Nanoparticles Help Deliver Treatment in DM1 Cell Study

2023-01-12
Nanoparticles loaded with antiparasitic medicine pentamidine eased signs of DM1

The approved antiparasitic medicine pentamidine, loaded into biocompatible and biodegradable nanoparticles, successfully eased signs of myotonic dystrophy type 1 (DM1) in cell-based models, a study shows.

The researchers noted that these findings show the potential of nanoparticles to deliver therapeutic agents to treat muscle cells in people with DM1 and support further studies in DM1 animal models.

The cell-based study, “Repurposing pentamidine using hyaluronic acid-based nanocarriers for skeletal muscle treatment in myotonic dystrophy,” was published in the journal Nanomedicine: Nanotechnology, Biology and Medicine.

Pentamidine is approved to treat certain parasitic infections

DM1 is an adult-onset form of muscular dystrophy caused by defects in the DMPK gene. Such defects lead to abnormally long messenger RNA (mRNA), the molecule derived from DNA that guides protein production, forming clumps in cells called nuclear foci. These nuclear foci bind to and sequester the RNA-processing protein MBNL1, disrupting muscle cell function.

Pentamidine is a medicine approved for certain parasitic infections. Recently, cell-based

experiments demonstrated that pentamidine specifically interacted with abnormally long mRNAs, reduced the formation of nuclear foci, and prevented MBNL1 sequestration.

However, pentamidine showed substantial toxicity at the potentially effective doses.

To overcome this barrier, researchers in Italy and France designed biocompatible and biodegradable hyaluronic acid-based nanoparticles (HA-NPs) as a pentamidine carrier.

Hyaluronic acid is an essential component of the meshwork of molecules outside cells that regulate muscle cell function. It also binds to the CD44 protein receptor commonly found on cell surfaces. In this way, HA-NPs have the potential to deliver pentamidine directly to muscle cells, lowering its required dose and reducing side effects.

In this study, the team evaluated pentamidine-loaded nanoparticles in mouse muscle cells, muscle tissue isolated from mice, and a DM1 cell-based model.

Initial experiments tested increasing doses of empty nanoparticles, nanoparticles loaded with pentamidine, and pentamidine alone in myoblasts and myotubes. Muscle fibers generally form via the fusion of precursor myoblast cells into fibers called myotubes. Doses were identified whereby both empty nanoparticles and pentamidine-NPs resulted in cell viability (survival) above 75% after two days of exposure.

Imaging experiments showed HA-NPs appeared in myoblasts after two hours of incubation, distributed in the cytoplasm, which is the region inside the cell but outside the nucleus. After one and two days of incubation, nanoparticles accumulated in the perinuclear region, immediately adjacent to the nucleus. Similar results were seen in myotubes. Overall, 85% of myoblasts and 75% of myotubes showed nanoparticle uptake.

Nanoparticles were not found inside the cell nucleus, nor were there any signs of damage or alterations to cellular structures in both myoblasts and myotubes.

The team then incubated HA-NPs with the large muscle at the back of the lower leg isolated from mice. Over time, the levels of nanoparticles increased inside muscle fibers, while the levels in connective tissue decreased due to the action of local immune cells, the team noted. Further, nanoparticles were evenly distributed within cells along the entire length of the leg muscle.

Nanoparticles are potential candidates for delivering therapeutic agents

To mimic DM1 processes, mouse cells were modified with and without the abnormally long mRNA caused by DMPK gene defects. Tests confirmed that only DM1 cells showed accumulated MBNL1 protein in nuclear foci.

After one day, untreated DM1 cells developed up to six nuclear foci per cell nucleus, while the remaining majority contained 1–2 foci per cell. In contrast, DM1 cells treated with pentamidine-NPs showed four foci per nucleus, while many cells did not have foci. Although pentamidine alone also reduced the number of nuclear foci, the highest dose of pentamidine-NP led to significantly fewer foci.

The team found similar results after two days of pentamidine-NP incubation. Still, at both low and high doses, there was a more substantial reduction in the number of foci versus pentamidine alone. Moreover, the higher pentamidine-NP dose reduced foci significantly more than the lower dose.

“All these features make these nanocarriers potential candidates for delivering therapeutic agents … for treating muscle cells in DM1,” the team wrote. “The results obtained herein using an established muscle cell line provide the experimental background for further studies to test these nanocarriers in DM1 animal models.”

Read the original article on Muscular Dystrophy.