Sex-Related Differences in the Mouse Tail Lymphedema Model

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Study Background and Objectives

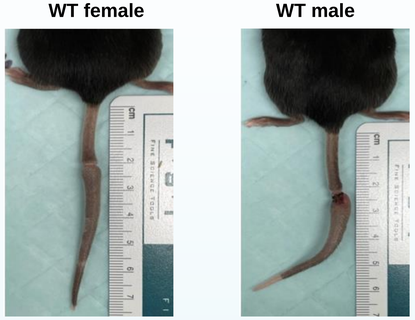
The mouse tail model is frequently used to study post-surgical lymphedema. We have anecdotally observed that male mice have significantly more inflammation and swelling compared with female mice. Although primary lymphedema is more common in females, the effect of sex on secondary lymphedema remains largely unknown. The purpose of this study was, therefore, to study the effect of sex on tail lymphedema in the mouse tail model.

Methods

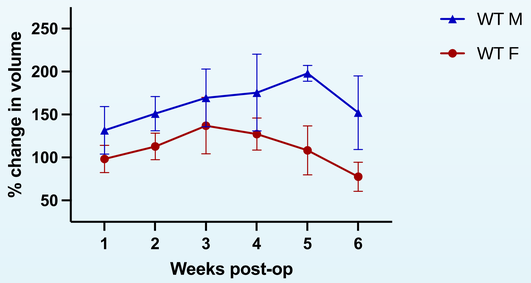
We performed microsurgical tail lymphatic excision on male and female wildtype (WT) and constitutive iNOS knockout (iNOS-KO) mice. To assess the progression of the lymphedema phenotype, we performed weekly tail diameter measurements over a 6-week period. Each week, we also recorded the number of necrosed tails in each group. The Evans blue vascular permeability assay and the Griess test assay were used to assess differences in vascular permeability and nitrosative stress species generation, respectively. Additionally, we assessed changes in fibroadipose deposition using histology and immune cell tissue infiltration using immunofluorescence (IF).

Results

a)



b)



c)

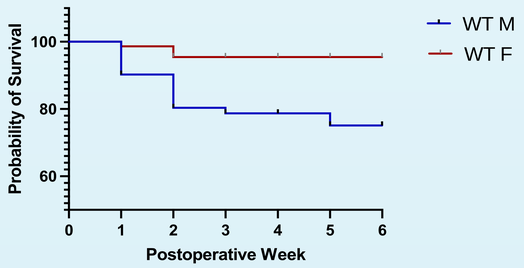
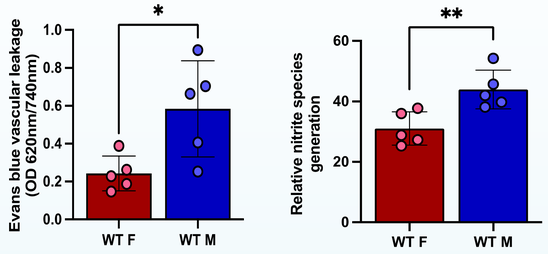


Fig 1: (a, b) Compared to wildtype females, wildtype males have increased tail swelling following tail skin lymphatic excision **(c)** Compared to wildtype females, wildtype males have higher rates of tail necrosis following tail skin lymphatic excision

Results (continued)

a)



b)

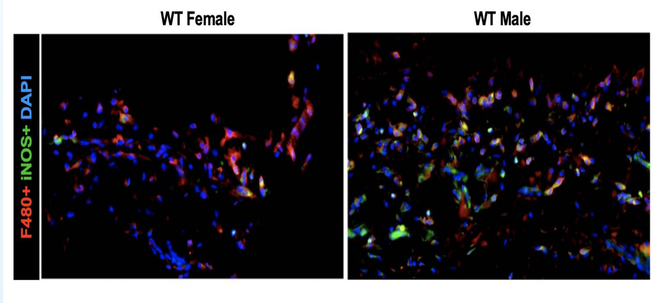
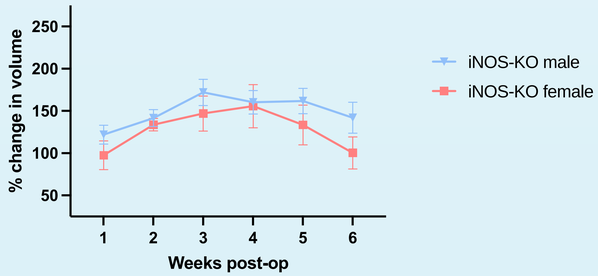


Fig 2: (a) Compared to wildtype females, wildtype males exhibit a greater degree of vascular permeability and generation of nitrosative stress species after tail skin lymphatic excision **(b)** Compared to wildtype females, wildtype males exhibit greater expression of iNOS+ F480+ macrophages following tail skin lymphatic excision

a) **Tail swelling progression in iNOS-KO males vs females**



Results (continued)

b)

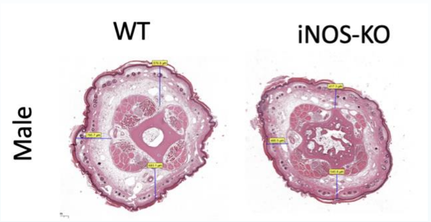


Fig 3: (a) iNOS knockout males and iNOS knockout females exhibit comparable degrees of tail swelling after surgery. **(b)** Compared to WT males, iNOS-KO males exhibit decreased fibroadipose deposition at 6 weeks after surgery

Conclusions

Our preliminary findings suggest that male mice have an increased propensity for developing inflammation and oxidative stress after lymphatic injury. It is possible, therefore, that hormonal agents used for treatment of breast cancer may have an effect on the development of lymphedema. Our findings further suggest that anti-oxidative treatments may have some efficacy for preventing/treating lymphedema. Finally, our findings suggest that other mechanisms may be responsible for the increased rates of primary lymphedema in females. Future studies will determine how oxidative stress injures lymphatics, and how sex-related differences contribute to primary or secondary lymphedema.