

Orphans and inflammation

Many are now well-aware of the negative impact of inflammation on our health, including cancer as well as rheumatologic, metabolic and neurologic disorders. Insults to the body either through injury (acute or chronic), or poor diet can result in inflammation. Improving our omega-3 to omega-6 intake ratio is important, but why? As it turns out, fatty acid metabolites or so-called bioactive lipids can initiate programs in the body much the same way that hormones do. This is accomplished through their interactions with specific proteins called receptors that recognize them and in turn translate the interaction into chemical programs that carry out functions in cells and tissues. Depending on the bioactive lipid-receptor combination, the “chemical app”, as it were, can be pro-inflammatory, anti-inflammatory, or it can be pro-resolving to actively resolve existing inflammation. There are bioactive lipid receptors that fall into each of those three categories. One can imagine that regulation of these pathways could be advantageous. Among other strategies, this can be accomplished in part through dietary choices. There are numerous examples of bioactive lipids that are vitally beneficial to our well-being. Drugs that mimic their structure and function, or that impact their synthesis, metabolism or receptor interactions are highly sought after for therapeutic benefits.

Through the science of genomics many genes have been discovered, but not all of these have a known function yet. The genes that encode the receptors discussed above have been decoded and classified according to the structures they assume that are predicted based on genetic codes. Many have been paired with their binding partners or ligands. However, a number of these pairings have remained at large so that there are “orphan” receptors for which binding partners remain to be determined and there are ligands for which we are still seeking receptors. Our study falls into this latter example. There is a particular Omega-6 lipid metabolite that is very pro-inflammatory, called 12(S)-HETE. This molecule is known to affect many diseases, but its receptor was always inferred. For decades it remained unknown until we de-orphaned it and discovered it was a protein called generically until this point GPR31, and now 12HETER1 for the *12(S)-HETE Receptor-1*. 12(S)-HETE can be considered a master regulator. It causes inappropriate blood clotting, which is a process that cancer cells usurp and take advantage of to metastasize. It can also direct blood vessels to grow where they are unwanted, for example in the cornea of the eyes, potentially causing loss of vision, or in tumors where new blood vessels sustain the tumor tissue. 12(S)-HETE can direct unwanted survival apps in cancer cells making them resistant to radiation and chemotherapy too. Ironically, some inflammation is beneficial. Wound-healing, immune system development, de-webbing our fingers during development, ovulation, and labor in childbirth all rely on inflammation and on molecules like 12(S)-HETE, which in these contexts is physiologic and not pathologic as in the examples above and in such devastating diseases like diabetes or Alzheimer’s dementia. By cloning and characterizing the receptor for this bioactive lipid, we now have a concrete foundation for placing into context a large body of work by our group and others. We screened publicly available ‘omic-type databases and determined that the receptor is associated with many cancers including prostate cancer. Our interference with 12HETER1/ GPR31 either by genetic deletion or chemically, significantly hinders processes that cancer cells

rely on to generate tumors and hampers prostate tumor growth in our test model. Others have already used this discovery to demonstrate a role for 12HETER1 in dysfunctional pancreatic islet cells. We are currently validating several classes of receptor drugs discovered through structural modeling.

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Publication

[12-HETER1/GPR31, a high-affinity 12\(S\)-hydroxyeicosatetraenoic acid receptor, is significantly up-regulated in prostate cancer and plays a critical role in prostate cancer progression.](#)

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