tissue damage and activation of the coagulation system.<sup>89</sup> M2 macrophages secrete anti-inflammatory cytokines (IL-10, arginase 1, transforming growth factor- $\beta$ , etc). to reduce inflammation and promote tissue repair, while also exhibiting fibrinolytic properties.<sup>90</sup> Research indicates that thrombin can facilitate the polarization of M1 macrophages, thereby eliciting inflammatory responses.<sup>91</sup> Proinflammatory cytokines such as IL-6 and IL-8 released by M1 macrophages can stimulate the release of TF and enhance thrombosis.<sup>92,93</sup> The interplay between coagulation activation and inflammatory activation contributes to the development of microvascular thrombosis.<sup>94</sup> In addition, Schönfelder et al<sup>95</sup> demonstrated that reducing the number of inflammatory monocytes could inhibit the growth of thrombus and promote thrombus regression. Consequently, altering the balance between M1 and M2 macrophages could potentially enhance thrombus regression,<sup>90</sup> suggesting that the regulation of macrophage phenotype may serve as a promising therapeutic target for DIC.

The effect of MSC-Exos on macrophages, particularly in regulating the M1/M2 polarization balance, underscores their therapeutic potential in DIC treatment (Figure 2). Numerous studies have shown that MSC-Exos can reduce M1 macrophage polarization and/or facilitate M2 macrophage polarization. Domenis et al<sup>96</sup> reported that the stimulation of MSCs with interferon gamma and TNF- $\alpha$  resulted in the release of immunosuppressive exosomes, which subsequently induced macrophage polarization towards the M2 phenotype. Additionally, other research has indicated that, under hypoxic conditions, MSCs secrete a substantial quantity of EVs enriched with proteins and microRNAs. These EVs are involved in promoting M2 macrophage polarization and possess angiogenic potential.<sup>97</sup>

The capacity of MSC-Exos to regulate the balance between M1/M2 macrophage polarization balance is primarily employed to suppress inflammation and mitigate tissue damage. In myocardial tissues, MSC-Exos decrease pro-inflammatory cytokine levels (IL-6) and increase anti-inflammatory cytokine levels (IL-10), reducing M1 marker



**Figure 2** Mesenchymal stem cell-derived exosomes (MSC-Exos) regulate M1/M2 macrophages to alleviate inflammatory cytokine storms. Upon cytokine and LPS stimulation, monocytes mainly differentiate into M1 and M2 macrophages. M1 macrophages secrete tumour necrosis factor- $\alpha$ , interleukin (IL)-6, and other pro-inflammatory cytokines, and induce inflammatory cytokine storms. To alleviate inflammatory damage, M2 macrophages play an anti-inflammatory role by secreting IL-10, transforming growth factor- $\beta$ , and other anti-inflammatory cytokines. MSC-Exos can inhibit M1-type macrophages, promote M2-type macrophages, restore balance to the polarization of M1/M2 macrophages, and exert anti-inflammatory repair functions, with the potential to alleviate DIC.

**Abbreviations:** LPS, lipopolysaccharide; TNF, tumour necrosis factor; IL, interleukin; DIC, disseminated intravascular coagulation; TGF, transforming growth factor; INF, interferon; Arg-1, arginase 1; FGF, fibroblast growth factor; MSC-Exos, mesenchymal stem cell-derived exosomes.

expression and elevating M2 marker expression.<sup>57</sup> In addition, exosome-shuttled miR-216a-5p from hypoxia-preconditioned stem cells can change the M1/M2 polarization balance of microglia and repair traumatic spinal cord injury.<sup>58</sup> Li et al<sup>59</sup> showed that MSC-Exos can promote macrophage M2 polarization, diminish atherosclerotic plaque area and macrophage infiltration, and consequently ameliorate atherosclerosis.

Sepsis is a significant contributor to DIC,<sup>98</sup> and several studies have indicated that MSC-Exos can mitigate sepsis by modulating macrophage phenotype. Yao et al<sup>60</sup> demonstrated that, after IL-1 $\beta$  pretreatment, miR-21 within MSC-Exos induced macrophage M2 polarization and improved sepsis. Similarly, Zheng et al<sup>61</sup> reported that miR-150-5p in MSC-Exos, subsequent to lipopolysaccharide (LPS) pretreatment, down-regulates the PI3K/Akt/mTOR pathway, thereby enhancing M2 macrophage polarization and providing protective effects against sepsis.

In conclusion, MSC-Exos has the ability to induce polarization of M2 macrophages, which can alleviate inflammation, reduce tissue damage, and improve sepsis.<sup>99,100</sup> However, specific studies directly linking MSC-Exos to the modulation of DIC through macrophage polarization are currently lacking. Given the interdependent relationship between inflammation and coagulation,<sup>101</sup> as well as the function of fibrinolysis in M2 macrophages,<sup>90</sup> MSC-Exos is a promising candidate for the treatment of DIC.

## MSC-Exos Exert Anti-Inflammatory Effects Through the Nrf2/NF- $\kappa$ B Signalling Pathway

DIC can be triggered by coagulative and anticoagulative disequilibrium, which is induced by the systemic spread of inflammation. There is a two-way relationship between inflammation and coagulation; inflammation initiates coagulation,



and coagulation processes amplify inflammatory responses.<sup>102</sup> NF- $\kappa$ B, a pivotal cytokine in mediating inflammatory and immune reactions, catalyses the production of various pro-inflammatory cytokines.<sup>103</sup> NF- $\kappa$ B is implicated in the pathogenesis of DIC through multiple mechanisms. (1) Promote the expression of TF genes,<sup>104</sup> thereby promoting the coagulation cascade and accelerating the progression of DIC.<sup>105</sup> Zhang et al<sup>105</sup> showed that miR-19a-3p can inhibit NF- $\kappa$ B phosphorylation, directly suppressing TF expression and consequently attenuating the coagulation cascade in DIC. Jiang et al<sup>104</sup> reported that the translocation of NF- $\kappa$ B and P65 to the nucleus facilitates FXA-induced TF upregulation and trigger a coagulation cascade. (2) NF- $\kappa$ B mediates TNF- $\alpha$ -induced activation of the FVIII promoter and gene expression,<sup>106</sup> leading to clotting activation. (3) Thrombin stimulates NF- $\kappa$ B and enhances NF- $\kappa$ B-dependent gene expression,<sup>107</sup> establishing a positive feedback loop to amplify coagulation. (4) NF- $\kappa$ B activates the expression of plasminogen activator inhibitor type 1 (PAI-1) genes,<sup>108</sup> leading to impaired fibrinolysis, further promoting coagulation.<sup>109</sup> (5) The expression of TM mediated by NF- $\kappa$ B is down-regulated,<sup>20</sup> which enhances the procoagulant activity of thrombin and inhibits the inactivation of coagulation factors FVa and FVIIIa,<sup>110</sup> further aggravates coagulation and contributes to the progression of DIC. (6) NF- $\kappa$ B can mediate the transcription of inflammatory genes, thereby amplifying inflammatory response,<sup>111</sup> and exacerbating tissue damage.

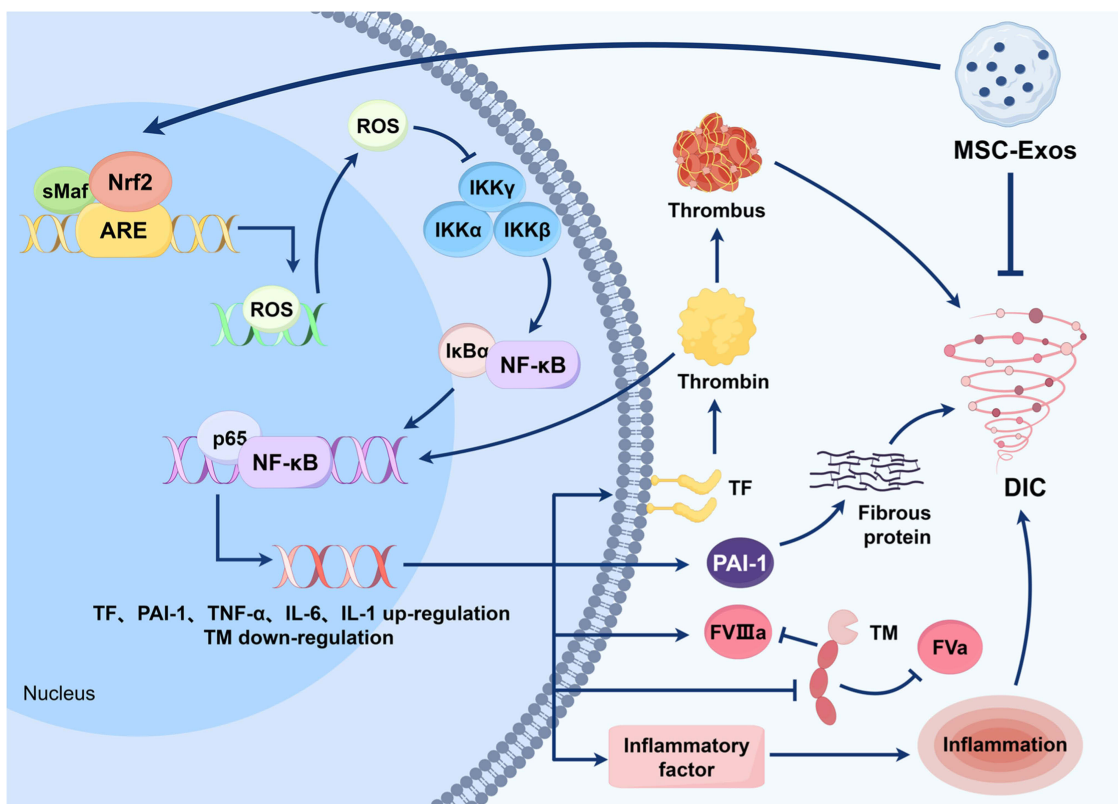
Nrf2, a key transcription factor with antioxidant and anti-inflammatory effects, mitigates oxidative stress by modulating numerous protective enzymes.<sup>112</sup> A broad spectrum of interactions between Nrf2 and NF- $\kappa$ B has been extensively documented, wherein Nrf2 pathway activation can impede the progression of the NF- $\kappa$ B pathway, thereby exerting anti-inflammatory and antioxidant effects.<sup>113</sup> Research indicates that Nrf2 facilitates the polarization of M2 macrophages while inhibiting the polarization of M1 macrophages, thus exerting an anti-inflammatory effect.<sup>114</sup> In addition, Nrf2 has been shown to specifically diminish thrombus activators and confer a protective effect against vascular diseases.<sup>115</sup> Given the critical role of NF- $\kappa$ B in the pathogenesis of DIC and the inhibitory influence of Nrf2 on NF- $\kappa$ B, it is hypothesized that modulating the Nrf2/NF- $\kappa$ B pathway may represent a viable therapeutic target for DIC.

Several studies have demonstrated that MSC-Exos play a regulatory role in the Nrf2/NF- $\kappa$ B signalling pathway. Specifically, MSC-Exos enhance Nrf2 expression while inhibiting LPS-induced NF- $\kappa$ B p65 phosphorylation and NLRP3 inflammasome activation, significantly attenuating the expression of pro-inflammatory cytokines, such as IL-6 and TNF- $\alpha$ .<sup>62</sup> Xian et al<sup>116</sup> illustrated that MSC-Exos mitigated astrocyte activation induced by inflammation through modulation of the Nrf2-NF- $\kappa$ B signalling pathway. Chen et al<sup>63</sup> reported that MSC-Exos alleviated pneumonia induced by cytomegalovirus infection in murine models via the NF- $\kappa$ B/NLRP3 signalling pathway. Shen et al<sup>64</sup> demonstrated that exosomes derived from adipose MSCs alleviate LPS-induced inflammation via modulation of Nrf2/HO-1, offering protection against sepsis. Thus, we postulate that MSC-Exos could modulate inflammatory markers through the Nrf2/NF- $\kappa$ B signalling pathway, contributing to DIC treatment. (Figure 3)

## Mechanism of Action of MSC-Exos in Anticoagulation and Alleviation of Thrombus

In the diseased state, disturbances, such as secondary inhibition or hyperactivity within the body's fibrinolytic system, can precipitate either excessive formation of microthrombi or bleeding. This dysregulation in coagulation and fibrinolytic processes is characteristic of DIC.<sup>98</sup> The activation of plasmin is regulated by the balanced expression of t-PA and its specific inhibitor, PAI-1.<sup>83</sup> PAI-1 can significantly impede fibrinolytic activity.<sup>109</sup> In DIC, endothelial cells subjected to trauma secrete substantial amounts of PAI-1, resulting in thrombin production surpassing that of plasmin, showing a procoagulation state.<sup>8</sup> Additionally, elevated levels of PAI-1 have been associated with adverse outcomes in DIC.<sup>117</sup> Conversely, tPA represents the principal endogenous fibrinolysis promoter,<sup>118</sup> which is capable of systemic plasminogen activation to facilitate thrombolysis with minor systemic activation of the fibrinolytic system.<sup>119</sup> The concurrent elevation of tPA levels and downregulation of PAI-1 levels results in increased fibrinolysis and coagulation factor activation, culminating in bleeding risk. Thus, circulating t-PA and PAI-1 levels serve as suboptimal prognostic indicators for DIC.<sup>120</sup>

Thrombin is a pivotal element in DIC pathogenesis, and its production is stimulated either through TF-driven exogenous pathways<sup>121</sup> or via endogenous routes, such as vascular trauma.<sup>122</sup> This triggers immune and endothelial cells to produce pro-inflammatory cytokines and chemokines,<sup>123</sup> exacerbating inflammation and triggering microvascular thrombosis. Modulation of thrombin activation is mediated by innate anticoagulant mechanisms, including TFPI,



**Figure 3** Schematic diagram of the role of MSC-Exos in Nrf2 pathway activation and NF-κB pathway inhibition. MSC-Exos mitigate inflammation and the coagulation cascade through activation of the Nrf2 pathway and inhibition of the NF-κB pathway.

**Abbreviations:** MSC-Exos, mesenchymal stem cell-derived exosomes; TF, tissue factor; PAI-I, plasminogen activator inhibitor type I; TNF, tumour necrosis factor; IL, interleukin; TM, thrombomodulin; ROS, reactive oxygen species; ARE, antioxidant response element; DIC, disseminated intravascular coagulation.

activated protein C (APC), antithrombin, and vascular endothelial control.<sup>14</sup> In DIC, the synthesis of APC is decreased, whereas its degradation is accelerated.<sup>124</sup> Additionally, there is an increase in TF, vWF, and clotting factors (FXa and FVII), which collectively promote thrombotic activity.<sup>83</sup> Due to the depletion of blood clotting components, the level of anticoagulants is reduced, resulting in uncontrolled coagulation dysfunction.<sup>125</sup>

MSC-Exos exhibit promising anticoagulation and thrombolytic properties. For instance, Pan et al<sup>65</sup> reported that miR-342-3p, transferred via exosomes from hUC-MSCs, mitigates deep vein thrombosis via endothelin A receptor down-regulation. Further investigations suggest that adjunctive MSC-EV therapy alongside tPA after ischemic stroke may diminish the associated bleeding risk while enhancing thrombolysis.<sup>88</sup> The anticoagulative and thrombolytic efficacies of MSC-Exos predominantly arise from their ability to attenuate inflammatory responses;<sup>89</sup> however, the mechanisms underlying this effect remain poorly understood.

## Summary and Future Prospects

Anticoagulant therapy is the standard treatment modality to counteract the pathological progression of DIC. However, anticoagulants, such as heparin, low-molecular-weight heparin, and antithrombin, are associated with significant adverse reactions, including bleeding complications. Recent advancements in exosome technology have demonstrated the potential of MSC-Exos in alleviating symptoms of DIC. This is achieved through the inhibition of NET formation, modulation of macrophage polarization from M1 to M2 phenotypes, and suppression of inflammatory responses via the Nrf2/NF-κB signalling pathway. Moreover, MSC-Exos exhibit anticoagulant and thrombolytic properties, highlighting their potential in DIC treatment.

However, the mechanisms by which MSC-Exos function in DIC pathogenesis remain poorly understood. The pathogenesis of DIC is complex, with the progression of the disease delineated into multiple stages. Currently, it remains

unclear at which specific stage MSC-Exos exert their therapeutic effects in the context of DIC. Furthermore, the technology for the extraction and purification of exosomes is complicated and not amenable to large-scale production, which brings significant challenges for experimental research. Additionally, their clinical application in the treatment of DIC is impeded by various obstacles, including product heterogeneity, rapid clearance from the body, and instability during prolonged storage.<sup>126</sup> Consequently, further research is necessary to optimize the therapeutic utility of MSC-Exos for DIC and improve their stability to facilitate clinical use.

## Abbreviations

APC, activated protein C; BMSC, bone marrow mesenchymal stem cell; COVID-19, coronavirus disease 2019; DIC, disseminated intravascular coagulation; EVs, extracellular vesicles; HMGB1, high-mobility group box 1; hUC-MSC, umbilical cord mesenchymal stem cell; IL, interleukin; MSC, mesenchymal stem cell; MSC-Exos, mesenchymal stem cell-derived exosomes; NET, neutrophil extracellular trap; PAI-1, plasminogen activator inhibitor type 1; TM, thrombomodulin; TF, tissue factor; TFPI, tissue factor pathway inhibitor; TLR4, Toll-like receptor 4; TNF, tumour necrosis factor; tPA, tissue plasminogen activator; vWF, von Willebrand factor; LPS, lipopolysaccharide.

## Ethics Approval and Consent to Participate

This paper serves as a review that excludes animal experiments or human subjects, thus eliminating the need for ethics approval and consent to participate.

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## Disclosure

The authors report no known conflicts of interest in this work.

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