Macrophage polarization impacts tunneling nanotube formation and intercellular organelle trafficking.

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Authors: Spencer Goodman, Swati Naphade, Meisha Khan, Jay Sharma, Stephanie Cherqui

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Public Summary:
Tunneling nanotubes (TNTs) are cellular extensions enabling cytosol-to-cytosol intercellular interaction between numerous cell types including macrophages. Previous studies of hematopoietic stem and progenitor cell (HSPC) transplantation for the lysosomal storage disorder cystinosis have shown that HSPC-derived macrophages form TNTs to deliver cystinosin-bearing lysosomes to cystinotic cells, leading to tissue preservation. Int his study, we characterized the type of macrophages that are able to form TNT and lead to tissue repair. We developed unbiased image quantification systems that probe mechanistic aspects of TNT formation and function in vitro, and also studied the macrophages the in vivo disease model. Our finding will advance the use of HSPC for regenerative medicine.

Scientific Abstract:
Tunneling nanotubes (TNTs) are cellular extensions enabling cytosol-to-cytosol intercellular interaction between numerous cell types including macrophages. Previous studies of hematopoietic stem and progenitor cell (HSPC) transplantation for the lysosomal storage disorder cystinosis have shown that HSPC-derived macrophages form TNTs to deliver cystinosin-bearing lysosomes to cystinotic cells, leading to tissue preservation. Here, we explored if macrophage polarization to either proinflammatory M1-like M(LPS/IFNgamma) or anti-inflammatory M2-like M(IL-4/IL-10) affected TNT-like protrusion formation, intercellular transport and, ultimately, the efficacy of cystinosis prevention. We designed new automated image processing algorithms used to demonstrate that LPS/IFNgamma polarization decreased bone marrow-derived macrophages (BMDMs) formation of protrusions, some of which displayed characteristics of TNTs, including cytoskeletal structure, 3D morphology and size. In contrast, co-culture of macrophages with cystinotic fibroblasts yielded more frequent and larger protrusions, as well as increased lysosomal and mitochondrial intercellular trafficking to the diseased fibroblasts. Unexpectedly, we observed normal protrusion formation and therapeutic efficacy following disruption of anti-inflammatory IL-4/IL-10 polarization in vivo by transplantation of HSPCs isolated from the Rac2(-/-) mouse model. Altogether, we developed unbiased image quantification systems that probe mechanistic aspects of TNT formation and function in vitro, while HSPC transplantation into cystinotic mice provides a complex in vivo disease model. While the differences between polarization cell culture and mouse models exemplify the oversimplicity of in vitro cytokine treatment, they simultaneously demonstrate the utility of our co-culture model which recapitulates the in vivo phenomenon of diseased cystinotic cells stimulating thicker TNT formation and intercellular trafficking from macrophages. Ultimately, we can use both approaches to expand the utility of TNT-like protrusions as a delivery system for regenerative medicine.