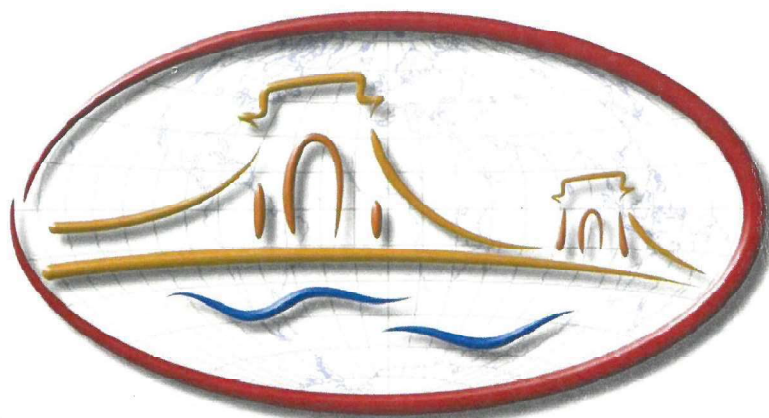




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Characterization of lymphedema in a transgenic experimental mouse model

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Introduction: Loss or dysfunction of lymphatics leads to the development of primary or secondary lymphedema. In addition to accumulation of extracellular fluids, chronic lymphedema may result in fibrosis, swelling and recurrent infections in the affected organs. These complications seriously reduce the function of the affected organs and lead to the degradation of the quality of life for patients. Development of novel therapeutic approaches requires the understanding of the organ specific functions of the lymphatic system and the pathophysiology of lymphedema.

Aims: We aimed to characterize the pathophysiology of lymphedema in a novel transgenic experimental mouse model.

Methods: To induce the organ specific elimination of lymphatics the *Flt4-Cre^{ERT2}; iDTR^{flax/flax}* mouse strain was used. Tamoxifen was administered to induce the expression of the diphtheria toxin receptor (DTR) followed by the injection of diphtheria toxin into the paws, ears and peritoneum to eliminate the lymphatic endothelial cells. The development of the lymphedema was assessed by daily measurement of paw and ear thickness and monitoring of clinical disease signs. Paraffin based histology followed by routine histopathology and immunostainings were performed.

Results: We found that *Flt4-Cre^{ERT2}; iDTR^{flax/flax}* mice develop significant swelling of the ear and paw within one week after the diphtheria toxin injections. We demonstrated that this genetic system allows us to eliminate the lymphatic endothelial cells in the affected organs. The edema reaches its peak 7 days after the diphtheria toxin treatment (acute phase), and after a transient decrease it develops again during the chronic phase. In our experiments we performed the detailed characterization of the histological changes in the acute and chronic phases of lymphedema. We also successfully eliminated the lacteals by intraperitoneal injection of the toxin.

Conclusions: We have successfully applied and characterized a genetic system, which allows us to induce the organ specific elimination of lymphatic endothelial cells. The transgenic experimental disease model provides an excellent tool for studying the molecular mechanisms that are involved in the development of lymphedema, which may serve as novel therapeutic targets in the future.

Ethical Committee or Institutional Animal Care and Use Committee Approval: Animal protocol: PEI/001/404--8/2015

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