Environmental stressors contribute to Alzheimer's disease-related protein misfolding

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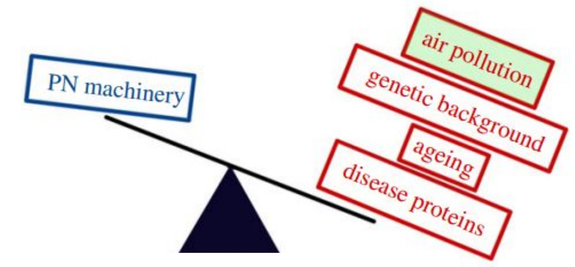
Abstract

Air pollution has been previously identified as a known risk factor for Alzheimer's Disease (AD) development. As a progressive neurodegenerative disease, AD is associated with symptoms such as memory loss, cognitive deterioration, dementia, and difficulty completing daily activities. The causes of AD development are complicated and partially unknown, but are thought to be associated with protein aggregation and overarching proteostasis collapse. The proteostasis network works to control and maintain protein synthesis, restoration, and degradation in the cell. Amyloid beta (Aβ) and tau are proteins shown to misfold and aggregate during AD progression, and exposure to the environmental stressor nano-particulate matter (nPM) derived from air pollution has been shown to increase Aβ aggregation in mouse models. We asked whether there is a specific link between nPM exposure and proteostasis collapse. To determine whether this is true, we utilized the model organism *Caenorhabditis elegans* expressing disease-associated proteins polyQ and Aβ as sensors of proteostasis decline in a variety of tissues. We found that animals expressing polyQ35 and polyQ40 in the body wall muscle cells and polyQ44 in their intestinal lining cells exhibit increased aggregation. Decreased mobility upon exposure to nPM was also shown when compared to controls. Animals expressing Aβ in body wall muscle cells showed increased formation of large, visible, protein aggregates and associated toxicity upon exposure to nPM when compared to controls. To determine whether these findings reflect changes in proteostasis network gene expression, wild type N2 animals were exposed to nPM and showed increased gene expression of the oxidative stress responsive *gst-4* and dysregulated gene expression of the molecular chaperones hsp-4, C12C8.1, and F44E5.4. Overall, our data suggests that exposure to air pollution exacerbates AD via protein misfolding.

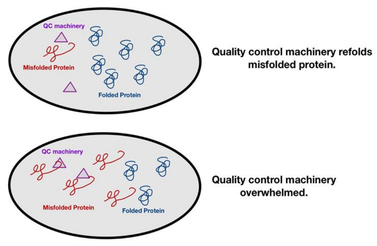
Scientific Question

The proteostasis network works to control and maintain protein synthesis, restoration, and degradation in the cell. We asked whether there is a specific link between nPM exposure and proteostasis collapse associated with AD progression (1).

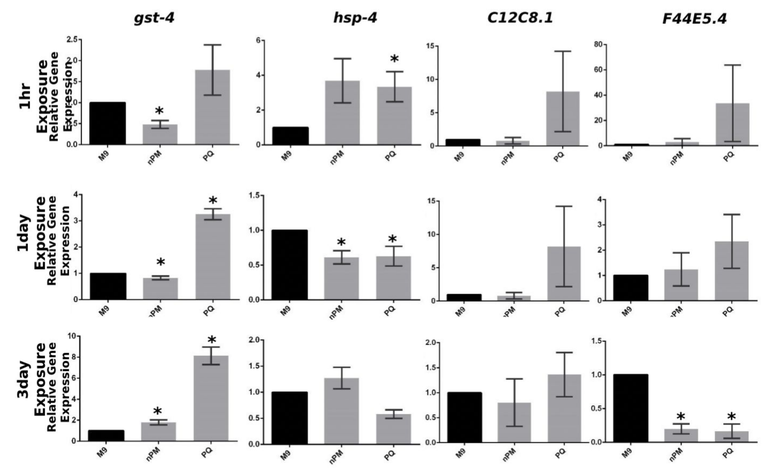
Genetic background, aging, and diseased proteins are known causes of proteostasis collapse - we have identified air pollution as yet another influencing factor (2).



Stress can cause quality control machinery (such as heat shock proteins) to become overwhelmed, resulting in protein misfolding and aggregation (2).



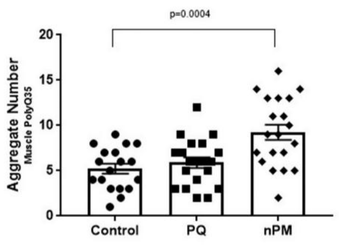
Nanoparticulate matter alters stress-responsive gene expression



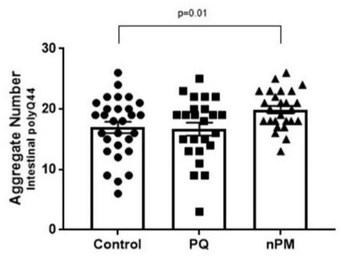
Wild type (N2) animals were exposed to nPM for 72 hours and expression levels of stress-responsive genes gst-4, hsp-4, and the hsp-70s C12C8.1 and F44E5.4 were measured by qRT-PCR.

gst-4 expression was upregulated in response to paraquat exposure. F44E5.4 expression was decreased following 3 hours of nPM or paraquat exposure.

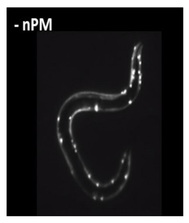
Nanoparticulate matter exposure exacerbates toxicity and protein aggregation in multiple tissues in polyglutamine-expressing animals

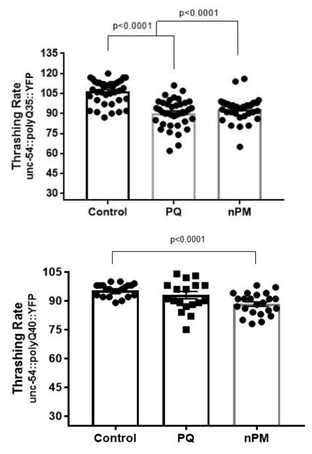


Increased aggregation in animals expressing polyQ in their muscle tissue cells as a result of nPM exposure. Exposed at the L4 stage for 72 hours.

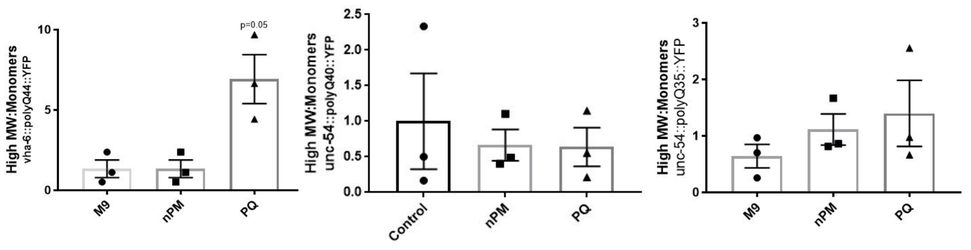


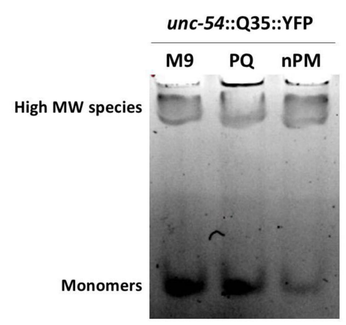
Increased aggregation in animals expressing polyQ in their intestinal lining cells following nPM exposure. Animals were exposed at the L4 stage for 72 hours.





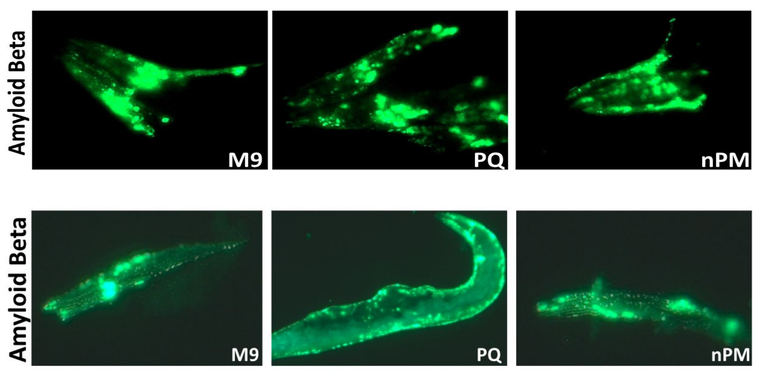
Decreased thrashing rates were shown in animals expressing polyQ (35/40) when exposed to nPM indicating proteotoxicity.





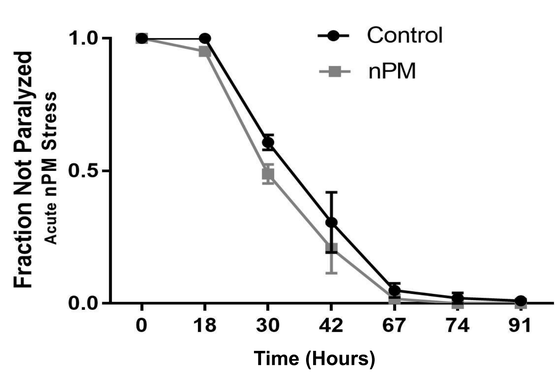
polyQ44:
No significant difference was found between the ratio of high molecular weight species:monomers as a result of nPM exposure.
polyQ40:
No significant difference was found between the ratio of high molecular weight species:monomers as a result of nPM exposure.
polyQ35:
Exposure to nPM showed a trend of increased high molecular weight species, although this was not significant.
***Animals were exposed to nPM at the L4 stage for 72 hours.

Nanoparticulate matter accelerates amyloid-beta aggregation in *C. elegans*

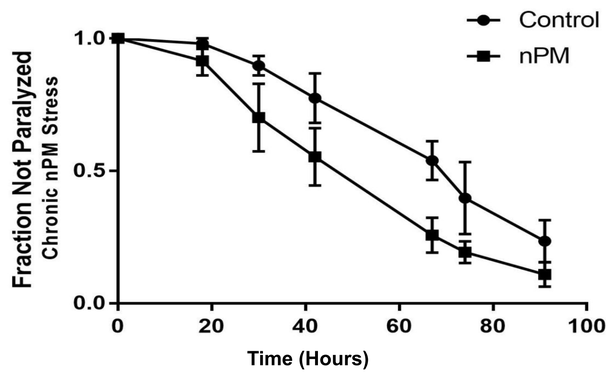


24 hour exposure:
Changes in Aβ toxicity in body wall muscle cells qualified through visible protein aggregates. L4 animals were exposed for 24 hours. Protein aggregates were then made visible through immunofluorescence.

Exposure to nanoparticulate matter triggers amyloid-beta toxicity in *C. elegans*



1 hour exposure to nPM:
Changes in Aβ toxicity in body wall muscle cells measured as a function of paralysis. L4 animals were exposed to nPM for 1 hour to stimulate acute stress conditions. Exposed animals were then monitored for paralysis at 25°C for at least three days.



3 day exposure to nPM:
Changes in Aβ toxicity in body wall muscle cells measured as a function of paralysis. L4 animals were exposed to nPM for 3 days to stimulate chronic stress conditions. Exposed animals were then monitored for paralysis at 25°C for at least three days.

References

1. Green EH, Kikis EA (2020) Determining the effects of nanoparticulate air pollution on proteostasis in Caenorhabditis elegans. *PLoS ONE* 15(12): e0243419.
2. Kikis EA (2020) The proteostatic effects of traffic-derived air pollution on Alzheimer's disease risk. *Open Biol.* 10: 200146.

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