EMBO
reports

editorial

Cycles

If you arrived at this editorial by using 'cycles' as a search term, you may be disappointed to find no further information on the latest *Tour de France* doping scandal. You may also be deprived of the surprises and pleasures that come from browsing a journal in its entirety rather than selecting a paper using a single keyword. This editorial is about cycles in living cells, as we highlight a new review series on cycles in cellular processes, which starts in this issue.

In addition to our regular review articles, *EMBO reports* selects topics that we believe are worthy of more detailed coverage in the form of a review series. Last year, the Molecular Medicine Review Series focused on proteins that are responsible for, and named after, a particular disease. This year, we highlight the concept of cycles by selecting four themes from different levels of complexity: organisms, cells, receptors and molecules. In this and future issues of *EMBO reports*, the Cycles Review Series will examine the topics of circadian rhythms (see page 930, in this issue), the coordination of replication and segregation in the chromosome cycle, the insulin-dependent recycling of the glucose transporter GLUT4 between intracellular compartments and the plasma membrane, and the cycles of the ATPase machinery.

While reflecting on this theme, I was struck by how the realization of the importance of cycles is slowly but inevitably changing our view of living systems. For a long time, molecular biology painted a rather static and linear picture of cellular components and events. However, biology is undergoing a profound change as it examines the dynamic, interactive and four-dimensional aspects of how life functions at the molecular level. Such paradigm changes occur occasionally in other sciences; there was once a time when it was believed that the world was flat, and that the sun circled around the Earth. Although these theories explained some observations at the time, they were ultimately misleading and did not explain more detailed observations of the sun's movements. Nikolaus Copernicus's proposal—that the sun lies at the centre of the solar system—changed the view of humans being at the epicentre of the universe, to man as a mere blip on a small speck in the universe. This profound insight triggered many other revolutionary breakthroughs in astronomy and physics. Similarly, biology may be undergoing its own Copernican revolution.

The era of molecular biology began with insights into the structure and function of DNA, together with crystallization studies that finally allowed scientists to investigate and define the functioning components of proteins at the level of amino acids. These were, without a doubt, huge scientific breakthroughs, but the strength of biochemistry at the time caused molecular biology to become a static science. Proteins were studied and viewed in isolation, with little interest in how they interact with each other or with other components of the cell. The 'Second Coming' of molecular biology, when recombinant DNA technology allowed the isolation of individual genes and RNA transcripts, further reinforced this static view. The genome became a concatamer of gene blocks. The activation of genes was seen as a linear process during which a protein binds a promoter to activate the transcription machinery, the RNA transcript is processed and the messenger RNA is translated into protein.

What these images, long portrayed in biological textbooks and reviews, did not show were the complex and dynamic interactions between a huge variety of cellular components—the feedback loops and interactions that could be described as cycles. The failure to address fully the consequences of this essential, but obvious, feature of life constrained our understanding of biological processes. To borrow an example from my own research laboratory, we found that the oestrogen receptor interacts with a target gene in a cyclical manner. The ligand–receptor complex binds to the promoter to start the multistep process of activating the transcriptional machinery. The receptor is subsequently cleaved by the proteasome complex, and this is essential for the steps leading to the transcription of the gene. It required a change in perspective to realize that the destructive phase of this cycle—when the receptor is removed by the proteasome—is as essential for the proper functioning of the cell as is the constructive phase, during which the ligand–receptor complex triggers transcription. Describing and viewing each step in isolation is therefore as inappropriate as describing a bicycle wheel as having an upper and a lower part.

Once this change in perception becomes an integral part of our reasoning, we are challenged to consider the whole dynamic system when studying biological phenomena rather than examining individual components and events in a static manner. It is not surprising that global analyses of transcripts and large complexes of molecules are now becoming key components of biological studies. The catchphrase 'systems biology' covers this transition in focus from static to dynamic, and from linear to cyclic processes. The *EMBO reports* Cycles Review Series is therefore a necessary reminder that biological components do not perform their tasks in isolation, but are constantly interacting, and are created and broken down, while carrying out their roles as loyal members of the intracellular peloton.

Frank Gannon

doi:10.1038/sj.embor.7400549