hyperplasia and vascularity, in absence of detectable levels of plasma hFVIII. In both studies, local production of FVIII may explain the hemostatic and chondroprotective effects of MSCs by reducing acute bleedings in joints but it cannot be excluded that the engineered MSCs, and even the native MSCs, might retain their endogenous chondroprotective functions that were not specifically evaluated. Recently, we developed an in vitro model of blood-exposed murine chondrocytes mimicking hemarthrosis conditions.[91] In this model, syngeneic BM-MSCs improved the survival and reduced the apoptotic rate of chondrocytes when added either during the resolution or the acute phases of hemarthrosis but not in a preventive manner. They were shown to exert a chondroprotective effect by upregulating the expression of anabolic markers, and downregulating catabolic and inflammatory markers. This is the first study demonstrating the therapeutic interest of native MSCs to counteract blood-induced cartilage damage and suggesting the need to determine the best window for MSC administration to optimize their effectiveness in vivo. Although the therapeutic efficacy of MSCs deserves to be evaluated in a relevant animal model of hemarthrosis, the study provided the proof-of-concept that MSCs-based treatments could be a therapeutic option in patients with HA. Finally, the homing capacity of native MSCs to a joint afflicted with hemarthrosis was confirmed in a patient with hemophilia A.[88] Even though the effect to prevent arthropathy was not evaluated, the study suggests that MSC-based treatment might be of interest for improving the patients' quality of life, including physical activities.

Conclusions and perspectives

Currently, there is some evidence that the paracrine activity of MSCs may dampen blood-induced alterations in cartilage but it warrants to be demonstrated on other joint compartments, in particular on the synovial membrane that plays a key role in inflammation, angiogenesis and oxidative stress activation in HA. The promising data obtained in vitro on chondrocytes and the demonstration of safety in gene therapy-based strategies highlight MSCs as promising therapeutics for treating patients with HA. The available data from patients are case reports and therefore represent studies for safety evaluation with low-level evidenced proofs of efficacy. However, hemophilia is a rare disease that represents a niche indication for MSC-based therapies. It will therefore be difficult to design clinical trials for treating/delaying arthropathy in this indication.

A number of issues will need to be addressed in animal models before clinical evaluation in humans. One of these will be to identify the right dose, the best route and the right therapeutic window for MSC administration since multiple joints can be impacted by bleedings and this will determine whether a local or systemic route should be envisioned. Systemic injections might be prioritized as MSCs have been shown to target the diseased joints.[88] The window for MSC administration is of importance and will be particularly difficult to determine since a number of hemarthroses are asymptomatic and irreversible lesions may occur as soon as 48 h of bleedings.

While the therapeutic efficacy of MSCs has still to be demonstrated in HA, we may already discussed on the possibilities to evaluate MSC-derived EVs as novel medicinal biological drugs for HA treatments. Most of the paracrine effects of MSCs have been reproduced by their EVs and MSC-derived EVs are effective to prevent OA and RA development in murine models.[92,93] Clinical translation of MSC-derived EVs presents several advantages compared to MSCs, including low risk of blood toxicity on EVs, no risk of tumor formation or differentiation and, off-the-shelf availability of EV batches as soon as a hemarthrosis occurs. Such approach warrants to be tested in the near future.

Role of the funding source

We acknowledge the Agence Nationale pour la Recherche for support of the national infrastructure: "ECELLFRANCE: Development of a national adult mesenchymal stem cell based therapy platform" (PIA/ANR-11-INSB-005).

Authors' contributions

All authors contributed to the analysis and interpretation of the data, drafting of the article, critical revision of the article for important intellectual content and final approval of the article.

Acknowledgments

We acknowledge funding support from the Inserm Institute, the University of Montpellier and the Coordination Médicale pour l'Etude et le Traitement des maladies Hémorragiques et constitutionnelles (CoMETH). We are grateful to the Association Française des Hémophiles for its support and funding.

Competing interests

The authors declare no competing interests.

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