３つの関連論文の紹介。DHA の代謝と Lactonase（Paraoxonase）との関連。特に、２番目の論文（*Science*）は、DHA の代謝物（**4-HDHA**）が糖尿病性網膜症に効くかもしれない、ということで注目されている。この場合、**4-HDHA** は酵素的に出来ると考えられているが、2005 年の JLR の論文（1 番目）は、Lactonase の基質にもなっているとしているものの、**4-HDHA** は非酵素的にできると考えている。3 番目の論文は HDL にある Lactonase が LDL の酸化を抑えるかもしれない、としている。これらの報告は、DHA の代謝物が直接、網膜症に効くらしいことと、さらなる代謝物が LDL の酸化を抑える働きをするかもしれない、ということを示唆している。（YS; 2010/02.28）

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http://www.jlr.org/content/46/6/1239.long

1. J Lipid Res. 2005 Jun;46(6):1239-47. Epub 2005 Mar 16.

Human paraoxonases (PON1, PON2, and PON3) are lactonases with overlapping and distinct substrate specificities.

Draganov DI, Teiber JF, Speelman A, Osawa Y, Sunahara R, La Du BN.

The paraoxonase (PON) gene family in humans has three members, PON1, PON2, and PON3. Their physiological role(s) and natural substrates are uncertain. We developed a baculovirus-mediated expression system, suitable for all three human PONs, and optimized procedures for their purification. The recombinant PONs are glycosylated with high-mannose-type sugars, which are important for protein stability but are not essential for their enzymatic activities. Enzymatic characterization of the purified PONs has revealed them to be lactonases/lactonizing enzymes, with some overlapping substrates (e.g., aromatic lactones), but also to have distinctive substrate specificities. **All three PONs metabolized very efficiently 5-hydroxy-eicosatetraenoic acid 1,5-lactone and 4-hydroxy-docosahexaenoic acid**, which are products of both enzymatic and nonenzymatic oxidation of arachidonic acid and docosahexaenoic acid,
respectively, and may represent the PONs' endogenous substrates. Organophosphates are hydrolyzed almost exclusively by PON1, whereas bulky drug substrates such as lovastatin and spironolactone are hydrolyzed only by PON3. Of special interest is the ability of the human PONs, especially PON2, to hydrolyze and thereby inactivate N-acyl-homoserine lactones, which are quorum-sensing signals of pathogenic bacteria. None of the recombinant PONs protected low density lipoprotein against copper-induced oxidation in vitro.

2. Sci Transl Med. 2011 Feb 9;3(69):69ra12.

5-Lipoxygenase Metabolite **4-HDHA** Is a Mediator of the Antiangiogenic Effect of {omega}-3 Polyunsaturated Fatty Acids.

Sapieha P, Stahl A, Chen J, Seaward MR, Willett KL, Krah NM, Dennison RJ, Connor KM, Aderman CM, Liclican E, Carughi A, Perelman D, Kanaoka Y, Sangiovanni JP, Gronert K, Smith LE.

Lipid signaling is dysregulated in many diseases with vascular pathology, including cancer, diabetic retinopathy, retinopathy of prematurity, and age-related macular degeneration. We have previously demonstrated that diets enriched in ω-3 polyunsaturated fatty acids (PUFAs) effectively reduce pathological retinal neovascularization in a mouse model of oxygen-induced retinopathy, in part through metabolic products that suppress microglial-derived tumor necrosis factor-α. To better understand the protective effects of ω-3 PUFAs, we examined the relative importance of major lipid metabolic pathways and their products in contributing to this effect. ω-3 PUFA diets were fed to four lines of mice deficient in each key lipid-processing enzyme (cyclooxygenase 1 or 2, or lipoxygenase 5 or 12/15), retinopathy was induced by oxygen exposure; only loss of 5-lipoxygenase (5-LOX) abrogated the protection against retinopathy of dietary ω-3 PUFAs. This protective effect was due to 5-LOX oxidation of the ω-3 PUFA lipid docosahexaenoic acid to **4-hydroxy-docosahexaenoic acid (4-HDHA)**. 4-HDHA directly inhibited endothelial cell proliferation and sprouting angiogenesis via peroxisome proliferator-activated receptor γ (PPARγ), independent of 4-HDHA's anti-inflammatory effects. Our study suggests that ω-3 PUFAs may be profitably used as an alternative or supplement to current anti-vascular endothelial growth factor (VEGF) treatment for proliferative retinopathy and points to the therapeutic potential of ω-3 PUFAs and metabolites in other diseases of vasoproliferation. It also suggests that cyclooxygenase inhibitors such as aspirin and ibuprofen (but not lipoxygenase inhibitors such as zileuton) might be used without losing the beneficial effect of dietary ω-3 PUFA.

http://www.jbc.org/content/275/43/33435.long

3. J Biol Chem. 2000 Oct 27;275(43):33435-42.

Rabbit serum paraoxonase 3 (PON3) is a high density lipoprotein-associated lactonase and protects low density lipoprotein against oxidation.

Draganov DI, Stetson PL, Watson CE, Billecke SS, La Du BN.

The paraoxonase gene family contains at least three members: PON1, PON2, and PON3. The physiological roles of the corresponding gene products are still uncertain. Until recently, only the serum paraoxonase/arylesterase (PON1) had been purified and characterized. Here we report the purification, cloning, and characterization of rabbit serum PON3. PON3 is a 40-kDa protein associated with the high density lipoprotein fraction of serum. In contrast to PON1, PON3 has very limited arylesterase and no paraoxonase activities but rapidly hydrolyzes lactones such as statin prodrugs (e.g. lovastatin). These differences facilitated the complete separation of PON3 from PON1 during purification. PON3 hydrolyzes aromatic lactones and 5- or 6-member ring lactones with aliphatic substituents but not simple

lactones or those with polar substituents. We cloned PON3 from total rabbit liver RNA and expressed it in mammalian 293T/17 cells. The recombinant PON3 has the same apparent molecular mass and substrate specificity as the enzyme purified from serum. Rabbit serum PON3 is more efficient than rabbit PON1 in protecting low density lipoprotein from copper-induced oxidation. This is the first report that identifies a second PON enzyme in mammalian serum and the first to describe an enzymatic activity for PON3.