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Mini-review

The future of mesenchymal stem cell-based therapeutic approaches for cancer – From cells to ghosts

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ABSTRACT

Mesenchymal stem cells (MSCs) are multipotent stromal cells which can differentiate into a variety of cell types including osteoblasts, adipocytes and chondrocytes. They are normally resident in adipose tissue, bone marrow and the umbilical cord, but can also be found in other tissues and are known to be recruited to sites of wound healing as well as growing tumours. The therapeutic potential of MSCs has been explored in a number of phase I/II and III clinical trials, of which several were targeted against graft-versus-host disease and to support engraftment of haematopoietic stem cells (HSCs), but currently only very few in the oncology field. There are now three clinical trials either ongoing or recruiting patients that use MSCs to treat tumour disease. In these, MSCs target gastrointestinal, lung and ovarian cancer, respectively. The first study uses MSCs loaded with a HSV-TK expression construct under the control of the CCL5 promoter, and has recently reported successful completion of Phase I/II. While no adverse side effects were seen during this study, no outcomes with respect to therapeutic benefits have been published. The other clinical trials targeting lung and ovarian cancer will be using MSCs expressing cytokines as therapeutic payload. Despite these encouraging early steps towards their clinical use, many questions are still unanswered regarding the biology of MSCs in normal and pathophysiological settings. In this review, in addition to summarising the current state of MSC-based therapeutic approaches for cancer, we will describe the remaining questions, obstacles and risks, as well as novel developments such as MSC-derived nanoghosts.

1. MSCs and their potential use in cancer treatment

MSCs were first isolated and characterised by Friedenstein and his colleagues in the 1960–1970s [1]. They are non-haematopoietic cell precursors, initially found in the bone marrow, but actually present in many other tissues [2]. The International Society of Cellular Therapy (ISCT) uses three criteria to define MSCs [3]: Firstly, MSCs can adhere to plastic under standard culture conditions; secondly, MSCs express cell surface markers including CD105, CD73 and CD90 with no expression of endothelial, haematopoietic, or immunological cell markers such as CD45, CD34, CD14, CD11b, CD79α, CD19 and HLA-DR; thirdly, MSCs have the ability to differentiate into osteoblasts, adipocytes, and chondroblasts when exposed to the appropriate stimuli [4]. MSCs can be readily transduced by a variety of vectors such as Adenovirus, Lentivirus and Adeno-associated virus (AAV) [5–9]. Owing to their relative immune-privilege/-evasiveness and general immune-dampening activities, MSCs can be used in an allogenic setting and are therefore well suited as an off-the-shelf cell therapeutic agent [10,11].

Even though MSCs have been found in and derived from various tissues, the most frequently used MSCs are from bone marrow (BM-MSCs), adipose tissue (AT-MSCs) and umbilical cord (UC-MSCs) [12–14]. As for this good availability and the relative straightforward culturing conditions, MSCs gained increasingly clinical attraction over the last ten years including the treatment of cancer. Generally, the use of MSCs as cellular vehicles in the latter context is based on their ability to home to tumours as they are recognised by MSCs as a “wound that never heals” [15]. This tumour tropism is part of the normal repair function in which MSCs are recruited by sites of tissue injury and inflammation. They are capable of extravasating into tumours when introduced into the organism via the blood stream [16], and although the molecular mechanisms

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behind the migration of MSCs are still not fully understood, studies have shown that the migration is regulated by various cytokines and their corresponding receptors, i.e. SDF-1/CXCR4, HGF/c-Met, VEGF/VEGFR, PDGF/PDGFR, MCP-1/CCR2, and HMGB1/RAGE [17].

In the context of such cell therapeutic approaches, MSCs are used as gene delivery vehicles for tumour targeted therapies. In several preclinical cancer models, MSCs have been genetically modified to express cytokines, growth factor antagonists, anti-angiogenic factors, prodrug-converting enzymes and proapoptotic proteins (Fig. 1 and Supplementary Table 1). Another relatively early-stage approach uses MSCs as carrier for oncolytic viruses [18,19]. Such modified MSCs have been used in different tumour type models including colon cancer [20,21], pancreatic cancer [22–24], lung cancer [25–29], breast carcinoma [30–32], ovarian cancer [33], prostate cancer [34,35], hepatocellular carcinoma [36–39], glioma [40–44], melanoma [45], malignant mesothelioma [46] and lymphoma [47]. Although these pre-clinical studies clearly demonstrated therapeutic benefits of MSC-based targeted approaches, very few clinical trials utilising MSCs as delivery vehicles for anti-cancer treatments have been approved [48,49]. This delay in transition from bench to bedside is at least in parts due to reports that MSCs not only display a potential to undergo malignant transformation, but can also lead to metastasis induction. Both of these issues embody possible barriers for the safe use of MSCs in cancer treatment and will be discussed below.

2. Potential problems with MSCs in cancer therapies

2.1. Do MSCs undergo malignant transformation and form tumours?

In the 2000s it was reported that MSCs could undergo spontaneous, malignant transformation and form tumours *in vivo*, dramatically increasing the risk of therapeutic use of MSCs [50–52]. However, these initial reports were subsequently retracted as it turned out that the observed tumour formation was the result of cross-contaminations with cancer cells [53,54]. In detail, the subsequent analyses showed that the MSC cultures were cross-contaminated with a human sarcoma cell line in one case, and in the second case the presence of two glioma cell lines was detected by DNA fingerprinting and short tandem repeat (STR) analysis [54]. These results underscore the need for stringent cell culture procedures when it comes to the use of primary cell cultures, including MSCs, for therapeutic purposes. Notwithstanding, the acquisition of genetic abnormalities *in vitro* has been observed by several groups [55–57]. However, despite these chromosomal abnormalities no evidence of subsequent malignant transformation was found in these studies [58]. More importantly, there are no reports on MSC-related tumour formation in human patients after MSC administration [59,60]. It cannot be ruled out though, that there is still a hypothetical and residual risk of developing tumours after treatment with MSCs, which harboured cytogenetic abnormalities at the time of injection or develop them later post-administration. Follow-up studies of patients who received MSCs as part of their treatment will add clarity to their tumorigenic potential. However, out of an abundance of caution standardised purification and expansion protocols should be established, as chromosomal abnormalities are mainly related to culture conditions [61]. As part of these considerations, culture conditions with low proliferation rates and minimal expansion rates are recommended to minimise the risk of acquired chromosomal aberrations [61].

In conclusion, while the risk from malignant transformation of MSCs has been overstated in the past, it will be essential to put stringent quality-control and standardisation procedures in place for MSCs to fulfil their potential in clinic applications.

2.2. MSCs and their pro-metastatic activity

Another issue that arose with MSCs is their potential to promote metastasis development in different cancer models [62–64]. In this context, MSCs can induce cancer cell dissemination in tumours that normally do not form metastatic lesions, whereas in tumours with a high potential to metastasise, MSCs cannot further increase the dissemination process [62]. The ability of MSCs to promote tumour metastasis was demonstrated in mammary carcinoma mouse models as well as osteosarcoma and colorectal cancer in these reports. While the initial results were obtained from cancer cells co-implanted with MSCs [63], it was later shown that established tumours could also be induced to form metastatic lesions by

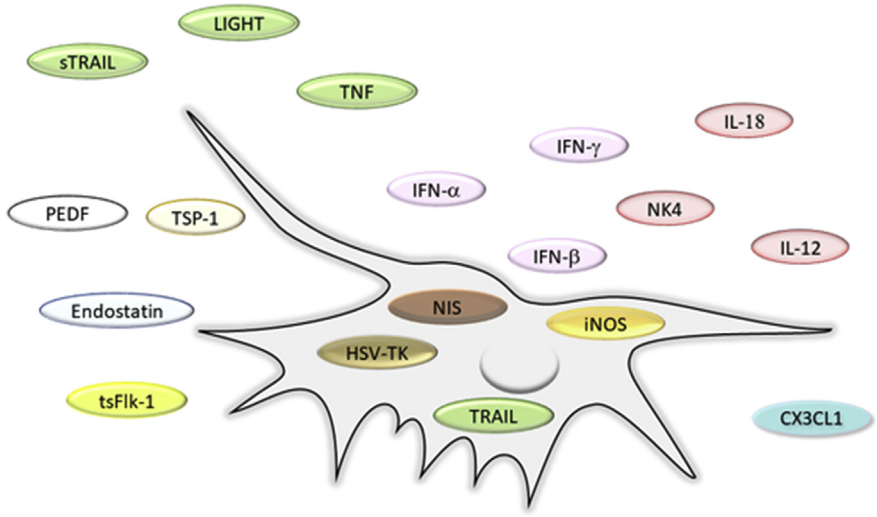

Fig. 1. Overview of therapeutic transgenes delivered by MSCs in pre-clinical cancer studies. Transgenes depicted inside the cells are either expressed as intracellular proteins (e.g. HSV-TK) or as transmembrane proteins (e.g. full-length TRAIL). Most pre-clinical approaches however, target cancer cells by MSCs expressing soluble and secreted proteins such as interleukins, interferons, death-ligands (e.g. sTRAIL) or various other proteins. Further details, including a detailed reference list, of MSC-based pre-clinical studies are provided in Supplementary Table 1.