Lymphatic vessel and lymph node function are restored with growth factor treatment

3 December 2007

The frequent spread of certain cancers to lymph nodes often necessitates surgery or radiation therapy that damages the lymphatic system and can cause lymphedema, a condition of localized fluid retention that often increases susceptibility to infections.

The researchers of the University of Helsinki, Finland, and the Ludwig Institute of Cancer Research show that application of vascular endothelial growth factor-C (VEGF-C) to replace excised mouse lymph nodes and lymph vessels ensures formation of mature lymphatic vessels and incorporation of lymph node transplants into existing lymphatic vasculature. An improved outcome of lymph node transplantation is evidenced by improved lymphatic drainage and restoration of normal lymphatic vascular anatomy in VEGF-C-treated mice.

The ability to transfer lymph nodes that reconstitute a functional network of lymphatic vessels in adult tissues is of particular importance in cancer follow-up therapy, as lymph nodes can prevent systemic dissemination of metastases. Accordingly, VEGF-C-treated lymph nodes were more effective in trapping metastatic tumor cells than control transplants.

It has been estimated that approximately 20-30% of patients that have undergone irradiation or surgery of the armpit in response to lymph node metastases develop lymphedema later on. Damage to the large collecting lymphatic vessels, which resemble smaller veins, causes the vast majority of all lymphedemas. It has been estimated that several million patients suffer from such acquired lymphedema worldwide. The treatment of lymphedema is currently based on physiotherapy, compression garments and occasionally surgery, but means to reconstitute the collecting lymphatic vessels and cure the condition are limited.

The Finnish researchers applied vascular endothelial growth factor-C (VEGF-C) gene therapy in mice after surgery removal of axillary lymph nodes, a procedure that mimicked removal of axillary lymph nodes in patients in response to metastatic breast cancer. They found that treatment of lymph node-excised mice with adenoviral VEGF-C gene transfer vectors induced robust growth of the lymphatic capillaries, which gradually underwent an intrinsic remodeling, differentiation and maturation program into functional collecting lymphatic vessels, including formation of uniform endothelial cell-cell junctions and intraluminal valves.

As VEGF-C quite potently increases the rate of lymph node metastasis, the researchers sought to develop a mode of therapy that could be safely applied also in patients that had been treated for cancer. They established that the VEGF-C therapy greatly improved the outcome of lymph node transplantation. As a result, they were able to reconstruct the normal gross anatomy of the lymphatic network in the axilla, including both the lymphatic vessels and the nodes, suggesting that VEGF-C therapy combined to autologous lymph node transfer is feasible in the clinical setting.

The advantage of this rationale is increased patient safety in instances of recurrent malignancies, as the transplanted lymph nodes provide an immunological barrier against systemic dissemination of cancer cells, as well as other pathogens.

The findings demonstrate for the first time that growth factor therapy can be used to generate functional and mature collecting lymphatic vessels. This, combined with lymph node transplantation, allows for complete restoration of the lymphatic system in damaged tissues, and provides a working model for future treatment of lymphedema in patients. Effective lymph node transplantation holds tremendous potential for immunotherapy applications in the treatment of diseases such as

cancer and chronic infections. Furthermore, the findings encourage the use of growth factor therapy to enhance the vascular integration and viability of transplanted tissues.

The group is currently pursuing this form of therapy in larger animal models in order to eventually treat lymphedema patients. Further the group aims to discover methods that would accelerate lymphatic vessel maturation.

Source: University of Helsinki