Gallium nanodroplets as anti-inflammatory reagents for biomedical and pharmaceutical applications

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Gallium (Ga) compounds, as the source of Ga ions (Ga^{3+}), have been historically used as anti-inflammatories. Currently, the widely accepted mechanisms of the anti-inflammatory effects for Ga^{3+} are rationalized based on their similarities to ferric ions (Fe^{3+}), which permits Ga^{3+} to bind with Fe-binding proteins and subsequently disturbs the Fe homeostasis in the immune cells. Here in contrast to the classic views, our study presents the mechanisms of Ga as anti-inflammatory by delivering Ga nanodroplets (GNDs) into lipopolysaccharide-induced macrophages and exploring the processes. The GNDs show a selective inhibition of nitric oxide (NO) production without affecting the accumulation of pro-inflammatory mediators. This is explained by GNDs disrupting the synthesis of inducible NO synthase in the activated macrophages by upregulating the levels of eIF2α phosphorylation, without interfering with the Fe homeostasis. The Fe^{3+} transferrin receptor-independent endocytosis of GNDs by the cells prompts a fundamentally different mechanism as anti-inflammatories in comparison to that imparted by Ga^{3+}. This study reveals the fundamental molecular basis of GND–macrophage interactions, which may provide additional avenues for the use of Ga for anti-inflammatory and future biomedical and pharmaceutical applications. This work has been published in *ACS Nano* [1].

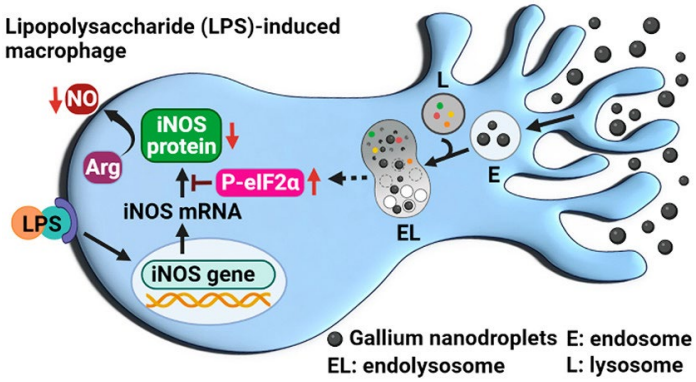

Figure 1: GNDs as anti-inflammatory reagents in LPS-induced macrophages. GNDs can be endocytosed and remain in the endosomes. When lysosome fuses with endosome, GNDs upregulate the levels of eIF2α phosphorylation to interfere with the iNOS mRNA translation, which results in the reduced iNOS protein expression and can further inhibit the synthesis of NO from l-arginine (Arg).

Reference

[1] Zhang C. Gallium Nanodroplets are Anti-Inflammatory without Interfering with Iron Homeostasis. *ACS Nano* **2022**, *16*, 8891-8903.