Roles of Progenitor Cells for Intervertebral Disc Regeneration in "Healer" Mice

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Introduction: Intervertebral disc (IVD) degeneration is a major cause of back pain that can also lead to sciatica, affecting the quality of life. Current treatments are limited to salvage surgical operations. Biological treatments to relieve symptoms or to restore disc are not available as we know little about the biology of IVD degeneration and its potential to regeneration. While most people will develop disc degeneration with aging, there are individuals who are protected even at the age (older than 50 years) when over 90% of the population would succumb to the problem, suggesting the presence of protective genes. Furthermore, maintenance of progenitor cells within the nucleus pulposus (NP) is thought to play an important role in disc homeostasis. A hypothesis is that genetic factors can confer a protection against disc degeneration via better maintenance of resident progenitor cells. There exist strains of "healer" mice (MRL/MpJ, LG/J) that have better regenerative potentials of cartilage tissues[1,2]. Thus, we propose to address the NP progenitor cell pools in these healer mice in relation to the degeneration and potential repair/regeneration potentials of the disc.

Materials and Methods: Good healer (MRL and LG/J) and poor healer (C57/BL6C, and SM/J) mice were used in this study. Histological comparison of tail disc sections was assessed from 8 to 24 weeks of age. Progenitor cell pools and differentiated NP cells were assessed using immunohistochemistry using specific cell markers, Tie-2 and disialoganglioside (GD2), that were recently identified[3]. Tail looping at 8 weeks of age for a fixed period was used as an environmental perturbation that will induce degeneration. Unlooping the tail after the period of looping can assess healing processes with appropriate controls.

Results: A comparison of MRL and C57 mice showed neither observable histological differences, nor signs of degenerative processes from 8-week to 24-week of age. Following tail looping for 4, 5, 6 and 8 weeks, there were significant distortion of the annulus fibrosus (AF) and NP at the compressed and distended sides; in terms of loss of NP cells, AF tears and ruptures, and cell death in the AF. After the tails are unlooped for 4 weeks, there are restoration of NP and AF structures such as cell number in both MRL and C57 mice. However, superior healing is seen for MRL mice at all time-points studied; especially in TL6/TL7, TL7/TL8 and TL8/TL9 disc levels, in which the disc structure restores better via continuous expansion of NP region, cell repopulation and lamellae orientation recovers in the compressed AF sides with a clear NP AF boundary. In C57 mice, the AF lamellae structure remained disorganized following unlooping. Interestingly, in the absence of tail looping, SM/J tail discs already showed severe degeneration even at 8-week-old, while that of LG/J mice were relatively normal, suggesting an impact on developmental or maturation in SM/J IVDs. Immunohistochemistry analysis of progenitors related marker Tie-2 and GD2 shows different expression pattern from 4 to 24 weeks, in which MRL maintain more Tie-2 negative, GD2 positive cells during aging, indicating a role of this cell pool in maintaining disc homeostasis.

Conclusion: LG/J and MRL/MpJ mice have better IVD structure and maintenance than C57BL/6J and SM/J with aging, indicating genetic variations can significantly influence disc function. MRL/MpJ mice can better maintain a NP and AF boundary than C57BL/6J mice from mechanical loading, suggesting a potential "protective" effect and also MRL/MpJ mice maintain a higher number of Tie-2-/GD2+ cells, suggesting this pool of cells may have better function for disc maintenance. In depth analyses with more time points and molecular markers of IVD cells are needed to gain a better understanding of the "protective" genetic influences in the "healer" mice

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