Without a Trace: The Pirin and NF-κB Interaction

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Pirin is a non-heme iron binding protein and was recently identified as a protein target of the CCG-20391 series of small molecules. The CCG compounds were originally discovered in a high-throughput Rho/MRTF/SRF dependent luciferase screen and have since been shown to have anti-fibrotic and anti-metastatic properties, but the mechanism of how Pirin affects MRTF/SRF signaling has yet to be identified. Pirin has been shown to have a role in many different cellular processes, namely epithelial to mesenchymal transition, ferroptosis, senescence, and more. Interestingly, Pirin has also been thought to be a nuclear co-transcription factor to various transcription factors, one of which is the NF-κB family of proteins. Therefore, our hypothesis was that modulation of Pirin through the binding of the CCG compounds may modulate NF-κB pro-inflammatory signaling. To investigate this, we used recombinant biochemical techniques like Fluorescence Polarization, Size Exclusion Chromatography, and Gel Shift Assays to investigate the interaction between Pirin and NF-κB. Additionally, we developed a novel Pirin knockout (KO) mouse model to further determine the functional relationship between Pirin and NF-κB. Surprisingly, we are not able to detect a stable complex of Pirin and the RelA subunit of NF-κB nor do we observe any modulation of inflammatory genes by qPCR in a Pirin KO mouse model. Upon closer investigation of the cellular location of Pirin we found that Pirin is localized in the cytoplasm and does not translocate to the nucleus upon NF-κB activation. We therefore conclude that, based on our observations, Pirin has cellular functions other than a co-transcription factor. These functions may include modulation of MRTF/SRF signaling and actin polymerization, but do not affect NF-κB signaling.

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