"FPPARS"

Gaining insight in the biology of fish lipid metabolism

In aquaculture, problems related to lipid metabolism in fish are of considerable importance for two principal reasons. First, farmed fish tend to accumulate fat in their tissues, which has consequences for the quality of the product and its market price. Second, the aquaculture industry is presently dependent on fish oil and fish meal for high quality feeds, needed to support aquaculture production and an ever increasing demand for (sea)food. These feedstuffs should therefore be used as efficiently as possible. Both problems could be solved by manipulating the fish' lipid metabolism.

This was exactly the goal of the FPPARS project, and to achieve this goal, the project focused on the study of peroxisome proliferator-activated receptors in fish. **Peroxisome proliferator-activated receptors (PPARs)** are a group of nuclear receptors, i.e. proteins found within the interior of cells that are responsible for sensing the presence of hormones and certain other molecules. Nuclear receptors have the ability to directly bind to DNA and thus to regulate the expression of specific genes. For this reason, they play key roles in both the embryonic development and adult homeostasis of organisms.

In humans, PPARs are known to be key regulators of lipid homeostasis, controlling the metabolic pathways leading to both fatty acid catabolism and fat storage. In fish, they had never been studied before; it was therefore unknown whether or not PPARs in fish – or fPPARs – showed the same functional properties as in humans (or other mammals).

The FPPARS project studied the genetic structure of fPPARS from four species of particular importance for the aquaculture industry, i.e. sea bass (*Dicentrarchus labrax*), sea bream (*Sparus aurata*), Atlantic salmon (*Salmo salar*) and plaice (*Pleuronectes platesa*). For these four species, the project partners were able to clone and characterise the three PPAR subtypes (PPARα, PPARβ and PPARγ) that also exist in humans.

After this, a battery of tools was developed for the study of the functional properties of the fPPARs (and a comparison with PPARs from other species), those properties being DNA binding, ligand recognition, and transcriptional activation, all taking place in the first step of gene expression (see box).

Finally, the expression of the PPAR-subtypes in fish tissues was studied, with a specific focus on their effect on fat accumulation and lipid composition in these tissues. This gained the following results:

- In the marine fish species (plaice, sea bream and sea bass) PPARα was most highly expressed in liver and heart, and in the red muscle for sea bream and sea bass, whereas PPARβ was ubiquitously expressed in all tissues tested. PPARγ was highly expressed in adipose (or fat) tissue, as is the case in mammals, but its expression in other tissues was markedly different from

Project acronym:
FPPARS

Full title of Project:
Cloning and functional analysis of fish peroxisome proliferator-activated receptors: The transcriptional control of lipid metabolism in farmed fish species.

EU contract number:
Q5RS-CT-2000-30360

Web-site:
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"THE EFFECTS OF THE DIETS CONTAINING VEGETABLE OILS ON PPAR EXPRESSION IN FISH TISSUES WERE IN GENERAL NON-SIGNIFICANT"

that in mammals, thus suggesting that the function of this receptor may differ between fish and mammals.

- In salmon, the expression pattern of PPARα and γ appeared to be markedly different from that observed in the marine fish species or in mammals. Here, PPARα appeared to be mainly expressed in tissues where PPARγ expression would have been expected, i.e. in the adipose tissue, spleen, and intestine. In contrast, high level expression of PPARγ appeared to be limited to the intestine.

These findings were then used to investigate the effects on the PPAR expression pattern in sea bream and Atlantic salmon tissues, when fed vegetable oils (VO) instead of fish oil. In both species, no great effects of the VO diets on growth were observed. On the other hand, these diets clearly affected fatty acid composition in the fish tissues. Finally, VO diets did not have any significant effects in fatty acid oxidation (energy release) in neither Atlantic salmon or sea bream liver or muscle, consistent with these diets having no significant effect on the lipid content of the flesh or the whole body.

By cloning fPPARS and analysing their properties, the FPARRS project has provided new insights in the biology of these transcription factors and in their role in fish physiology and development under aquaculture conditions. In addition to the scientific contributions of this work, it has also provided new tools for the industrial development of novel dietary formulations for marine fish culture, thus benefiting the aquaculture industry.

Gene expression: the process
Gene expression is the process by which inheritable information from a gene (DNA sequence) is made into a functional gene product (RNA, proteins). This is done in the following steps:

- **Transcription**: the synthesis of RNA from a DNA sequence
- **Translation**: the first stage of protein biosynthesis, based on the transcribed RNA
- **Posttranslational modification**: the chemical modification of a protein after its translation, extending the range of functions of the protein

Because of their ability to bind to DNA, PPARs are modulators for DNA transcription and are therefore classified as "transcription factors".