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Meeting Report

Cell cycle and cell death associates in western France

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'Cancer cell growth and survival' meeting in Nantes France, 18–20 October 2006

The 'Cancer cell growth and survival' meeting took place in Nantes from 18 to 20 October 2006. This was the third of a series of meetings on 'Apoptosis and Pathology' driven by the notion that even programmed cell death, whose biological end point is in essence unambiguous, relies on mechanisms that can be bypassed, rerouted or simply involved in other cellular functions. The influence of such detours on carcinogenesis was one of the main objectives of this year's meeting. Mechanistic aspects of both apoptosis (in line with previous meetings) and proliferation control, the role of cell death in tumor biology, development and cell differentiation, and the impact these molecular characteristics have on cancer therapy were addressed.

Proliferation Control in Development, Carcinogenesis and Therapy

Cell-cycle inhibitors associated with oncogene-induced cell death provide a barrier to tumor progression. *Martine Roussel* nicely demonstrated that the cyclin-dependent inhibitor p18Ink4c functions as a tumor suppressor for the induction of medulloblastoma, a childhood brain tumor, by collaborating with either p53 deficiencies or mutations in the patched signaling pathway. In addition to $p18^{Ink4c}$ inactivation, N-Myc amplification or increased copies of cyclin D1 were also frequently found in both mouse and human medulloblastoma. Importantly, these observations were confirmed in mice *in vivo*, as primary cerebellar granule neuron progenitors with defined mutations (i.e. Ptc+/−, Ink4c−/−) and N-Myc or cyclin D1 overexpression produce medulloblastomas in the CNS of naïve recipient animals.

Although cyclins are well known to associate with cdk to induce cell-cycle progression, *Peter Sicinski* described a novel, cdk-independent function of cyclin E in cell-cycle re-entry.

In many immortalized and transformed cell lines, cyclin expression and cell-cycle progression are regulated by the p52 nuclear factor kappa B (NF-κB) subunit. *Neil Perkins* showed that p53 recruits p52 directly to DNA, so that this subunit cooperates with the tumor suppressor to regulate the expression of its target genes. p52-DNA binding is not required for recruitment to p53-regulated promoters. This implies that p52 can either activate or repress p53, probably to regulate the induction of cell-cycle arrest and cell death following DNA damage or oncogene activation.

Besides apoptosis, senescence provides a barrier to abnormal proliferation that was initially believed to rely on p53–p21Cip1 and p16Ink4a. *Igor Roninson* reported that senescence can occur in the absence of p53, p21 or p16, and that the impact of senescence might rely on various secreted proteins that possess either growth-inhibitory or tumor-promoting activities. In particular, p21- or p16-expressing cells surprisingly secrete more proteins with tumor-promoting activities. In contrast, retinoid-treated cells produce tumor-suppressing mediators upon growth arrest but do not activate p21. *Igor Roninson* also described the discovery of chemical compounds that block the induction of tumor-promoting genes in senescent cells. Therefore, paracrine effects appear to play important roles during senescence induction and may generate new therapeutic approaches.

Mechanistic and Molecular Aspects of Programmed Cell Death

One important regulatory mechanism exerted by survival stimuli depends on the control of the activity of caspases by members of the inhibitor-of-apoptosis (IAP) family. *Pascal Meier* reported that different IAP molecules inhibit caspases through distinct mechanisms, ranging from direct enzymatic inhibition to indirect modulation of their activity, This has important implications for the development of small therapeutic compounds designed to neutralize caspases. Importantly, IAPs may have additional functions that do not necessarily involve caspase inhibition. For example, the second *Drosophila* IAP (DIAP2) is an essential component of innate immunity.

In mammalian cells, the Bcl-2 family of proteins lies at the pinnacle of the 'decision network' for death and survival. The pro-apoptotic multidomain proteins Bax and Bak play a critical role in the apoptotic response of these cells, in part through their ability to affect mitochondrial permeability. *François Vallette* described the events involved in Bax conformational

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changes and the function(s) of the distinct domains within Bax that control its insertion into mitochondria membranes.

Bax and Bak are linked to various upstream signals by the BH3-only proteins of the Bcl-2 family. *Peter Daniel* showed how the expression of natural born killer is regulated, and the mechanism on which its activity relies. This presentation advanced the attractive notion that, owing to their diversity and ability to initiate distinct cooperative death signals, differing BH3-only proteins can exert distinct additive, possibly synergistic, functions in apoptosis.

Redundancies and specificities in BH3-only protein function were investigated by crucial *in vivo* experiments presented by *Andreas Villunger*. The multiple post-natal defects developed by mice lacking both *bim* and *puma* genes indicate that the corresponding proteins have overlapping functions. The fact that their combined loss promotes spontaneous tumorigenesis also underscores the role played by cell death in tumorigenesis, as discussed in the following session.

Cell Death in Tumor Biology and Physiology

Although genomic instability is a hallmark of cancer cells, its relationship to abnormalities in apoptosis remains elusive. The experiments presented by *Maria Castedo* suggested that activation of the mitochondrial apoptotic pathway actively contributes to the elimination of wild-type p53 polyploid cells, whereas tetraploidy causes a shift towards apoptosis resistance.

Gerry Melino demonstrated that p63, a member of p53 family that can activate cell-cycle arrest and proapoptotic genes, also plays an important role in epidermal development. He also showed that the ubiquitin protein ligase Itch has a fundamental role in the mechanism that controls endogenous p63 protein levels *in vivo*.

The interrelationship between death pathways and other cellular processes is emphasized by the fact that core components of the apoptotic machinery, such as caspases, also have nonapoptotic, physiologically relevant, functions. *Eric Solary* observed that caspase-8 is specifically involved in the differentiation of monocytes into macrophages by cleaving RIP1, which prevents sustained NF-κB activation. Moreover, protection of GATA-1 against caspase cleavage by HSP70 allows erythroid differentiation.

Clinical Aspects of Anticancer Therapy

The molecular characterization of tumor suppressor mechanisms brings the promise of more effective cancer therapies. The frequent involvement of tyrosine kinases from signaling pathways in cell proliferation and survival suggests that they may be good therapeutic targets. *Gerard Milano* showed how small molecule inhibitors of tyrosine kinases are developed, and used in the clinic.

Another process that is key to tumor pathogenesis is angiogenesis, which sustains malignant cells with nutrients and oxygen. *Jean Pierre Armand* showed how advances in molecular biology have allowed the characterization of mechanisms underlying angiogenesis, and how this can be translated into a therapeutic reality.

Erick Gamelin presented new approaches to personalize and optimize the treatment of colorectal cancers. To predict the risk of toxicity, the role of host proteins involved either in the catabolism, activation or efficacy of chemotherapeutic drugs has been characterized through their genetic polymorphisms. The tumor response is simultaneously predicted by linking the Src-STAT3 oncogenic pathway to an intrinsic drug resistance phenotype. This double approach provides the opportunity to use optimal doses of existing cytotoxic drugs in combination with newly targeted therapies.

In the same context, *Hervé Watier* presented new data that open the way to optimization of monoclonal antibody therapy. Fc-γ-RIIIa is one of the receptors for the Fc portion of immunoglobulin G (IgG), mainly expressed on natural killer cells and macrophages. A significant link between a functional polymorphism in the Fc-γ-RIIIa gene and efficacy of several cytolytic-IgG1 monoclonals was established. This 'immunopharmacogenetic' approach has proved useful in stratifying patients into responders and nonresponders, and has implications for the development of new therapeutic strategies.

A Few Concluding Remarks

As organizers, we were happy to see that the presentations by invited speakers, and the short selected talks by young researchers, stimulated many discussions. The informal environment, in which breaks, poster sessions and meals were organized was particularly important here. Moreover, this meeting established many contacts between scientists, that this meeting helped to establish also benefited first year postgraduate students from Nantes and Angers Universities who attended the conference as part of their teaching program. These are very encouraging aspects for the organization of forthcoming editions of this biennial meeting in Western France.

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