Récepteurs à la Provençale

EMBO Workshop on the Biology of Nuclear Receptors

Johan Auwerx^{1,2}, Jacques Drouin³ & Vincent Laudet⁴

¹Institut de Genetique et Biologie Moléculaire et Cellulaire, Illkirch, France, ²Institut Clinique de la Souris, Illkirch, France,

³Institut de Recherches Cliniques de Montréal, Québec, Canada, and ⁴CNRS UMR 5161, Lyon, France

This EMBO Workshop on the Biology of Nuclear Receptors took place between June 4 and 7 2003 and was organized by P. Chambon, J.-Å. Gustafsson, V. Laudet, A. Maggi, L. Nagy, M. Parker, T. Perlman, G. Schuetz, J. Schwabe and W. Wahli. (Photo courtesy of the Town Hall of Villefranche-sur-Mer.)

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Introduction

About 200 scientists gathered in the splendid settings of the French Riviera in Villefranche-sur-Mer to discuss the latest findings on nuclear receptors (NRs), a family of about 50 related transcription factors, that are implicated in a wide array of biological responses (for more information on NRs, see Laudet & Gronemeyer, 2001;

<http://www.nursa.org>; and <http://www.ens-lyon.fr/LBMC/laudet/nurebase.html>). Despite their relatedness, NRs are highly specific in their target gene selection, their mechanism of activation (ligand-dependent or -independent), and in the genes they repress or activate. This meeting highlighted the great versatility of these transcription factors in achieving specificity in different signalling paradigms. The more we learn about NRs, the more we discover new recipes for differential gene control, which use the same ingredients but in a different mix.

A menu of molecular choices

To be or not to be on DNA. A striking discovery from the past few years has been that NRs are not associated for long periods of time with their target regulatory sequences. For example, G. Hager (Bethesda, MD, USA) has used photo-bleaching in conjunction with green fluorescent protein-tagged glucocorticoid receptor (GFP-GR) to document the exchange of GR and its coactivators at the mouse mammary tumour virus (MMTV) promoter. These *in vivo* experiments suggest average residence times for GR in the range of seconds, which is in stark contrast with the classical view of target-site occupancy. However, a different type of periodicity has been documented for various NRs using the chromatin immunoprecipitation (ChIP) method. ChIP performed either in reconstituted systems or in living cells measured cyclic-receptor occupancy with periods in the range of tens of minutes. At present, the relationship between fast exchanges (seconds) and the longer cycles of DNA occupancy (minutes) remains unclear. In an *in vitro* reconstituted system, GR occupancy of the MMTV promoter is about 1 min every 5 min, and this occupancy is dependent on the chromatin remodelling SWI–SNF complex and ATP. In a proposed 'return-to-template' model, regulatory sequences are cyclically occupied by GR, which recruits the SWI–SNF complex and is followed by chromatin remodelling and dissociation of the complex to allow for the initiation of another cycle of GR binding.

This model is consistent with other ChIP analyses of the pS2 gene promoter that were presented by F. Gannon (Heidelberg, Germany). His group used α -amanitin to clear the pS2 promoter of its associated proteins and on release of this block, followed the kinetics of recruitment of the oestrogen receptor (ER) in both unliganded and liganded forms. The cyclical recruitment of ER to the pS2 promoter occurs in both forms, with ligand binding slowing down the cycles of recruitment from a period of about 20 to 45 min. This cycling is

¹Institut de Génétique et de Biologie Moléculaire et Cellulaire, CNRS/INSERM/Université Louis Pasteur, 67404 Illkirch, France

²Institut Clinique de la Souris, Génomole de Strasbourg, 67404 Illkirch, France

³Laboratoire de Génétique Moléculaire, Institut de Recherches Cliniques de Montréal, 110 avenue des Pins ouest, Montréal, Québec, Canada H2W 1R7

⁴CNRS UMR 5161, Laboratoire de Biologie Moléculaire de la Cellule, Ecole Normale Supérieure de Lyon, 46 Allée d'Italie, 69364 Lyon Cedex 07, France

*Corresponding author. Tel: +33 38 8653425; Fax: +33 38 8653201;

E-mail: auwerx@igbmc.u-strasbg.fr

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dependent on the activity of the proteasome complex, which is also required for transcription. On proteasome inhibition, not only is the cycling of promoter occupancy prevented, but also ER becomes poly-ubiquitinated and is targeted to the nuclear matrix (Fig. 1).

These experiments indicate that the question for NRs is not whether or not they are bound to DNA, because they cyclically associate with their target sequence even in the absence of ligand. Rather, the important parameter is whether ligand-dependent cofactors are recruited to ligand-activated NRs and if so, how long this complex is associated with the promoter. The dynamic picture that is now emerging suggests that transcriptional regulation is a continuously re-assessed process in which proteins and DNA associate and dissociate regularly to adjust the rate of transcription to immediate conditions. In the case of NR-dependent transcription, ligand concentration is the primary determining factor. In contrast to classical static models of transcription, this meeting introduced a new dimension in our thinking about NR action: time.

To have or not to have a ligand. Ever since the concept of orphan NRs (NRs that are not ligand activated) emerged in the 1990s, it has been an ongoing debate whether there are indeed true orphans. V. Laudet (Lyon, France) offered evolutionary arguments that support not only the existence of orphans, but also their precedence. He proposed that the ancestor of all NRs is likely to be an orphan transcription factor. The phylogenetical analysis of NRs in complete genomes suggests that most liganded NRs are recent innovations that are found only in chordates. However, only a small number of

metazoan genomes have been sequenced and we cannot exclude that some liganded NRs can be found in other phyla. Indeed, analysis of the *Caenorhabditis elegans* genome was surprising because most of its 270 NRs represent a massive amplification of a unique ancestral hepatocyte nuclear factor 4 (*hnf-4*) gene. The strong diversity of the ligand-binding domain (LBD) of nematode HNF-4 duplicates suggests that these are real orphan receptors.

Further evidence in favour of true orphans was provided by the structural work of T. Perlmann (Stockholm, Sweden), who showed that the NUR-related factor 1 (NURR1) LBD has an 'active' fold in the absence of any ligand; furthermore, the putative ligand-binding pocket of NURR1 is filled by large hydrophobic side chains, such that it is difficult to imagine a ligand occupying the same space. The crucial residues of this pocket are also conserved in the related orphans' nerve growth factor I-B (NGFI-B), neuron-derived orphan receptor 1 (NOR1) and *Drosophila* hormone receptor 38 (DHR38). In some cases a structural 'ligand', such as a fatty acid in the case of HNF4, might be present inside the LBD without having any functional role. In other cases—such as oestrogen-related receptor (ERR)- γ (see below) and liver receptor homologue 1 (LRH1)—the pocket is empty but the receptor nevertheless has an active conformation. Thus, the LBDs of orphan NRs can vary in their structural organization (filled with side-chain residues, containing structural ligand, or empty) and it is unclear which represents the ancestral state. J.-P. Renaud (Illkirch, France) showed that the conformation of the ERR- γ LBD crystallized in the absence of ligand, but in association with a steroid receptor coactivator (SRC) peptide was 'active'. This conformation retains a

Fig. 1 | Transcriptional cycles of the oestrogen-responsive gene *pS2* induced by the oestrogen receptor. **(A)** Chromatin immunoprecipitation (ChIP) and Re-ChIP assays in MCF7 cells allowed the description of cycles of protein recruitment on this promoter. **(B)** On the left side is the first transcriptionally unproductive cycle, in which SWI-SNF is followed by the recruitment of histone methyltransferases (HMTs), histone acetylases (HATs) and then components of the basal transcription machinery. After the action of GCN5 and TAFp130, the oestrogen receptor (ER) is targeted to the proteasome for degradation by the APIS complex. This cycle, which epigenetically activates the pS2 promoter, is followed by transcriptionally productive cycles, for which the p68 RNA helicase is first required, followed by the combinatorial mobilization of HMTs and HATs. After the recruitment of TAF250, GCN5 and polymerase II (Pol II), Mediator allows the phosphorylation of Pol II through TFI_H. This phosphorylation event allows the mobilization of the elongator in conjunction with histone deacetylase (HDAC)-SWI/SNF complexes. Coincidentally, ER is again targeted to the proteasome by the APIS complex. **(C)** Red arrowheads denote steps in which combinatorial recruitments were observed, that is, a mobilization of different proteins exhibiting the same activity (for example, CARM1 or PRMT1). (Figure provided by F. Gannon.)

small putative ligand-binding pocket that could accommodate the synthetic antagonists diethylstilbestrol (DES) and 4-hydroxytamoxifen (4-OHT). Structures of the ERR- γ LBD in complex with both antagonists show that they destabilize helix 12, which becomes disordered, and this prevents the interaction with coactivators. Altogether, this work suggests that certain NRs might not have a natural ligand but still could be the target of pharmacological agents, which is a feature that was recently reviewed (Li *et al.*, 2003).

For receptors with ligands, the model in which the LBD serves as a molecular activation switch on ligand binding was further supported by J. Schwabe (Cambridge, UK). Using fluorescence anisotropy, helix 12 of peroxisome proliferator-activated receptor (PPAR)- γ was found to become more rigid on ligand binding, which is a requirement for efficient coactivator interactions. Two natural mutations of PPAR- γ (Pro467Leu and Val290Met), which are associated with insulin resistance and diabetes mellitus, were found to prevent the ligand-induced stabilization of helix 12 and support the model that helix 12 is the molecular switch that triggers coactivator recruitment and transcriptional activity.

If orphan NRs do not have classical ligands, do they function as constitutively active developmental regulators, or are there other mechanisms that regulate their activity? J. Drouin (Montreal, Canada) provided evidence that the NUR-related orphans (NGFI-B/NUR77, NURR1 and NOR1) are potent mediators of signals that are transduced by the mitogen-activated protein (MAP) kinase and protein kinase A (PKA) signalling pathways. Similarly, C. Rochette-Egly (Illkirch, France) showed how the phosphorylation of two serine residues of the retinoic-acid receptor (RAR)- γ 2 amino-terminal region contribute to transcriptional potency, and R. Schuele (Freiburg, Germany) reported on the RhoA-dependent androgen-independent activation of the androgen receptor (AR) through the protein kinase C-related kinase PRK1.

To activate or to repress. Depending on their target genes, NRs may activate or repress transcription. Both actions may be ligand dependent and often repression does not involve direct DNA binding by NRs, but depends on their interactions with other transcription factors. Such mechanisms explain also how glucocorticoids exert their anti-inflammatory effects. K. Yamamoto (San Francisco, CA, USA) has implicated the coactivator GRIP1/TIF2/SRC2 in the process of transrepression, an activity that is not shared by the related coactivators SRC1 and SRC3. He also discussed the striking differences between two different tumour necrosis factor- α (TNF- α)- and NF- κ B-inducible promoters, only one of which is subject to GR repression. Indeed, both interleukin 8 (IL-8) and I κ B- α genes are induced by NF- κ B, but only the IL-8 promoter is repressed by GR despite the fact that GR is also recruited to the I κ B- α promoter. At the IL-8 promoter, NF- κ B interacts with cyclin T1, which leads to the recruitment of the elongation factor pTEFb (containing cyclin-dependent kinase 9 (CDK9) and cyclin T1 kinase) and Ser2 phosphorylation of the RNA polymerase II carboxy-terminal repeat. GR interferes with this retention of pTEFb on the IL-8 promoter. By contrast, cyclin T1 is not recruited at the I κ B- α promoter, due to a difference of one base pair between the two NF- κ B binding sites. This subtle difference in DNA sequence therefore provides a molecular explanation for the absence of GR repression at the I κ B- α promoter.

S. Kato (Tokyo, Japan) identified a multiprotein complex (WINAC) that interacts with the vitamin D nuclear receptor (VDR) through the Williams' syndrome transcription factor (WSTF). WINAC has

ATP-dependent chromatin-remodelling activity and contains both SWI/SNF components and DNA replication-related factors. WINAC mediates the recruitment of unliganded VDR to VDR target sites, whereas subsequent binding of coregulators requires the presence of ligand. This recruitment order exemplifies that an interaction between a sequence-specific regulator and a chromatin-remodelling complex can organize nucleosomal arrays to make promoters accessible to coregulators. WINAC dysfunction could contribute to the Williams' syndrome, which could therefore be considered a chromatin-remodelling factor disease. In the future, we will investigate how these many protein interactions determine the difference between repression and transcription, and the interested reader is referred to a recent review for more information (Belandia & Parker, 2003).

To proliferate or to differentiate. Another emerging theme at this meeting was that many NRs have key roles in the decision between cell proliferation and differentiation. This was highlighted for the NUR/NGFI-B subfamily by O. Conneely (Houston, TX, USA), who showed that mice that lack both NOR1 and NUR77 develop a rapidly lethal myeloproliferative disease, because of deregulation of the G1/S transition. This disease, which may constitute a model of chronic myeloid leukaemia, is sensitive to gene dosage. Another orphan NR is responsible for an immune neoplasia when inactivated: indeed, A. Jetten (Research Triangle Park, NC, USA) showed that RAR-related orphan receptor (ROR)- γ ^{-/-} mice develop T-cell lymphomas that are associated with increased proliferation and apoptosis, the latter possibly resulting from silencing of Bcl-X(L).

Ligand-dependent NRs also have roles in cell-cycle regulation. L. Nagy (Debrecen, Hungary) showed that PPAR- γ orchestrates dendritic lineage specification and the development of a dendritic-cell subtype with increased internalizing capacity and lipid specificity for natural killer T-cell presentation. P. Chambon (Illkirch, France) showed, using both germ-line and hepatocyte-specific knockout mice, that ER- α signalling is an important factor in the early phase of liver regeneration after partial hepatectomy (PH). Circulating oestradiol, which is increased within minutes after PH, induces ER- α in hepatocytes. In the absence of ER- α , liver regeneration is delayed, and liver dysfunction leads to increased lethality. In the absence of hepatocyte ER- α , DNA synthesis and cell proliferation are impaired, whereas apoptosis is enhanced. The main molecular effects of ER- α signalling are mediated by NF- κ B, whose activation by TNF- α is known to be a crucial early post-PH event, both to trigger cell proliferation, through AP1 and Stat3, and to prevent apoptosis, through increased nitric oxide (NO) synthesis by inducible NO synthase (iNOS). In hepatocyte-selective ER- α -deficient mice, NF- κ B activation by TNF- α is impaired, which alters hepatocyte proliferation due to a lack of AP1/Stat3 and apoptosis due to decreased iNOS activity. M. Zenke (Berlin, Germany) used microarrays to show how T3 or the retinoid X receptor (RXR) ligand 9-*cis* retinoic acid (9cRA) modify gene expression during red-blood-cell differentiation. The addition of T3 and 9cRA to red-cell progenitors induced cell-cycle arrest and accelerated differentiation, with the combination of T3 and 9cRA being most effective. Only few genes were induced by T3, but not by 9cRA. Among these, GAR22, a growth arrest specific 2 (GAS2)-related gene on chromosome 22, was shown to be a novel direct target gene of thyroid hormone receptor (TR), which is suggested to induce cell-cycle arrest and differentiation. H. Gronemeyer (Illkirch, France) discussed the mechanism of RA-dependent TRAIL promoter regulation and showed that it is not only operative in acute promyelocytic leukaemia but also in breast-cancer

cells. Furthermore, he discussed that RA and interferons use converging signalling pathways to induce apoptosis and that rexinoids, in the presence of elevated levels of cAMP, are powerful inducers of differentiation and apoptosis in RA-resistant acute myeloid-leukaemia cells. P.G. Pelicci (Milano, Italy) showed that the recruitment of cofactors such as histone deacetylases and methyltransferases is common in haematological malignancies and alters RA signalling. The results highlighted by these speakers clearly opened up alternative therapeutic avenues to treat diseases characterized by deregulated cell proliferation.

RXR- α /RAR (α , β and γ) heterodimers have key roles in normal embryonic development and mediate the harmful effects of RA during this period. M. Mark (Illkirch, France) showed that RXR- α must be transcriptionally active for many developmental events. By treating wild-type and RAR-null-mutant embryos with specific ligands, he showed that malformations typical of the RA embryopathy are mediated through RXR-RAR- β heterodimers in which the activity of RXR is subordinate to that of RAR- β .

Many ingredients generate physiological diversity

A salade niçoise of receptors. Villefranche is close to Nice, the origin of the famous *salade niçoise*. Just as it is difficult to understand the role of each component in the final taste of the salad, the number of physiological processes in which the two subtypes of ER, ER- α and - β , are implicated is so great that it is difficult to understand their respective roles. Deciphering how a single hormone controls such a large number of events is of paramount importance and several talks addressed this question. It has long been known that oestrogens promote uterine growth and that other growth factors, such as epidermal growth factor (EGF) or insulin growth factor 1 (IGF1) also affect the uterus. The uterine response to oestrogens occurs in two phases: an early phase (within 2 h) that is characterized by increased transcription, and a late phase (16–24 h post-treatment) that is associated with DNA synthesis and mitosis of epithelial cells. K. Korach (Research Triangle Park, NC, USA) used knockout mice to show that ER- α mediates most uterine growth effects and, using DNA microarrays, he found that unique gene clusters are activated or inhibited at different times; these included IGF1 (increased), and IGFBP3 and EGF receptor (decreased). Similarly, A. Maggi (Milano, Italy) provided *in vivo* evidence for the regulation of unliganded ER by circulating IGF1. Her analysis of luciferase (Luc) activity generated by an oestrogen response element (ERE)-tk-Luc reporter in prepubertal and ovariectomized mice indicated that ERs are active in the absence of oestrogen. IGF1 appears to be responsible for ER activation in non-reproductive organs during dioestrus, as an IGF1 receptor antagonist (JB-3) prevents, whereas IGF1 increases, ER activity (Fig. 2). ERs may thus provide a mechanism for crosstalk to integrate signals from different pathways. J.-A. Gustafsson (Stockholm, Sweden) provided evidence for a role of ER- β in the modulation of ER- α -mediated responses and cell proliferation. Interestingly, he reported ER- β -/- mice develop splenomegaly and a myeloproliferative disease that resembles chronic myeloid leukaemia.

A given NR can crosstalk with different classes of transcription factors, for example GR affects both AP1 and NF- κ B signalling. G. Schütz (Heidelberg, Germany) and colleagues performed a now 'classical' knock-in experiment to introduce a specific mutation that abolishes GR DNA binding but not AP1/NF- κ B crosstalk. In a hepatocyte-specific GR mutation, it was shown that GR acts as a coactivator for Stat5-dependent transcription *in vivo*. Using a similar approach, T. Wintermantel (Heidelberg, Germany) described a knock-in mouse with an ER- α point mutation that selectively

Fig. 2 | *In vivo* imaging of oestrogen receptor activation. 50 $\mu\text{g kg}^{-1}$ of 17- β -oestradiol (E2) was injected subcutaneously into the ERE-tk-Luc reporter mouse. At the indicated time points the mouse was i.p. injected with 15 $\mu\text{g kg}^{-1}$ of luciferin and emitted photons were recorded and projected on to an image of the animal. (Figure provided by A. Maggi.)

interferes with ERE binding but still antagonizes NF- κ B. These animals have a hypoplastic uterus as well as abnormal ovaries similar to ER- α -/- mice. This suggests that ovarian and uterine function are dependent on the ER- α DNA-binding domain.

J. Drouin (Montreal, Canada) revealed that the product of the retinoblastoma gene, *Rb*, a crucial component in cell-cycle control, alters gene expression in the pituitary through the orphan receptor NGFI-B. Indeed, *Rb* interacts directly with NGFI-B and with the coactivator transcription intermediary factor 2 (TIF2), resulting in transcriptional enhancement of NGFI-B activity. This finding was extended to other receptors because *Rb* was also found to interact functionally with HNF4, SF1, ER- α and ER- β but not with GR, RXRs or RARs. *Rb* association with pituitary NGFI-B signalling enhanced hormone responsiveness.

Metabolism and inflammation, all in the bouillabaisse. The important role of NRs as metabolic regulators (Chawla *et al.*, 2001; Francis *et al.*, 2003) was bolstered by the observation that PPAR- α controls β -oxidation and lipid catabolism, and that PPAR- γ determines fat formation and glucose homeostasis. Much less is known about PPAR- β/δ and two groups now assign a role for this NR in metabolism and inflammation. R. Evans (San Diego, CA, USA) used mice with germ-line null alleles, conditional knockouts and mice expressing a constitutively active PPAR- β/δ , to show that this receptor controls metabolism and inflammation. In macrophages, unliganded PPAR- β/δ sequestered the transcription factor BCL-6, an inhibitor of the transcription of pro-inflammatory genes such as monocyte chemoattractant protein 1 (MCP1). Ligand binding by PPAR- β/δ released BCL-6, enabling this last factor to exert its repressive activity on the MCP1 promoter. In addition to this anti-inflammatory effect, PPAR- β/δ activation also reduced obesity because of increased energy dissipation subsequent to an enhanced recruitment of the coactivator PGC1 to

PPAR- β/δ in brown and white adipose tissue and muscle. B. Desvergnès (Lausanne, Switzerland) showed that PPAR- β/δ also has a role in the skin during wound healing. During the initial inflammatory phase of wound healing, inflammatory cytokines induce PPAR- β/δ expression, which contributes to keratinocyte survival and migration through activation of Akt1 signalling. In the later phases of wound repair, transforming growth factor- β then reduces PPAR- β/δ expression. These effects on PPAR- β/δ expression are mediated through AP1 binding to the PPAR- β/δ promoter. It would be interesting to find out whether these anti-inflammatory effects in the atherosclerotic plaque and skin could be translated into therapeutic uses for PPAR- β/δ . D. Metzger (Illkirch, France) generated mice in which PPAR- γ was selectively deleted in the adipocytes. Ablation of PPAR- γ in the adipocytes led to a transient decrease in body weight due to the disappearance of adipocytes, which was followed by compensatory adipocyte proliferation. This underlined not only the vital role of PPAR- γ in adipocyte survival, but also the presence of precursor cells that could lead to the 'regeneration' of adipocytes.

The heirs of the PPARs in the metabolic kingdom are the liver X receptors (LXRs)- α and - β . P. Tontonoz (Los Angeles, CA, USA) highlighted their important role in the control of lipid homeostasis and inflammation, which both contribute to the development of atherosclerosis. Through the concerted induction of three important genes in cholesterol efflux—the cholesterol transporter *ABCA1*, apolipoprotein E and phospholipid transfer protein—LXR promotes cholesterol efflux out of the macrophages to high-density lipoprotein particles, and stimulates reverse cholesterol transport. LXR activation also inhibits the expression of inflammatory mediators, such as IL-6, iNOS and cyclooxygenase 2 (COX2), which in combination with the effects on lipid metabolism, explains the potent anti-atherogenic activity of LXR activation *in vivo*. Although these attributes suggest that LXR agonists could represent an interesting therapeutic option for atherosclerosis, this development has been hampered by the hypertriglyceridaemia that LXR agonists induce. This hypertriglyceridaemia is subsequent to the induction of sterol regulatory element binding protein 1c (SREBP-1c) expression, the key driver of a lipogenic programme. J. Auwerx (Illkirch, France) showed that natural (bile acids) and synthetic farnesoid X receptor (FXR) agonists decrease hepatic expression of SREBP-1c and its lipogenic target genes. Through the use of mice mutant for the short heterodimer partner (SHP), he showed that SHP induction by either natural or synthetic FXR agonists attenuates the ability of LXR to induce SREBP-1c gene expression. These results suggest that strategies aimed at increasing FXR activity and the repressive effects of SHP should be explored to correct hypertriglyceridaemia. Also, ROR- α , whose structure was presented by B. Fournier (Basel, Switzerland), could be a candidate for the modulation of cholesterol homeostasis. With her team, she showed that cholesterol is present in the crystal structure of the ROR- α LBD. These data suggest that ROR- α activity is modulated by cholesterol and cholesterol-sulphate, but not by oxidized cholesterol metabolites.

The ERRs are also part of the metabolic bouillabaise. Two speakers discussed the fact that PGC1 modulates ERR- α activity. V. Giguère (Montreal, Canada) first reported on a polymorphism in a hormone-response element-like repeat in the human ERR- α promoter. The copy number of this repeat interacted genetically with the common PPAR- γ Pro12Ala mutation to determine bone density. He further showed that ERR- $\alpha^{-/-}$ mice have decreased fat mass, an effect that, through microarray experiments, has been attributed to abnormal lipid metabolism and intestinal fat absorption. Almost all of the

genes identified were PPAR- γ /PGC1 target genes. This observation was highlighted by N. Kralli (San Diego, CA, USA), who discussed that PGC1 induces ERR- α expression levels and stimulates its transcriptional activity. Interestingly, this effect is transduced through the polymorphic repeat present in the ERR- α promoter described above. Using RNA interference, she also showed that PGC1 requires ERR- α to control mitochondrial β -oxidation.

J. Samarut (Lyon, France) showed that TR- α -deficient animals have diabetes secondary to a defect in their pancreatic β -cells. J. Baxter (San Francisco, CA, USA) discovered a class of TR- β modulators that lower both cholesterol and triglyceride levels and body weight, but have no effect on heart rate in several species, including non-human primates. Most striking was the observation that these compounds also reduce the levels of Lp(a), a lipoprotein that represents an independent risk factor for coronary artery disease, but which is not affected by current therapeutic strategies to reduce coronary risk factors, such as statins and fibrates. B. Vennström (Stockholm, Sweden), analysed the effects of a dominant-negative mutation in the TR- α gene on the central nervous system. Mice carrying such an allele exhibited both a perturbed motor coordination and extreme anxiety. Interestingly, both deficiencies were remedied by hormone treatment if delivered at an appropriate time of development, indicating that patients carrying similar mutations may be treatable.

From the above, it is clear that NR signalling has a big impact on metabolic control. It is therefore not surprising that their coregulators are not innocent bystanders either, and metabolic activities for PGC1, p300, TRAP 220, SRC1 and TIF2 have been described. M. Parker (London, UK) now extended this paradigm to include receptor-interacting protein (RIP)140, a platform protein for transcriptional repression. RIP140 $^{-/-}$ mice have an increase in basal metabolism and do not gain weight on ageing. Further evidence for the importance of cofactors in NR signalling was brought forward by S. Kato (Tokyo, Japan). Dioxins and other environmental contaminants often have adverse and so far ill-understood oestrogen-related actions. This was pinpointed to be due to the co-activation of unliganded ER by the dioxin receptor (AhR)—Arnt heterodimer, which induces the transcription of ER target genes through the subsequent recruitment of the coactivator p300.

Back to the 'real' Provence

As shown, it is clear that southern France brought out the best in NR science and provided everyone with some new, exciting food for thought. We are, however, convinced that by now everyone is ready to sample the real Provençal taste such as is found in the *salade niçoise*, the *soupe au pistou*, or the *bouillabaise*. Don't forget to try a good local wine, such as a *Côtes de Provence*, a *Bandol*, or *Bellet*! Enjoy all of it, while trying to identify the endocrine disruptors present in the mixtures.

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