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Commentary

The right and wrong of DOKing the nuclear receptor

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In this issue, Burgermeister et al., present very interesting data on the function of DOK1, an enigmatic multifunctional adaptor protein (Friedrich et al., 2016). Previous studies nicely summarized by the authors, have shown that DOK1 functions as a tumor suppressor by negatively regulating signaling via its interaction with p120 RAS GTPase-activating protein (GAP) to dampen MAPK signaling cascades downstream of receptor and non-receptor kinases in various cellular contexts (Songyang et al., 2001; Shinohara et al., 2004; Zhao et al., 2006). Remarkably, *Dok-1* knockout studies demonstrated hematopoietic defects (Yasuda et al., 2004) and development of sarcomas with the loss of other DOK members (Mashima et al., 2010). The studies of DOK1 function were not only complicated by the presence of several protein isoforms encoded by the same DOK1, but also dynamic shifts of the protein between the nucleus and the cytosol in resting and proliferating cells, respectively. Regarding the docking of DOK1, the full-length p62 DOK1 has an N-terminal plextrin homology (PH) domain for membrane binding, and a phospho-tyrosine-binding (PTB) domain thought to be involved in interactions with other protein partners. Unexpectedly, the authors convincingly demonstrate that the C-terminal PTB domain has yet another partner which directly regulates cell growth. And this is when peroxisome proliferator-activated receptor gamma (PPARg) enters the stage. Detailed experiments demonstrate not only the physical interactions between the two novel partners, but also a sensitivity of common cancer cell lines to PPARg agonists in a DOK1-dependent manner. The potential for repurposing of PPARg agonists, an established class of anti-diabetic medications, is one of the practical implications of the results of the Burgermeister et al. paper. As for the clinical relevance, the authors demonstrate that the loss of DOK1 expression portends worse survival in patients with colorectal cancer.

Obviously, the devil is always in the detail. And those are multiple, and generously supplied in the Supplement to the paper. Not only the loss of DOK1, but also the expression of several isoforms with C- and N-terminal truncations differs in between the analyzed cases. To make matters even more complicated, patients' survival seemed to depend on the DOK1 expression in the stroma suggesting a general role DOK1 in cell growth. Are these phenomena all mediated by PPARg? Or DOK1 continues to play many characters on the same stage shifting between the cellular and tissue compartments and changing its size and docking tools? The future will tell…

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