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Reexamining IFN-γ Stimulation of De Novo NAD+ in Monocyte-Derived Macrophages

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In his paper, Grant investigated altered kynurenine pathway (KP) metabolism in IFN-γ–activated human monocytes and macrophages. He observed increased activity of indoleamine 2,3-dioxygenase (IDO), the first and rate-limiting KP enzyme, and increased levels of quinolinic acid (QA), a KP intermediate and precursor to de novo NAD+. After noting an IFN-γ–induced decrease in NAD+ and subsequent rescue via PARP inhibition, the author concluded that IFN-γ stimulates increased de novo NAD+ biosynthesis and PARP-induced NAD+ catabolism. However, there are several key concerns in the paper that need to be addressed.

First, the author made the critical assumption that IFN-γ causes increased production of de novo NAD+, the end product of KP metabolism. He assessed flux through the KP by measuring KYN concentration in the cell homogenate as a proxy for IDO activity and used mass spectrometry to measure QA levels. IFN-γ–treated cells exhibited increased IDO activity and elevated QA levels, which was sufficient evidence for the author to conclude increased de novo NAD+ production. However, these data can support other interpretations as well. Considering that the author also saw IFN-γ–induced decrease in overall NAD+ concentration, he may have been observing QA accumulation and decreased de novo NAD+ because of reduced activity of QPRT, the rate-limiting enzyme responsible for converting QA to NAD+. The feasibility of this alternative interpretation warrants a better understanding of QPRT and its response to IFN-γ. By conducting a mass-labeling experiment—adding mass-labeled TRP to the media and tracking its metabolism through the KP—the author could have solidified or revised his claim that there is not only increased flux through the KP but also elevated de novo NAD+ production. Indeed, several studies have shown an increase in QA levels within microglia and macrophages on IFN-γ but have not documented changes in de novo NAD+ synthesis, bringing the author's claim into doubt.[1–4]

Second, despite observing robust decrease in NAD+ on IFN-γ treatment and implicating PARP activity, the author did not explore other NAD+ biosynthetic pathways.[5] In addition to the de novo NAD+ pathway, the salvage and Preiss-Handler pathways are major contributors to the intracellular NAD+ pool.[6] Therefore, the paper undermines the importance of these other pathways and offers a limited view of the effects IFN-γ has on overall NAD+ biosynthesis. To better understand NAD+ biosynthesis and catabolism in the context of IFN stimulation, future investigations should assess the activity of crucial enzymes in the other pathways, such as NAPRT and NAMPT, of the Preiss-Handler and salvage pathways, respectively. It would be interesting to see whether these enzymes and their respective pathways work in tandem with the de novo pathway to increase NAD+ production on IFN-γ treatment.

Grant's paper offers important insight into the effect that IFN stimulus has on KP metabolism of human macrophages at different stages of maturation. However, his assumptions about de novo NAD+ production and his exclusion of other NAD+ biosynthesis pathways undermine his overall argument and therefore should be rigorously assessed with additional methods. These experiments would complement his investigation and provide substantive evidence to reaffirm or invalidate his conclusions.

Author Contributions

PM wrote the introduction and summary of the paper in question, while PSM formulated the discussion and critique contained in this letter.

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