THURSDAY, MAY 4, 2017
SESSION 1 BEST PAPERS
2:45 PM – 4:15 PM

1

Topical Tacrolimus for the Treatment of Lymphedema

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PURPOSE: Lymphedema is a common, life-long complication of cancer treatment that currently has no cure. Patients with lymphedema have decreased quality of life and suffer recurrent infections, while current treatments are merely palliative and designed to prevent disease progression. Accumulating evidence indicates that T cells play a key role in the pathology of lymphedema by inhibiting lymphangiogenesis and promoting tissue fibrosis. Because the pathophysiology of lymphedema involves primarily the skin and subcutaneous tissues, it may be possible to target T cells locally using topical medications such as tacrolimus without inducing systemic immunosuppression. The purpose of this study was therefore to study the efficacy of topical tacrolimus for prevention and treatment of lymphedema using preclinical mouse models.

METHODS: Topical tacrolimus (0.1%) was used to treat mice that underwent tail superficial/deep lymphatic ablation or popliteal lymph node dissection (PLND). To test the hypothesis that this therapy prevents development of lymphedema, mice were treated after a short delay following surgery (2 weeks). Other animals were treated once lymphedema was established (6 weeks postop) to test the hypothesis that topical tacrolimus can be used to treat established lymphedema. Outcomes including fibroadipose tissue deposition, limb volumes, inflammation, lymphangiogenesis, lymphatic transport and pumping capacity were then measured.

RESULTS: Treatment with topical tacrolimus did not result in significant systemic absorption or immunosuppression. However, this treatment markedly decreased swelling, soft tissue thickness, and fibrosis in the tail model of lymphedema. In addition, topical tacrolimus treatment significantly decreased T cell infiltration. Preventative treatment eliminated more than 95% of lymphedema-associated swelling while late treatment reduced swelling by more than 70%. Technetium^{99} lymphoscintigraphy showed that preventative treatment resulted in a 5-fold increase in interstitial fluid transport to regional lymph nodes. This increased transport capacity corresponded to a more than 2 fold increase in collecting lymphatic pumping capacity as measured by near infra-red lymphangiography. Interestingly, tacrolimus application significantly increased formation of collateral superficial lymphatics and increased inflammatory lymphangiogenesis in 2 other in vivo lymphangiogenesis assays. We observed more collateral lymphatic vessels in both the tail and the PLND models.

CONCLUSION: Treatment with topical tacrolimus markedly decreased chronic T cell inflammation, significantly improved formation of lymphatic collaterals, and decreased tissue fibrosis. These changes were associated with significant decreases in lymphedema and improved lymphatic function. These results have significant implications for the treatment of lymphedema because there is currently no effective pharmacologic treatment for this chronic disease.

2

Macrophage-specific TGF-B is a Targetable Cytokine to Prevent Heterotopic Ossification

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PURPOSE: Transforming growth factor beta (TGFβ) signaling is central to both normal and pathologic wound healing. However the source of TGFβ ligand during wound healing remains unknown. Heterotopic ossification (HO)