

EFFECTS OF AGE ON RETINAL MACROPHAGE RESPONSES TO ACUTE ELEVATION OF INTRAOCULAR PRESSURE

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Background

Evidence suggests that aging shifts the central nervous system milieu towards a proinflammatory state, with increased reactivity of microglia in the aging eye and brain having been implicated in the development of age-related neurodegenerative conditions. Indeed, alterations to microglial morphology and function have been recognized as a part of normal aging. Here, we sought to assess the effects of age on the retinal microglial and macrophage response to acute intraocular pressure (IOP) elevation and further, determine whether the age of bone marrow would alter the macrophage response to injury in bone marrow chimeric mice.

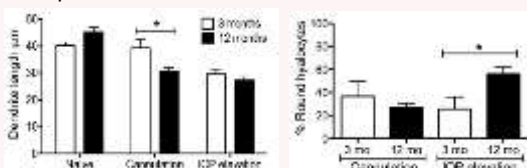
Material & Methods

In the first part of this study, C57BL/6J mice (3 and 12 months) underwent intraocular pressure (IOP) elevation to 50 mmHg for 30 minutes. For controls, the anterior chamber was cannulated and pressure was maintained at physiological IOP (12 mm Hg). In the second part of this study, bone marrow from young (8 week old) or middle-aged (12 month old) mice was used to reconstitute the bone marrow of whole-body irradiated 12 month old mice. Bone marrow chimeric mice underwent IOP elevation 8 weeks after bone marrow transplantation. For both studies, eyes were analyzed 1 week after IOP elevation. Immunofluorescence staining of retinal wholemounts was used to assess changes to the density of retinal macrophages, microglial morphology and activation of glial cells.

Results

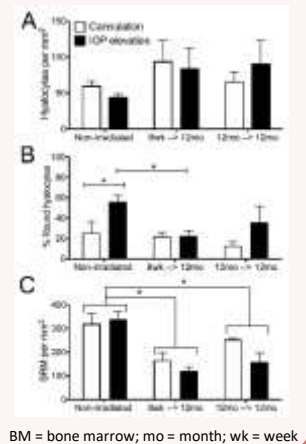
1. Retinal macrophage reactivity and microglial morphological changes were altered in older mice when compared to younger mice in response to injury

- Microglial dendrite length was significantly shorter in 12 month old mice when compared to 3 month old mice after cannulation/injury alone
- There was enhanced reactivity (increase in % round) of retinal hyalocytes in 12 month old mice following IOP elevation
- Subretinal macrophage density following IOP elevation was significantly less in 12 month old mice when compared to 3 month old mice.



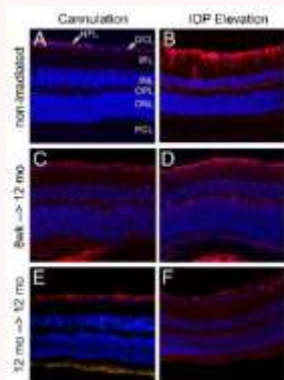
2. Irradiation and bone marrow transplantation with young or old bone marrow altered macrophage responses after IOP elevation

- Experimental groups:
8wk BM → 12 mo old mice
12mo BM → 12 mo old mice
- No significant difference in the density of hyalocytes 1 week after cannulation and/or IOP elevation
- Significantly reduced reactivity of hyalocytes after IOP elevation
- Significantly reduced density of subretinal macrophages after cannulation alone and IOP elevation



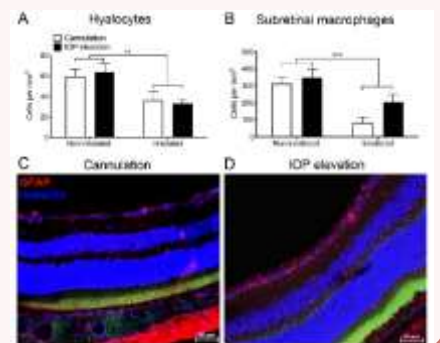
3. Upregulation of GFAP expression after IOP elevation was attenuated by irradiation and bone marrow treatment

- Attenuation of the expression of GFAP was not dependent on the age of bone marrow transplanted



4. Sublethal irradiation (5 Gy) without bone marrow transplantation followed by IOP elevation 8 weeks later:

- Accumulation of hyalocytes and subretinal macrophages was reduced after IOP elevation in irradiated mice
- GFAP upregulation was attenuated after IOP elevation in irradiated mice



Conclusion

- Retinal macrophage reactivity was enhanced in older mice (12 months vs 3 months) following IOP elevation
- Retinal macrophage and glial cell responses to injury were altered in bone marrow chimeric mice:
 - Reactivity of hyalocytes was reduced after injury
 - Subretinal macrophage accumulation was reduced following IOP elevation
 - Gliosis was attenuated following IOP elevation
- Altered macrophage responses in chimeric mice was independent of the age of bone marrow
- Sublethal irradiation treatment (without bone marrow transplant) significantly reduced retinal macrophage density and attenuated GFAP upregulation following IOP elevation

Our data suggest irradiation itself may alter the macrophage and glial responses to retinal injury rather than the age of bone marrow.