Editorial

Three decades of Wnt signalling

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Today it is accepted knowledge that the few signalling pathways that govern major developmental processes are also causally involved in devastating diseases such as cancer. Principal discoveries like this rely on experimental observations gathered across seemingly unconnected research fields. Some of the most significant breakthroughs therefore result from the combination of experimental findings in rather unpredictable ways.

The 2012 Focus Issue of *The EMBO Journal* celebrates the 30th anniversary of one of these crucial milestones, recognized today as the 'birthday' of Wnt research, an area that remains dynamic, exciting and productive.

When Roel Nusse and Harold Varmus reported in 1982 on 'a putative proto-oncogene, transcriptionally activated by MMTV proviruses in tumours', they had not only corroborated retroviral activation of a single-host gene as tumour-initiating event but also established 'proviral-tagging' as the future method of choice for the discovery of novel proto-oncogenes. Molecular cloning of the *int1* locus revealed the intriguing similarity to *Drosophila* Wingless, one of many segment polarity genes discovered and subsequently characterized by developmental biologists. This crucial convergence point laid the foundation for close interactions between developmental geneticists and cancer biologists. The discovery of the first mammalian Wnt gene provided molecular evidence that cancer can arise from developmental abnormalities, that is from cells that manage to escape developmental control mechanisms.

The Wnt pathway has by now been linked to a wide range of conserved biological processes. Wnt signals impinge on developmental decisions in many phyla due to the control of cell–cell communication, cellular polarization, cell behaviour and cell division.

Our review collection emphasizes recent discoveries within the areas of stem cells, synapse formation and cell cycle regulation. It further highlights the role of β -catenin as major convergence point and Wnt-signal 'executioner' before illuminating opportunities and challenges for the therapeutic exploitation of pathway components.

This Wnt Focus Issue of *The EMBO Journal* starts with a personal perspective from Roel Nusse and Harold Varmus. They reflect on some of the major discoveries and unifying principles within the network of Wnt signal transduction. This perspective also features the collaborative and interdisciplinary research approach among scientists within the Wnt community.

Hans Clevers reports on the journey from TCF4 knockouts that established the role of Wnt signals in the development of

the intestinal crypt. He then marks the way to the most recent discovery of the stem cell marker Lgr5 as functional receptor of the Wnt agonist R-spondin in adult stem cells.

Shifting to the neuronal system, Kang Shen highlights recent discoveries on the instructive role of Wnt signals in neuronal polarity, circuit formation, axon guidance and synaptic plasticity. These have been documented in a range of model organisms and are also discussed as potential therapeutic targets for neurological disorders.

Christof Niehrs focuses on the interplay of canonical Wnt signals with the cell division cycle. The general mitogenic activity of Wnt-signal is elegantly combined with recent mechanistic insights of how individual pathway components operate during mitosis.

The vast literature on β -catenin is decisively interpreted by Konrad Basler, offering a balanced introduction and at the same time a holistic view on one of the most versatile, evolutionary-conserved proteins.

Finally, as a tribute to the intimate involvement of Wnt signals in cancer initiation, progression and maintenance, Paul Polakis rationalizes approaches and current progress in targeting the canonical branch of the Wnt pathway for cancer therapy. We are particularly pleased to present this Focus Issue to mark the 30th anniversary of the discovery of the *int1* proto-oncogene in *The EMBO Journal* at the time of its own 30th anniversary. Launched in 1982, *The EMBO Journal* remains dedicated to the rapid dissemination of innovative, rigorous and insightful research across the life sciences. *The EMBO Journal* has considerably broadened its scope as molecular biology touched upon most fields of biological enquiry, a fact convincingly illustrated by the research presented in this special issue. Having reported significant discoveries within the field of Wnt research, we look forward to live up to this commitment in the future.

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