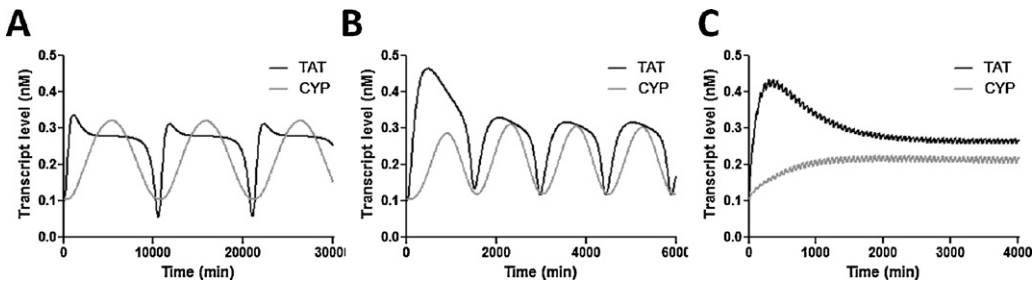

Fig. 1. Impact on network dynamics of repeat exposures to stimulus. Transcript levels of TAT and CYP3A4 were simulated using the single-ligand model, with repeat stress events at (A) low (1/week), (B) medium (1/day), or (C) high (1/h) frequency.

43/7708 significantly altered miRNA expression levels were observed in the non-exposed F_1 offspring of irradiated parents (shown in Fig. 1 – top left and top right boxes). The data also revealed three distinct groups of miRNA expression profiles, those which: (i) remain unaltered following parental irradiation (Fig. 1 – bottom center box); (ii) show a general response to parental irradiation; and (iii) are only altered following paternal exposure.

Pathway analysis (mirPATH) revealed that the miRNAs showing transgenerationally altered expression levels were enriched for putative interactions with genes in pathways relating to DNA recognition/repair, DNA methylation, cell signalling and carcinogenesis.

The miRNA alterations that are unique following paternal irradiation can be considered to represent important advances in the characterisation of key cellular pathways associated with the germline passage of radiation-induced genomic instabilty.

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P046

A systems biology approach towards understanding nuclear receptor interactions: Implications at the endocrine–xenobiotic signalling interface

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Endocrine signalling is a prerequisite for multi-cellular organisms, allowing the transfer of information between different cells and tissues, which is vital for coordination of biological responses. Such signalling networks must be able to both respond to external stimuli and to maintain homeostatic levels of endogenous messengers. To achieve this, a regulatory signal network controls two important aspects of the overall response; first, the physiological response to stimulation, such as increased glucose mobilisation from the liver as part of the fight or flight response; second, a catabolic response that returns glucocorticoid levels to within normal bounds, ensuring homeostasis and terminating the physiological response. Such signalling involves the nuclear receptors, a family of ligand-activated transcription factors that control expression of target gene sets involved in both the physiological and catabolic response to stimuli [1], using a series of feedforward and feedback loops to coordinate responses [2,3].

To examine the design principles underlying the performance of this regulatory signal network we have reconstructed the cellular response to glucocorticoid signalling, creating a realistic kinetic model based upon systems biological graphical notation. We demonstrate the utility of both feed-forward and feed-back signals in coordinating the physiological and metabolic responses to stimuli. In addition, we demonstrate that the network is robust to low and medium frequency perturbations, but once the stimulation frequency approaches once per hour, the system is unable to revert to baseline and permanently enhanced physiological responses are achieved (Fig. 1). Such permanent elevation of, for example, glucose mobilisation is a key driver the development of metabolic syndrome, demonstrating how perturbations in nuclear receptor signalling may play central roles in endocrine disease progression.

In conclusion, using a realistic kinetic model we have identified the design principals underlying how nuclear receptor interactions function at the xenobiotics–endobiotics interface for endocrine signalling. In addition, we demonstrate how repeated stimulation may result in dysregulation within this network, potentially resulting in adverse effects.

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P047

Design principles of nuclear receptor signalling: How complex networking improves signal transduction

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The 48 members of the human nuclear receptor (NR) family have been implicated in a diverse range of regulatory functions, such as in development, cellular growth, inflammation and metabolism [1].