Isoform-specific Ligands of Thyroid Hormone Nuclear Receptor and Structural Basis of Their Interactions with the Receptor.

Lucas Bleicher[1], Ana Carolina N. Figueira[1], Alessandro S. Nascimento[1],Fabio M. Nunes[1], Ricardo Aparicio[1], Sandra M. G. Dias[1], Maria A. M. Santos[1], Mario de Oliveira Neto[1], Leandro Martínez[2], Munir S. Skaf[2], James W. Apriletti[3], John D. Baxter[3], Paul Webb[3], Francisco A. R. Neves[4], Luis A. Simeoni[4] and Igor Polikarpov[1]

[1]Instituto de Física de São Carlos, Universidade de São Paulo, Av. Trabalhador São Carlense, 400 CEP 13560-970 São Carlos, SP, Brazil
[2]Instituto de Química, Universidade Estadual de Campinas, Cx. P. 6154, Campinas, SP 13084-862, Brazil.
[3] Diabetes Center, Metabolic Research Unit, and the Department of Medicine, University of California San Francisco, San Francisco CA, USA 94143
[4] Departamento de Ciências Farmacêuticas, Universidade de Brasília (UnB), Brasília, DF, Brazil 70900-910

The nuclear-receptor (NR) superfamily of transcription factors includes receptors for thyroid hormone (TH), retinoids, steroids, vitamin D, xenobiotics, fatty acids, bile acids and cholesterol derivatives, and orphan receptors for which ligands have not been identified. NRs play widespread roles in development, homeostasis and disease and, consequently, are major targets for pharmaceutical development. NR ligands bind to a discrete C-terminal ligand-binding domain (LBD), thereby influencing NR subcellular localization, coregulator recruitment, oligomerization and activities of the receptor N-terminal and DNA binding domains. The thyroid hormone receptor (TR) has received considerable attention in terms of LBD structure and pharmaceutical development. For example, TH analogues that bind selectively to TRβ vs. the TRα isoform, and that have other selective properties, reduce body fat content and circulating levels of cholesterol, triglycerides and lipoprotein Lp(a) without eliciting other unwanted effects of thyroid hormones. Although the LBDs of both TR isoforms have been crystallized in complex with the major form of TH (triiodothyronine, T_3), and several alternate agonists, the structural basis of the ligand specificity to TRβ vs. the TRα is not yet fully understood. Here we present our recent results on the TR? and TR? LBD complexes with several isoform specific and isoform non-specific ligands and discuss the structural basis of their specificity.

Isoform-specific Ligands of Thyroid Hormone Nuclear Receptor and Structural Basis of Their Interactions with the Receptor.

Lucas Bleicher^1$, Ana Carolina N. Figueira^1$, Alessandro S. Nascimento^1$,Fabio M. Nunes^1$, Ricardo Aparicio^1$, Sandra M. G. Dias^1$, Maria A. M. Santos^1$, Mario de Oliveira Neto^1$, Leandro Martínez^2$, Munir S. Skaf^2$, James W. Apriletti^3$, John D. Baxter^3$, Paul Webb^3$, Francisco A. R. Neves^4$, Luis A. Simeoni^4$ and \underline{Igor Polikarpov}^1$

^1$Instituto de Física de São Carlos, Universidade de São Paulo, Av. Trabalhador São Carlense, 400 CEP 13560-970 São Carlos, SP, Brazil; ^2$Instituto de Química, Universidade Estadual de Campinas, Cx. P. 6154, Campinas, SP 13084-862, Brazil. ^3$Diabetes Center, Metabolic Research Unit, and the Department of Medicine, University of California San Francisco, San Francisco CA, USA 94143 ^4$Departamento de Ciências Farmacêuticas, Universidade de Brasília (UnB), Brasília, DF, Brazil 70900-910

The nuclear-receptor (NR) superfamily of transcription factors includes receptors for thyroid hormone (TH), retinoids, steroids, vitamin D, xenobiotics, fatty acids, bile acids and cholesterol derivatives, and orphan receptors for which ligands have not been identified. NRs play widespread roles in development, homeostasis and disease and, consequently, are major targets for pharmaceutical development. NR ligands bind to a discrete C-terminal ligand-binding domain (LBD), thereby influencing NR subcellular localization, coregulator recruitment, oligomerization and activities of the receptor N-terminal and DNA binding domains. The thyroid hormone receptor (TR) has received considerable attention in terms of LBD structure and pharmaceutical development. For example, TH analogues that bind selectively to TR\beta}$ vs. the TR\alpha}$ isoform, and that have other selective properties, reduce body fat content and circulating levels of cholesterol, triglycerides and lipoprotein Lp(a) without eliciting other unwanted effects of thyroid hormones. Although the LBDs of both TR isoforms have been crystallized in complex with the major form of TH (triiodothyronine, T_3$), and several alternate agonists, the structural basis of the ligand specificity to TR\beta}$ vs. the TR\alpha}$ is not yet fully understood. Here we present our recent results on the TR\alpha}$ and TR\beta}$ LBD complexes with several isoform specific and isoform non-specific ligands and discuss the structural basis of their specificity.