Nanomaterial influences gut microbiome and immune system interactions

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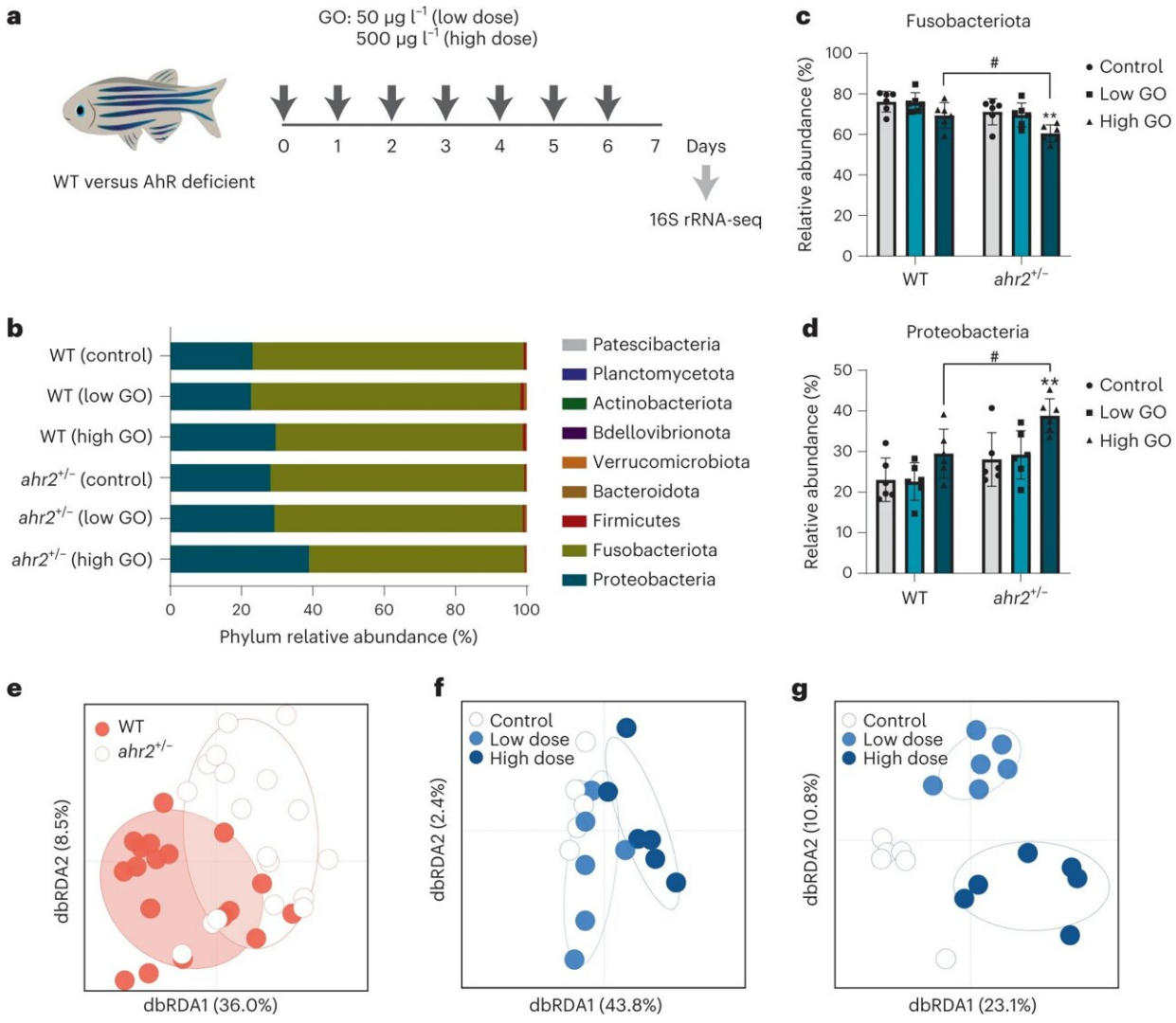

AhR-dependent changes in the gut microbiome of adult zebrafish. **a**, Experimental design for the seven-day exposure regimen in adult zebrafish (WT and *ahr2*$^{+/-}$). **b**, The most abundant bacteria phyla of the gut microbiota among

genotypes and treatments. Each bar represents the average of six individuals in each condition. **c**,**d**, Relative phylum abundance of Fusobacteriota (**c**) and Proteobacteria (**d**) in WT versus *ahr2*$^{+/-}$ fish exposed to GO. The error bars represent the mean values ± s.d. of six individuals. Significant differences between the treatments and genotypes are shown. Two-way analysis of variance using Tukey's multiple comparisons test was used to analyze the statistical differences (Fusobacteriota, $^{**}p = 0.0065$, $\#p = 0.0265$; Proteobacteria, $^{**}p = 0.0055$, $\#p = 0.0186$). **e**, Supervised analyses of the microbiota composition between the two genotypes. **f**,**g**, Impact of GO on gut microbiota composition among WT (**f**) and *ahr2*$^{+/-}$ (**g**) zebrafish. dbRDA, distance-based redundancy analysis. Credit: *Nature Nanotechnology* (2022). DOI: 10.1038/s41565-022-01260-8

The nanomaterial graphene oxide—which is used in everything from electronics to sensors for biomolecules—can indirectly affect the immune system via the gut microbiome, as shown in a new study on zebrafish by researchers at Karolinska Institutet in Sweden. The findings are reported in the journal *Nature Nanotechnology*.

"This shows that we must factor the gut microbiome into our understanding of how nanomaterials affect the immune system," says the paper's corresponding author Bengt Fadeel, professor at the Institute of Environmental Medicine, Karolinska Institutet. "Our results are important for identifying the potential adverse effects of nanomaterial and mitigating or preventing such effects in new materials."

Graphene is an extremely thin material, a million times thinner than a human hair. It comprises a single layer of carbon atoms and is stronger than steel yet flexible, transparent, and electrically conductive. This makes it extremely useful in a multitude of applications, including in "smart" textiles equipped with wearable electronics and as a component of composite materials, to enhance the strength and conductivity of

existing materials.

With the increased use of graphene-based nanomaterials comes a need to examine how these new materials affect the body. Nanomaterials are already known to impact on the immune system, and a few studies in recent years have shown that they can also affect the gut microbiome, the bacteria that naturally occur in the gastrointestinal tract.

The relationship between nanomaterial, gut microbiome and immunity has been the subject of the present study performed using zebrafish. The nanomaterial investigated was graphene oxide, which can be described as a relative of graphene that consists of carbon atoms along with atoms of oxygen. Unlike graphene, graphene oxide is soluble in water and of interest to medical research as, for example, a means of delivering drugs in the body.

In the study, the researchers exposed adult zebrafish to graphene oxide via the water and analyzed how it affects the composition of the microbiome. They used both normal fish and fish lacking a receptor molecule in their intestinal cells called the aryl hydrocarbon receptor, commonly abbreviated as AhR, a receptor for various endogenous and bacterial metabolites.

"We were able to show that the composition of the gut microbiome changed when we exposed the fish to graphene oxide, even at a low dose, and that the AhR also affected the gut microbiome," says the study's first author Guotao Peng, postdoc researcher at the Institute of Environmental Medicine at Karolinska Institutet.

The researchers have also generated zebrafish larvae that completely lack a natural gut microbiome, which makes it possible to study the effects of individual microbiome components, in this case butyric acid (a fatty acid), which is secreted by certain types of gut bacteria. Butyric

acid is known to be able to bind to AhR.

Doing this, the researchers found that the combination of graphene oxide and butyric acid gave rise to so-called type 2 immunity in the fish. The effect turned out to be dependent on the expression of AhR in the intestinal cells.

"This type of immunity is normally seen as a response to parasitic infection. Our interpretation is that the gut immune response can handle graphene oxide in a similar way to how it would handle a parasite," says Guotao Peng.

Using an advanced method for mapping the immune cells, the researchers were also able to show that a component of the immune system called innate lymphoid cells are found in zebrafish larvae.

"This shows that the zebrafish is a good model for studying the immune system, including the primitive or innate immune system," says Bengt Fadeel.

More information: Bengt Fadeel, Graphene oxide elicits microbiome-dependent type 2 immune responses via the aryl hydrocarbon receptor, *Nature Nanotechnology* (2022). DOI: 10.1038/s41565-022-01260-8. www.nature.com/articles/s41565-022-01260-8

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