The Good Cholesterol

Interplay between hormones and the receptors they bind regulates behavior and physiology of multicellular organisms. It is therefore surprising that we still don’t know the endogenous ligands for all of the nuclear receptors and therefore a large portion of our physiology remains in the dark. Wei et al. shine some light on the estrogen-related receptor α (ERRα) and show that cholesterol is a key endogenous ligand for this receptor.

Although seemingly unsurprising, this finding is front-page news. Technically, one would expect that ERRα would bind a steroid or a related lipid-like molecule, given the fact that it shares some sequence and structure similarity with the estrogen receptor (ER). Previous studies, however, showed that ERRα may be constitutively active and that its LBD has an occluded ligand binding pocket, which led researchers to propose that ERRα is an example of a ligand-less receptor. To approach the question of whether ERRα has an endogenous ligand or not, Wei et al. used a lipidomic strategy in which immobilized ERRα LBD was exposed to the entire mouse brain lipidome. When results from this experiment was compared to a control, the authors saw that one, and only one, lipid was highly enriched by ERRα LBD resin—the cholesterol. Wei et al. confirm this interaction using different in vitro experiments and go on to demonstrate that cholesterol increases ERRα transcriptional activity. In addition, Wei et al. show that muscle toxicity, an important side-effect of statins, the cholesterol lowering drugs in wide-spread use, is mediated by ERRα and that cholesterol, as well as statins and bisphosphonates, another class of compounds that targets cholesterol biosynthesis pathway, regulate ERRα-mediated osteoclast differentiation, myogenesis, and macrophage cytokine production. This work also nicely explains the ERRα constitutive activity “paradox.” With an endogenous ligand as ubiquitous as cholesterol, it is no wonder that ERRα is always on.


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