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Editorial

Nuclear Receptor Research: Contributions from Latin America

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On behalf of the Editorial Board of *Nuclear Receptor Research*, it is a great pleasure to welcome you to the inaugural issue of the journal. We are proud to introduce the first *thematic* issue of many to come.

The fact that virtually every single aspect of cell function and the complex network of regulatory processes in an organism involve crucial roles by nuclear receptors is not surprising at the present time. Accordingly, thousands of studies are published every year in hundreds of journals with very broad spectra, making it difficult for researchers in the field to find specific information of interest to them. This is the reason why *Nuclear Receptor Research* was born; to gather in one journal most of the advances covering all facets of this cardinal group of regulatory transcription factors. Thus, *Nuclear Receptor Research* is intended to meet a crucial need of researchers in an ever expanding and exciting field that has shown an extraordinary progress since the late 1800s.

Historical Events: Perhaps the first steps in the discovery of nuclear receptors may be traced to 1889, when the French physiologist Charles Édouard Brown-Séquard suggested to the *Society of Biology* in Paris that the testes might produce an active and invigorating substance able to act in the whole body, and proposed that it could be obtained from animals and injected into men, rejuvenating them. Actually, he assayed that "testicular liquid" by injecting himself and experiencing radical changes such as regaining his lost strength and natural impetuosity [1]. In 1902, the English physiologists William Bayliss and Ernest Starling discovered the first biological regulator produced by one tissue and conveyed by the bloodstream to another to effect physiological activity. They isolated the first *postman* that delivered biological messages, the secretin [2]. Three years later, Starling coined the name *hormone* [3] of this type of compounds, a word derived from the Greek meaning 'to arouse or excite'. He defined it as *"the chemical messengers*

which speeding from cell to cell along the blood stream, may coordinate the activities and growth of different parts of the body". Thus, the concept that *hormonal regulation* as a major biological event was first proposed in this sentence and early physiology took a major step forward. Some years later, Edward Kendall at the Mayo Clinic isolated an iodoamino acid, thyroxine, and also purified the compound E from the adrenal gland, which was used to treat rheumatoid arthritis and was renamed cortisone [4].

In 1958, Elwood Jensen synthesized a radioactive estrogen in the Fermi laboratory at the University of Chicago and administered it to ovariectomized rats. The hormone was retained in the uterus and other reproductive tissues; organs that grow in response to estrogen [5], and thus the steroid receptor theory was born. Such organ-specific retention of estradiol was arguably the first evidence for binding of a hormone to a receptor, yet even as late as 1968, some pharmacologists felt the use of the word "receptor", to describe the estradiol-binding entity, was inappropriate [6].

The first cloning of a nuclear receptor was achieved in 1985 [7], a development that led to the birth of a superfamily of ligand activated transcription factors; the nuclear receptor superfamily. Another term was also born at the same time, "orphan receptors". Unlike those members that had previously been identified with prior knowledge of a naturally occurring ligand, "orphan receptors" share sequence homology and structural similarity with the classic group of ligand-activated transcription factors, but their putative endogenous ligand(s) remained unknown.

To date, nuclear receptors constitute the largest group of transcription factors in animals comprising 48 family members in humans and 270 in *Caenorhabditis elegans* [8]. The study of how these receptors interact with genomic regions to control a plethora of biological processes has provided critical insight into physiology, signaling pathways, cell cycle, differentiation, development, evolution, and the molecular basis of most diseases. In view of these facts and the evident widespread relevance of the superfamily, their roles in the etiology of several human diseases have transformed these receptors into attractive therapeutic targets for the design and development of novel specific drug treatments.

The elucidation of the crystal structure of the nuclear receptor Ligand Binding Domain revealed various conformations and structure conservation among many members of this superfamily [9]. Moreover, the advent of structural biology combined with new technologies like high-throughput methods, novel biochemical methods, and pathway analysis tools have led to new discoveries of different ligand binding sites, allowing the elucidation of specific molecular mechanisms of activation of nuclear receptors and increasing the pharmacological efficacies of new drugs. Following this line, new molecules which modulate nuclear receptors have been discovered, making this family of receptors one of the top ten drug targets accounting for 13% of FDA approved drugs [10, 11].

Early contribution to the field from Latin America: Latin American scientists have made important contributions to the field of nuclear receptor research. The Argentinean Bernardo Houssay is one of the major contributors and first Nobel laureate in sciences in the region due to his discoveries on the role of the anterior hypophysis gland in carbohydrate metabolism. In the 1930s, Dr. Houssay showed the diabetogenic effect of anterior hypophysis extracts and the decrease in diabetes severity with anterior hypophysectomy, leading to other key discoveries such as the pituitary-adrenocortical relationship. These discoveries stimulated the study of hormonal feedback control mechanisms which are central to all aspects of modern endocrinology and hormone-receptor interaction. Latin America is also credited with a number of professors and institutions awarded prestigious prizes and fellowships from philanthropic institutions, like the John S. Guggenheim Foundation, the Howard Hughes Medical Institute, and the Pew Charitable Trusts, to name just a few. As economies of the continent improve, governments are devoting greater resources to research, as well as providing better infrastructure and policies to support science. Therefore, this inaugural issue was focused on some of the most recent contributions of Latin American researchers in the field.

Content of this issue: In this thematic issue of Nuclear Receptor Research, there is a collection of excellent review and research articles contributed by researchers in Latin America.

The paper by Thaís Soares Farnesi-de-Assunção *et al.* evaluates the effects of the PPARγ endogenous ligand 15-deoxy-$\Delta^{12,14}$-PGJ2 (15d-PGJ2) on the inflammatory response of dendritic cells. Usually, PPARγ ligands negatively regulate the innate and adaptative immune response in different experimental models. Although several studies have shown an anti-inflammatory action for 15d-PGJ2, a few reports have focused on the potential mechanism of its direct action on dendritic cells. Therefore, the authors have evaluated the expression of surface molecules such as MHC-II, CD80 and CD86 and have also compared cytokine production in cells treated with 15-d-PGJ2 or rosiglitazone. The natural ligand 15d-PGJ2 shows as a more efficient agent to reduce both the expression of CD80 and CD86 (without affecting the expression of MCH-class II) and the production of the proinflammatory cytokines IL-12, IFN-γ, and TNF-α. Because PPARγ is an attractive pharmacologic target where dendritic cells are involved, it is suggested that this natural PPARγ ligand could be a therapeutic strategy in disease to reduce the expression of costimulatory molecules and modulate the inflammatory response.

Gisela Mazaira *et al*. evaluate a novel model for the mechanism of action of steroid receptors. For several years, it was thought that receptor trafficking throughout the cytoplasm was a stochastic and passive mechanism triggered

by the dissociation of the Hsp90-based molecular complex from the receptor upon ligand binding. Here, is discussed the experimental evidence that has led to assign a key role to Hsp90-binding immunophilins in the regulation of this process, demonstrating that the Hsp90-based heterocomplex is indeed an essential component for receptor movement. Roles of Hsp90-binding immunophilins in the nuclear translocation of steroid receptors through the nuclear pore, how transcriptional activity is affected, and the consequence in cancer development are also discussed.

Judith Toneatto *et al.* have analyzed the relevance of molecular chaperones and co-chaperones in the process of adipocyte differentiation modulated by both the glucocorticoid receptor and the mineralocorticoid receptor. The potential coordinated action of glucocorticoids and mineralocorticoids in adipose tissue is evaluated in an attempt to understand the molecular basis of obesity and the metabolic syndrome. The roles of steroid metabolizing enzymes, adipocytes as a source of aldosterone, and the recently discovered influence of the FK506-binding immunophilin of 51-kDa are examined in detail.

Ana Liberman *et al*. dissect several aspects of the post-translational regulation of the glucocorticoid receptor in response to external stimuli. The pleiotropic actions of the glucocorticoid receptor depends on the different responsive sequences in different cell types, the multiple receptor isoforms generated by alternative splicing and translation initiation, the type of associated chaperones, and post-translational modifications. In this article, post-translational events on the receptor as well as associated proteins are analyzed. Events including actions of various protein-kinases, acetylation, ubiquitination, methyltion, sumoylation, etc., are presented. Cross-talk between neuroendocrine responses and immune system is also discussed.

The article by Juliana Fattory *et al.* evaluate and provide nuances on the modern methodology required for investigations focused on interactions between DNA and the DNA binding domain of nuclear receptors; an event which is necessary to shed light on important roles of the participation of these receptors in transcriptional mechanisms and in specific genes networks. The article discusses advantages and disadvantages of these methods, provides tools to answer some specific questions, and helps the reader to choose the most suitable methodology to study receptor-DNA interactions according to the specific question that researchers may wish to answer.

The article by Aliesha González-Arenas *et al.* studies the effects of ligand binding on the subcellular localization of progesterone receptor in a grade III human astrocytoma cell line, and have analyzed by microarray the profile of expression of genes regulated by the natural agonist progesterone (PR), the PR antagonist RU486, or both steroids. Inasmuch as a direct relation between PR expression and astrocytoma tumor grade exists, the authors focused their study on the identification of genes regulated by intracellular PR or through other signaling pathways that influence astrocytomas growth. Thirty genes were regulated by progesterone, forty-one genes by RU486, and thirteen genes by the co-treatment with both steroids. The genes that were modulated positively or negatively after 12 h of treatment with steroid encode for proteins involved in metabolism, transport, cell cycle, proliferation, metastasis, apoptosis, processing of nucleic acids and proteins, adhesion, pathogenesis, immunological processes, cytoskeleton organization and membrane receptors. This agrees with the fact that malignant astrocytomas have a complex process in which the expression of various genes is modified to allow the tumor cells to have oxygen supply and nutrients, escape the immune system and have the ability to migrate and invade.

Again, on behalf of all members of the Editorial Board of this new born journal, you are very welcome to this inaugural issue of *Nuclear Receptor Research*. We all look forward to the academic dialogue and prosperous collaborations we hope and wish to initiate with this challenging endeavor.

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