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EuroDYNA takes lid off the genome

European researchers have made significant progress unravelling how genes are governed and why this sometimes goes wrong in disease. The key lies in the dynamic ever-changing structure of the chromatin, which is the underlying complex of protein and DNA making up the chromosomes in which almost all genes are housed within the genome. The way this structure changes and responds to external signalling molecules within the cell determines how and when genes are expressed and also the mechanisms used to repair DNA damaged by a variety of internal and external insults, such as ultra violet radiation and free radical by-products of metabolism.

Understanding the structure of chromatin and its interactions with proteins and RNA within the cell was the goal of the European Science Foundation's (ESF) EuroDYNA programme, which held its last conference at the Wellcome Trust Conference Centre near Cambridge in May 2008. The study of genome structure involves interaction between various disciplines including cell biology, molecular physics, biomechanics and bioinformatics, as well as access to a wide range of expensive equipment such as electron microscopes, supercomputers, and scanners for simultaneous profiling of RNA expression across the whole genome. EuroDYNA helped broker these collaborations and enable projects to develop the critical mass needed to make real progress.

The expression of genes involves an apparatus comprised mostly of proteins for reading the DNA, leading to production of RNA. This RNA in turn is either transported within the cell to the protein factory called the ribosome, where the code is translated into proteins, or else it interacts with other genes to control their expression in turn. These processes are intimately related to the constantly changing physical and chemical structure of the chromatin. Furthermore the overall state of the genome evolves during the life cycle of the cell, leading to its duplication if and when the cell eventually divides. All these inter-related processes need to be understood in order to unravel the complex network of mechanisms controlling gene expression.

One of the big fundamental questions tackled within EuroDYNA concerned

the detailed structure of how the DNA double helix is folded in the nucleus of higher organisms. Although the double helix structure was discovered by Crick and Watson in 1953, the way it folds and stretches such that it fits in the cell nucleus is only now becoming clear, as is its relevance both for cell replication and gene expression.

At the EuroDYNA conference, John van Noort from Leiden University in the Netherlands reported that the DNA molecule, which in humans and most mammals is about two metres in length but only 2 nanometres in diameter, is coiled up like a spring in a solenoid structure. In such a folded structure it behaves according to the well known Hooke's law, stating that up to a certain point the extension is proportional to the force applied. It turns out chromatin is a very elastic molecular complex, capable of stretching to three times its normal rest length without breaking, according to van Noort. Even more remarkably – and here it differs from a familiar metal spring - even if stretched beyond three times its rest length, the chromatin solenoid is capable of repairing itself and regaining its former shape and elasticity.

Indeed the ability of DNA to repair itself is essential for the long term survival of the cell and ultimately of the whole organism. DNA damage occurs not just from factors outside the cell nucleus, but also during the process of cell division (mitosis). The overall objective is to hand down the correct genetic code to the daughter cells during mitosis, a process so important that a number of surveillance and repair systems have been put in place to ensure its completion. One of those systems is called PRR (Post Replicative Repair) and it is highly conserved among all organisms, from bacteria to eukarya. PRR was discovered in the 1970s, but here again the detailed mechanisms are only now being elicited. At the EuroDYNA conference, Simone Sabbioneda from the University of Sussex presented new findings about one of the key PRR mechanisms called Translesion DNA Synthesis (TLS). This project, like some of the others, involved direct observation of processes as they take place in living cells, in this case using a technique called Fluorescence Recovery after Photobleaching. This comprises an optical microscope combined with a probe to observe the radiation emitted (the fluorescence) by molecules within a cell in response to a laser source. Such work is yielding important clues on how the PRR pathways work, hoping to help in the long

term campaign to find novel, more specific, treatments for cancer, without the side effects of current therapies based on surgery, radiotherapy, or chemotherapy. One EuroDYNA project however yielded a more immediate insight into a treatment already used to alleviate the symptoms of another important disease, MS (multiple sclerosis). Pavel Kovarik from the University of Vienna's Department of Microbiology and Immunology noted that the only compound capable of alleviating MS symptoms was the protein interferon beta. This resembles the interferon produced naturally by the body in response to infection, but until now it has not been known how it relieves symptoms for MS sufferers. However Kovarik and colleagues have shown that interferon works by upregulating (increasing production of) members of the protein family Tristetraprolin (TTP), which have an anti-inflammatory affect by in turn inhibiting production of pro-inflammatory agents. "We have demonstrated a novel function for interferon," said Kovarik. By understanding how it works, there is the potential for delivering interferon beta more effectively for treating MS. There were other projects within EuroDYNA with great therapeutic potential, many of which will continue, but which would benefit greatly from an extension to this highly successful programme