



SYSTEMS BIOLOGY OF NUCLEAR RECEPTORS: THE IMPACT OF TRANSCRIPTIONAL CYCLING

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Transcription initiation is a complex, multi-step process, which involves coordinated action of numerous proteins. The 48 members of the nuclear receptor superfamily of ligand-dependent transcription factors play a multitude of essential roles in the development, homeostasis, reproduction and immune function. Peroxisome proliferator-activated receptors (PPARs) α , β , γ and δ and the vitamin D receptor (VDR) are members of the nuclear receptor family that act as sensors for macronutrients (dietary lipids) and micronutrients (vitamin D), respectively. Recently we described transcriptional dynamics of VDR and PPAR δ association with their chromatin targets and mRNA accumulation of their target genes (p21 and PDK4, respectively) on a cell population level by using a stochastic model for single gene transcription realistic kinetics for diffusion and protein complex dynamics (JBC 284:8073-82; Cell 138:489-501). We observed that gene induction caused an approximate 60 min periodicity of several transcription related processes: first, the covalent histone modifications and presence of many regulatory proteins at the transcription start site; second, RNA polymerase II activity; third, chromatin loop formation; and fourth mRNA accumulation. Our model can predict the precise timing of single-gene activity leading to transcriptional cycling on the cell population level when we take into account the sequential and irreversible multi-step nature of transcriptional initiation. We propose that the cyclic nature of population gene expression is primarily based on the intrinsic periodicity of the transcription process itself.