Identification of galectin-1 as a critical factor in function of mouse mesenchymal stem cell-mediated tumour promotion

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Ph.D. thesis

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I. Introduction

In spite of the increasing significance, the origin of the tumour-associated non-tumour-cell elements (tumour-associated fibroblasts and endothelium) has not been determined decisively. As it has recently been shown, one source of the tumour-associated stroma (TAS) is bone marrow-derived mesenchymal stem cells (BM-MSCs) which migrate into the solid tumour and there contribute to the establishment of TAS.

Exogenously administered MSCs migrate and specifically localize into tumours. However, the effect of transplanted MSCs in term of tumour progression is still actively debated, since both tumour-promoting and tumour-moderating functions have been indicated. Tumour promotion by MSCs has been primarily attributed to their immunosuppressive function and neo-vascularisation promoting effect. All effects of MSCs in solid tumours can be explained by two mechanisms: 1) differentiation of the multipotent MSCs into tumour-associated tissue elements such as fibroblasts, tumour-associated blood vessel endothelium and/or smooth muscle or 2) MSCs are not stably associated with these sites, rather they affect tumorigenesis *via* producing various angiogenic (VEGF, PDGF, FGF), immunosuppressive (TGF-β, IDO, IL-10, PGE2) and metastatic (CCL5) factors. These possibilities are not exclusive; however providing definite answer is difficult due to the lack of MSC specific molecular markers.

Galectin-1 (Gal-1) is an immunosuppressive and pro-angiogenic member of the β-galactoside-binding lectin family, galectins. Immunosuppressive function of Gal-1 has been confirmed in a number of *in vivo* and *in vitro* studies. Targeted inhibition of Gal-1 function or expression in tumour cells provokes immune response against the tumour and subsequent tumour rejection. Also, Gal-1 has recently been implicated in growth and metastasis of solid tumours. Accordingly, high expression of Gal-1 in the tumour cells and/or in TAS indicates poor prognosis of the disease. Crucial role of Gal-1 in tumour angiogenesis has also been confirmed. Additionally, genetically engineered carcinoma-associated fibroblasts expressing low level of Gal-1 failed to help tumour progression. High level of Gal-1 expression has been detected in BM-MSCs contributing to the T-cell regulating role of MSC *in vitro*.

II. Aims

It was previously shown that MSCs produce Gal-1 but functional studies revealed only the *in vitro* immunosuppressive role of MSC derived Gal-1. The effect of MSCs on the development of solid tumours and the key factors released by MSCs influencing tumour progression remained unknown. In order to elucidate these questions we addressed the following:

1.) What is the impact of Gal-1 produced by bone marrow derived MSCs on the growth, vascularisation and metastatic frequency of primary tumours in animal model?
2.) How does the bone marrow MSC-derived Gal-1 influence the incidence of primary tumours and the survival of tumour bearing mice?
3.) How can be sequestered the effect of MSC or tumour cell derived Gal-1 on the development of cancer?

III. Methods

1. Isolation of MSCs
2. Mammalian cell culturing
3. Characterisation of MSCs by flow cytometry
4. Characterisation of adipogenic and osteogenic differentiation property of MSCs
5. Gal-1 gene silencing in MSCs by siRNS transfection
6. Mouse tumour models
7. SDS gel-electrophoresis and Western blot analysis
8. Histology
9. *In vitro* capillary formation assay
10. *In vitro* migration assay
11. Statistical analysis
12. Preparation of buffers, solutions

IV. Results

IV.1. Characterization of MSCs and tumour cell lines

All types of MSCs used in this study: wild type (wtMSC), Gal-1 knocked down (siMSC), control cells transfected with scrambled RNA (scMSC) and Gal-1 knockout (MSC $^{\text{Gal-1-/-)}}$ cells uniformly expressed CD44, CD73, CD90 and Sca-1 but not markers of hematopoietic cell origin, CD34, CD45R, Ly6G, CD3, CD11b, TER119 and differentiated into adipogenic and osteogenic directions. Western blotting analysis showed that wt and scMSCs expressed abundant, siMSCs low level and MSC $^{\text{Gal-1-/-}}$ none of Gal-1. Tumour cell lines, 4T1 breast carcinoma and B16F10 melanoma cells also expressed high level of Gal-1.

IV.2. MSCs localize within the tumour tissue irrespective of their Gal-1 production

To determine whether Gal-1 expression in MSCs contributed to the localization and survival of MSCs within the tumour environment, first an *in vitro* migration assay was carried out. Neither absence of Gal-1 in MSC$^{\text{Gal-1-/-}}$ nor reduction of Gal-1 in siMSCs affected the number of the migrating cells toward 4T1 cells. In contrast, the migration of MSCs significantly slowed down. There was no migration observed when MSCs were cultured alone in the migration plate. Analysis of the frozen tumour tissue sections obtained from animals coinjected with 4T1 breast carcinoma cells and fluorescent dye labelled wtMSCs or MSC$^{\text{Gal-1-/-}}$ showed no difference between the localization of the different MSCs. The siMSCs and scMSCs persisted in the tumour similarly to wtMSCs.

IV.3. Gal-1-dependent enhancement of tumour growth

Balb/C mice were injected with syngeneic 4T1 breast carcinoma cells with or without wtMSCs or MSCs $^{\text{Gal-1-/-}}$. Tumour volume and weights were increased 3.5-fold and 4-5-fold, respectively by wtMSCs on the 40th day and the tumours were palpable much earlier (20th *versus* 32nd day) compared to that of induced by tumour cells alone. In contrast to wild type MSCs, co-injection of Gal-1 deficient MSC did not affect tumour development either in size, timing, or weight. Co-injection of siMSCs expressing low but detectable amount of Gal-1 or control scMSCs resulted in similar effects to that of wtMSCs indicating that low amount of

Gal-1 in MSCs was sufficient to exert tumour promoting effect. MSCs alone did not generate tumour development in 110 days follow up.
Analysis of incidence of palpable tumour showed that all mice, co-administered with 4T1 and wtMSC, developed tumours within 18 days. Nevertheless, injection of 4T1 alone or in combination with MSCs $^{Gal-1-/-}$ showed delayed tumour growth occurring between 21-32 days after initiation of the tumour. Evaluation of the animals' survival showed good correlation with the results of tumour incidence since all mice injected with 4T1 and wtMSC died within 45 days while those obtaining 4T1 or 4T1 and MSCs $^{Gal-1-/-}$ died between 45 and 85 days after tumour initiation. Moreover 1 and 2 animals survived over 110 days in the groups injected with 4T1 and MSCs $^{Gal-1-/-}$ and 4T1 alone, respectively.

IV.4. MSC-induced elevation of microvessel density of primary tumours requires Gal-1 expression by MSCs

Whether Gal-1 was implicated in MSC-regulated tumour vascularisation, an *in vitro* capillary assay was carried out. The absence of Gal-1 in MSCs resulted in diminished blood vessel-like structure formation when co-cultured with H5V murine endothelial cells as compared to the effect of wtMSCs. Accordingly, breast carcinoma was vascularised similarly when tumour cells were applied alone or together with MSC$^{Gal-1-/-}$. In contrast, wtMSCs dramatically increased the vascularisation of the tumour. These results strongly indicated that Gal-1 in MSCs played an essential role in generating new capillary networks of the tumours.

IV.5. Gal-1 in MSCs is an important factor in promotion of tumour metastasis

To determine the role of Gal-1 expression in MSCs regarding the frequency of lung metastasis, the lungs of differently treated animals were macroscopically surveyed after sacrificing them. Average lung weights were around 250 mg in all experimental groups, except those from mice co-injected with 4T1 and wtMSCs which was significantly higher. Moreover, co-transplantation of wtMSCs resulted in a significant elevation of the number of lung metastatic nodules compared to that induced with MSC $^{Gal-1-/-}$ or tumour cells alone. Decrease of Gal-1 production in siMSCs caused some but not significant change in the number of lung metastatic nodules. Accordingly, histochemical analysis of the lung tissues showed that the ratio of the metastatic area *versus* the whole lung section isolated from wtMSCs co-injected animals were much higher than in lungs of animals transplanted with tumour cells alone or in combination with MSC$^{Gal-1-/-}$. These results implied that Gal-1 expression in MSCs was critical in promoting metastasis.

IV.6. Tumorigenic effect of endogenous Gal-1 versus MSC-derived Gal-1

To find out whether endogenous Gal-1 affected tumour growth we changed breast carcinoma to melanoma model to be able to use syngeneic tumour conditions. Wild type (wt) C57BL/6 or Gal-1 knockout (Gal-1-/-) B6.Cg-*Lgals1*t^{m1Rob}/J mice were treated with syngeneic B16F10 melanoma cells with or without wtMSCs or MSCs $^{Gal-1-/-}$. Hardly detectable tumours were observed when Gal-1-/- mice were injected with melanoma cells alone compared to wt animals on the 24th day of injection. Co-transplantation of wtMSCs with tumour cells accelerated tumour development in wild type mice although the enhancement was not statistically significant in contrast to growth promoting effect of wtMSCs on the growth of breast carcinoma. The difference between the two tumour types could be attributed to the extremely high aggressiveness of melanoma. More importantly wtMSCs significantly and

dramatically supported melanoma growth in Gal-1-/- mice. In contrast, transplantation of tumour cells together with MSCs $^{\text{Gal-1-/-}}$ did not promote tumour appearance until the 23rd day in Gal-1 knockout mice. The presence of Gal-1 in MSCs seemed to be essential to support tumour development in knockout mice and Gal-1 expression in tumour cells was not sufficient to entirely by-pass the endogenous Gal-1 deficiency. Accordingly, tumour growth was urged in Gal-1-/- mice injected with tumour together with wtMSCs, resulting in no tumour free animals within 21 days after transplantation. Those Gal-1 knockout animals which were injected with tumour cells alone or in the presence of Gal-1 deficient MSCs showed a delayed tumour growth as the first animals developed visible tumours on the 21st and 25th day and even after 60 days of observation one and two animals remained tumour free, respectively. Co-application of wtMSCs in wt mice hardly influenced the appearance of the tumour indicating the aggressive growth of the melanoma.

V. Summary

Bone marrow derived mesenchymal stem cells (MSCs) have recently been implicated as one source of the tumour-associated stroma which plays essential role in regulating tumour progression. In spite of the intensive research, the individual factors in MSCs controlling tumour progression have not been adequately defined. In the present study we have examined the role of galectin-1 (Gal-1), a protein highly expressed in tumours with poor prognosis, in MSCs in the course of tumour development. These results confirm that galectin-1 is one of the critical factors in MSCs regulating tumour progression.

- Co-transplantation of wild type MSCs with 4T1 mouse breast carcinoma cells enhances the incidence of palpable tumours, growth, vascularisation and metastasis. It also reduces survival compared to animals treated with tumour cells alone or in combination with Gal-1 knockout MSCs.
- *In vitro* studies show that the absence of Gal-1 in MSCs does not affect the number but reduces the migration distance of migrating MSCs toward the tumour cells. Expression of Gal-1 in MSCs does not effect their localization in the tumour tissue *in vivo,*
- MSC-derived Gal-1 enhances tumour vascularisation *in vivo* and induces capillary-formation when co-cultured with H5V endothelial cells *in vitro*.
- Vital role of Gal-1 in MSCs has been further verified in Gal-1 knockout mice. By administering B16F10 melanoma cells into Gal-1 deficient animals, tumour growth is highly reduced compared to wild type animals. Nevertheless, co-injection of wild type but not Gal-1 deficient MSCs results in dramatic tumour growth and development.

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