Cell membrane repair in acute lung injury: from bench to bedside

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Disclosure

Jianjie Ma is founder of TRIM-edicine, Inc., a university spin-off biotechnology that is developing MG53 in regenerative medicine application.

Cell membrane repair is an elemental physiological process

Membrane Patch = Cell Survival

MG53 drives membrane repair

Many human diseases are linked to defects in membrane repair

MG53 repairs acute injury to cell membrane

Cells expressing fluorescent GFP-MG53 injured with micro-needle show rapid accumulation of MG53 at injury sites.
MG53 is an essential gene for cell membrane repair

MG53 nucleates assembly of cell membrane repair machinery.

Acute injury of the sarcolemmal membrane leads to entry of the extracellular oxidative milieu to the cell interior that induces oligomerization of MG53, followed by recruitment of MG53-containing vesicles to patch the injury site.


MG53 protein therapy for regenerative medicine

Extracellular MG53 protein can prevent injury to skeletal muscle

Control +MG53
Hydrogel

Topical application of rhMG53 for wound healing treatment

Application of rhMG53 hydrogel facilitates wound healing

Hydrogel + rhMG53

Application of rhMG53 for scarless wound healing

Hydrogel + rhMG53

MG53 as a biomarker for tissue injury

Basal serum levels of MG53 increase following eccentric treadmill running and exercise training. Ischemia-reperfusion injury to isolated mouse hearts also causes release of MG53. Thus, serum levels of MG53 can be used as a biomarker for tissue injury and exercise training.
Repetitive deliveries of recombinant MG53 protein do not appear to produce toxic effect in mice.

MG53 is an endogenous protein that is constantly present in the blood circulation, which reduces potential toxicity and immunogenicity associated with systemic application of recombinant MG53.

Informal toxicological studies indicate that intravenous delivery of rhMG53 is safe.

Production of recombinant human MG53 protein

- *E. coli* fermentation of full-length human MG53 protein
- Three-step chromatography
- Purity > 97%
- Stable at room temperature for >4 months as lyophilized powder
- Functional after reconstitution in saline solution suitable for intravenous or subcutaneous delivery

Treatment of acute lung injury is an unmet medical need

- ALI is a syndrome of widespread lung inflammation and increased pulmonary vascular permeability depicted by pulmonary edema and hypoxia.
- Approximately 190,000 cases/year with a mortality rate of 30-40%
- Cause remains unknown but ALI is secondary to sepsis, trauma, ischemia-reperfusion, drug overdose.
- Patients with ALI need to be in an intensive care unit, increasing care costs up to $80,000 per patient.
- Currently there is no effective treatment for ALI.
Under physiological condition, the lung faces constant injurious stresses, and defects in repair to injury of the lung epithelium will have pathological consequences.

Is MG53 protein present in the lung tissue?  
Do the mg53-/- mice show a lung phenotype?  
Can we target MG53-mediated membrane repair for protection and treatment of ALI?

MG53 is expressed in lung alveolar cells

Gene coding sequence for mg53 in the lung is identical to that in the muscle
MG53 repairs injury to lung epithelia cells

mg53-/- mice show increased susceptibility to over-ventilation induced lung injury

mg53-/- mice are susceptible to ischemia-reperfusion induced lung injury

Anoxia-reperfusion leads to recruitment of MG53 protein to plasma membrane of lung epithelial cells
Exogenously applied rhMG53 protein concentrates to A/R-induced injury sites on plasma membrane

Intravenously delivered rhMG53 protein prevents I/R-induced lung injury

rhMG53 protein reduces lung pathology associated with LPS-induced injury

rhMG53 protein as therapeutics for regenerative medicine

- Native MG53 protein appears in serum and increases with injury, reducing potential for immunogenicity and toxicity of rhMG53.
- Recombinant human MG53 protein has been produced and is shown to be stable as lyophilized powder and remains active in saline solution.
- Animal studies show rhMG53 is efficacious in prevention and restoration of acute injuries to multiple tissues, including the lung.
Porcine model of myocardia infarction

Application of rMG53 prior to ischemia protects injury to pig hearts