Beneficial effect of estrogen on lymphatic system is inhibited by hormone therapy to promote lymphedema.

F. Morfoisse, F. Tatin, F. Lenfant, AC. Prats, B. Garmy-Susini

INSERM, Institute of metabolic and cardiovascular diseases of Toulouse, UMR1048 INSERM - Toulouse III University, FRANCE

More than 10 percent of breast cancer survivors develop secondary lymphedema within weeks and months after surgery and radiotherapy. Lymphedema refers to a condition of lymphatic dysfunction, which results in a massive fluid and fat accumulation. Although it is a common disabling disease, treatment for this chronic pathology remains limited and largely ineffective. Here, we developed a new model of mice secondary lymphedema consisting in a mastectomy associated with axillary and brachial lymph nodes dissection. We observed lymphedema formation after 2 weeks associated with a massive dermal lymphatic leak and lipid accumulation. More than 10 percent of breast cancer survivors develop secondary lymphedema within weeks and months after surgery and radiotherapy. To evaluate the effect of hormone therapy on lymphedema, mice were treated with tamoxifen, an estrogen receptor antagonist and the major therapy for breast cancer. We found that the protective effect of estradiol on lymphatic endothelium is abolished in tamoxifen treated mice, whereas tamoxifen protects from edema and restores lymphatic flow. Estradiol insures a functional lymphatic network by promoting hyaluronan synthesis in the skin and improving lymphatic endothelial function. In conclusion, this study demonstrates for the first time the beneficial effect of estradiol on lymphatic endothelium. We showed that the hormone therapy abolish this effect by disrupting the lymphatic network and modifying the microenvironment. Our work should bring new insights for a better understanding on the lymphedema prevalence and constitute a first step to the treatment of secondary lymphedema.

1/ Estradiol protects against secondary lymphedema. This effect is dependent of Era

To induce secondary lymphedema, we designed a mice model in which we performed a skin flap surgery associated with axillary and brachial lymph nodes dissection [A]. Two weeks after surgery we observed an increase of leg size [B] reduced by a treatment with 17β-Estradiol [E2] [C]. In our model we observe also an increase in interstitial fluids after the surgery [D,E]. By qPCR analysis we also observed that only E2 is expressed in lymphatic cells (HDLEC) [F].

2/ Protective effect of estradiol is reversed by tamoxifen-induced disruption of lymphatic capillaries

Tamoxifen inhibits drainage of extra-tissue fluids by disrupting the lymphatic capillaries [A,D] but not collecting vessels [E,H].

3/ Chronic treatment but not bolus injection of tamoxifen induces lymphatic disruption

Bolus IP injections of tamoxifen have no effect on lymphatic network compared to a chronic treatment [A,H].

4/ Tamoxifen induces extracellular matrix remodeling not lymphangiogenesis

Neither estradiol nor tamoxifen induce lymphangiogenesis [A,D] but tamoxifen decreases estradiol-induced hyaluronan synthesis [E,H] and also increases skin thickness and fibrosis [L].

Conclusion

Tamoxifen : A risk factor for lymphedema

Lymphatic dysfunction

Secondary Lymphedema

A public health challenge