Brief reports: Lysosomal cross-correction by hematopoietic stem cell-derived macrophages via tunneling nanotubes.

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Public Summary:
Despite controversies on the potential of blood stem cells (HSCs) to promote tissue repair, we previously showed that HSC transplantation could correct cystinosis, a monogenic disease caused by mutation in the cystinosin gene that causes dysfunctional lysosomes (part of cells involved in degrading and recycling biomolecules and other cellular components). Addressing the cellular mechanisms, we here report gene correction after HSC differentiation into macrophages, a type of white blood cell. Upon coculture with cystinotic fibroblasts (i.e. fibroblasts with dysfunctional lysosomes), macrophages produced tunneling nanotubes (TNTs) allowing transfer of cystinosin-bearing lysosomes into Ctns-deficient cells, which exploited the same route to transfer cystine-loaded lysosomes back to macrophages, providing a bidirectional correction mechanism. TNT formation was enhanced by contact with diseased cells. In vivo, HSCs grafted to cystinotic kidneys also generated nanotubular extensions that delivered cystinosin into diseased kidney cells. This is the first report of correction of a genetic lysosomal defect by exchange via TNTs and suggests broader potential for HSC transplantation for other disorders.

Scientific Abstract:
Despite controversies on the potential of hematopoietic stem cells (HSCs) to promote tissue repair, we previously showed that HSC transplantation could correct cystinosis, a multisystemic lysosomal storage disease, caused by a defective lysosomal membrane cystine transporter, cystinosin (CTNS gene). Addressing the cellular mechanisms, we here report vesicular cross-correction after HSC differentiation into macrophages. Upon coculture with cystinotic fibroblasts, macrophages produced tunneling nanotubes (TNTs) allowing transfer of cystinosin-bearing lysosomes into Ctns-deficient cells, which exploited the same route to retrogradely transfer cystine-loaded lysosomes to macrophages, providing a bidirectional correction mechanism. TNT formation was enhanced by contact with diseased cells. In vivo, HSCs grafted to cystinotic kidneys also generated nanotubular extensions resembling invadopodia that crossed the dense basement membranes and delivered cystinosin into diseased proximal tubular cells. This is the first report of correction of a genetic lysosomal defect by bidirectional vesicular exchange via TNTs and suggests broader potential for HSC transplantation for other disorders due to defective vesicular proteins.