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Preface

DNA damage response, genetic instability and cancer: From mechanistic insights to personalized treatment

Over the last decade there have been many breakthroughs in our understanding of the biology and molecular pathogenesis of cancer, however, the sad truth is that cancer remains one of the top killers of mankind. In fact, due to the overall ageing of the world's population and ongoing changes of lifestyle in the populations of large developing countries such as China, the global incidence of cancer is expected to increase, rather than decrease, in the near future (Ferlay et al., 2010). This unfortunate scenario provides a strong motivation to translate the advances achieved by basic research into efforts aiming at improving the clinical management of cancer patients. Such translational efforts encompass improvements in early diagnosis, providing new function-based sub-classification schemes for various types of cancer, discovery and validation of potential novel drug targets and candidate drugs, as well as application of emerging innovative strategies to improve cancer treatment. The latter efforts include targeted biological therapies in a single agent setting as well as combinations with standard-of-care therapeutic options, both preferably in a biomarker-guided personalized manner to ensure maximal positive impact on survival and quality of life of cancer patients. It is in most, and possibly all, of the above-mentioned aspects of basic and translational cancer research that the field of DNA damage response (DDR) and genetic (in)stability can offer useful mechanistic insights and major advances, some of which are already now beginning to have an impact in the clinics (Ashworth et al., 2011; Halazonetis et al., 2008; Hanahan and Weinberg, 2011; Jackson and Bartek, 2009; Kastan and Bartek 2004; Luo et al., 2009; Negrini et al., 2010).

Indeed, DNA damage and cancer biology including clinical responses to therapy are inseparable. DNA damage and genetic instability lie at the heart of cancer development, as unrepaired or incorrectly repaired DNA lesions may give rise to cancer-initiating or –driving mutations, while genomic instability of various forms can fuel multistep tumor progression and resistance to therapy. In fact, apart from endogenous sources of DNA damage such as fortuitous replication errors and oxidative stress, or exogenous genotoxic insults such as UV light or cigarette smoke, also iatrogenic sources of DNA damage including radiotherapy and chemotherapy can (and will) induce mutations and destabilize the genome, thereby occasionally resulting in the development of secondary malignancies or allowing selection of treatment-resistant cancer cell clones within the initially therapy-responsive tumor. Thanks to a deeper mechanistic understanding of DNA damage signaling, checkpoint responses and DNA repair, we are beginning to grasp the fundamentals underlying the apparently simple yet puzzling issue of why radiotherapy and genotoxic chemotherapy will preferentially kill cancer cells, at least in some cases. The introduction of new high-throughput technologies including next-generation sequencing, has allowed us to better appreciate the unexpected complexity of the genetic landscape of common malignancies. Given the fact that components of the DDR machinery are often targeted during cancer development (Ashworth et al., 2011; Jackson and Bartek, 2009), one way to tackle cancer is to take advantage of such biological differences between cancer and normal cells and exploit the tumor-associated DDR defects in smart therapeutic strategies, various examples of which are presented in some of the articles in this Thematic issue. At the same time, we are learning how to lessen the detrimental side effects of standard-of-care treatment modalities, which are attributable to therapy-inflicted DNA damage in normal tissues, especially those that proliferate.

The cancer-associated genetic defects within the DDR machinery can be of germ-line origin or acquired somatically. The former mutations are known to cause cancer susceptibility human syndromes such as ataxia telangiectasia, xeroderma pigmentosum or Nijmegen breakage syndrome (Jackson and Bartek, 2009), and/or predispose to various types of familial tumors, such as breast and ovarian cancer in the case of BRCA1 and BRCA2 mutations (Ashworth et al., 2011). Indeed, the majority of germ-line mutations that predispose to breast cancer target genes whose products have been functionally implicated in the DDR, either as sensors, signal transducers, checkpoint components or DNA repair genes (Bartkova et al., 2008). Furthermore, since the underlying mutations remain unknown for a large fraction of breast cancer families, the striking prevalence of DDR-related genes in this

context has inspired searches for additional DDR-related germ-line defects in such 'orphan' families (Bartkova et al., 2008; Walsh et al., 2010). In addition to germ-line DDR defects, a wide spectrum of somatic mutations and epigenetic alterations affect genes of the DDR network during cancer progression and metastasis, allowing selection and 'survival of the fittest' among the cancer cell clones within a tumor. Such acquired DDR aberrations include for example loss-of-function events in the ATM-Chk2-p53 tumor-suppressive cascade and other checkpoint pathways the malfunction of which facilitates survival and proliferation of genetically unstable cancer cells. These and other cancer-associated changes, particularly aberrations of diverse DNA repair pathways, may contribute to radiation or drug resistance, for example by altered processing of therapy-evoked DNA lesions. At the same time, such differences, if better understood at the functional level, could provide a window of opportunity for novel therapies.

From a wider perspective, the multifaceted relationship between DNA damage and cancer can be briefly formulated in the following way: *If we want to understand cancer, we need to understand the cellular and molecular principles of response to damaged DNA. In addition, if we want to optimize existing treatments, combine them, or design new, smart, molecular targeted therapies, then we must understand the roles of DNA damage and genetic instability in tumorigenesis and the impact of DDR defects on tumor responses to various therapeutic modalities*. Given the large amount of data and rapid advances in recent years, it is obviously impossible to cover this entire field of research in a single thematic issue. In fact, to highlight even only the most promising and actively pursued research directions in DDR would still be a daunting endeavor. Overall, the eight articles contributed by recognized international experts, that collectively form this Thematic issue on Genetic instability and Cancer, provide authoritative overviews of various aspects of the field of DNA damage responses and genetic (in)stability from both basic biology and translational research standpoints. The emphasis is to illustrate recent advances in some of the most rapidly evolving directions of cancer research in this area, rather than an attempt to cover the entire field. The fundamental topics covered by the individual contributions include the roles of replication stress and endogenous DNA damage in cancer pathogenesis and genetic instability, novel insights into the functions of p53 and the related network of cancer-associated genes, the role of centrosomes in genetic instability, chromatin response to DNA damage, the resistance of cancer (glioma) stem cells to radiation, and DDR kinases and PARP as targets of inhibitors in cancer treatment.

In order to set the stage for this thematic issue, this short Preface provides readers with information that may help place the individual contributions into proper context. Thus, two examples of important directions of cancer research that started with two pairs of articles related to DNA damage and cancer, by coincidence published in the same issue of Nature a few years ago, will be briefly presented to illustrate progress in basic and translational work in this field, respectively. This will then be followed by brief introductions to the individual review articles of this thematic issue.

One of the fruitful DDR-related directions of basic cancer research has been the development of the concept of the DNA damage response as an intrinsic biological barrier to activated oncogenes and tumor progression, first formulated in 2005 (Gorgoulis et al., 2005; Bartkova et al., 2005). These studies showed that various types of oncogenes in cellular and animal models potently activate the DNA damage signaling and checkpoint responses, including the ATR/Chk1 and ATM/Chk2 kinase cascades, and that an analogous pattern of widespread constitutive DDR network activation observed in clinical specimens of early human lesions that have not been treated by any genotoxic modality, pointing towards an endogenous source of the damage. The DDR activation appeared to be the result of enhanced replication stress, as documented by various ways including evidence for preferential increase of DNA double strand breakage at so-called fragile sites of the genome in the clinical samples of early stages of tumor progression (Gorgoulis et al., 2005; Bartkova et al., 2005). Subsequent studies showed that this DDR activation is also the upstream force that drives the phenomenon of oncogene-induced senescence, consistent with the notion that such an oncogene-induced DDR barrier helps to delay or prevent progression of dangerous, oncogene-expressing nascent cancer cells (Di Micco et al., 2006; Bartkova et al., 2006; Malette and Ferbeyre, 2007). Since then, this direction has branched into studies confirming the concept in different types of cancer, for different types of oncogenes, and addressing the idea of exploiting the more pronounced dependency of cancer cells on the DDR machinery that copes with replication stress and repair of replication-induced DNA lesions (Branzei and Foiani, 2010; Cimprich and Cortez, 2008; Halazonetis et al., 2008; Negrini et al., 2010). Most recently the fate of the replication errors that are propagated into the next G1 phase of the cell cycle has been elucidated, by the identification of the so-called 53BP1 bodies (or OPT bodies) as structures that contain many activated DDR factors reminiscent of DSB signaling, and protect the replication-caused lesions until the next S phase where cells resolve these potential threats to genomic integrity (Harrigan et al., 2011; Lukas et al., 2011). Additional insights and suggestions, to exploit the selective replication stress scenario in cancer cells for treatment, are reviewed in two contributions in this thematic issue (Dereli et al., 2011; Toledo et al., 2011).

The other, more translational, but by no means less exciting, direction of DDR-related cancer research was set off by papers demonstrating the applicability of the so-called synthetic lethality principle for therapeutic purposes (Bryant et al., 2005; Farmer et al., 2005). These studies showed that tumors defective in BRCA1 or BRCA2 tumor suppressors, which function in the homologous recombination repair system, were exceptionally sensitive to inhibitors of PARP, an enzyme operating in a related (and partially functionally redundant) repair pathway, in sharp contrast to cells that preserved at least one intact copy of the BRCA1/2 genes. Importantly, the principle of synthetic lethality has since been extended to additional examples of cancer-associated DDR defects, suggesting that this strategy may be applicable well beyond the BRCA1/2-PARP combination (Ashworth et al., 2011; Jiang et al., 2009). In addition, initial clinical trials with PARP inhibitors showed very promising antitumor effects, accompanied by only minor or no toxicity in normal tissues despite the prolonged treatment of a cohort of ovarian cancer patients (Fong et al., 2009). The interpretation of the molecular basis of PARP inhibitor effects has been evolving, and this subject, including the emerging mechanisms of cancer resistance to PARP inhibitors, is discussed in detail in the contribution by Helleday (2011).

There are several genetic instability patterns that can be distinguished in human tumors, and the article contributed by Halazonetis and colleagues provides an up-to-date concise introduction into this important aspect of cancer (Dereli et al., 2011). This field has benefited enormously from the recent introduction of high-throughput technologies that allow assessment of total cancer genomes, and as explained by Dereli et al. (2011), the pattern that has until recently been regarded as CIN (chromosomal instability) in fact encompasses a handful of distinct subtypes of genetic instability. The authors focus particularly on large chromosomal deletions and insertions, a specific class of recently catalogued cancer-associated genomic aberrations that appear to target preferentially the fragile sites in mammalian genomes. The key message of this thoughtful overview supports and extends the above-mentioned concept of the DDR machinery as an inducible biological barrier to cancer progression, activated in response to oncogene-evoked replication stress. Dereli et al. (2011) argue that the type of genetic instability characterized by large insertions and deletions reflects replication stress and formation of DNA DSBs earlier in the development of such tumors. Overall, this review is an example of useful exploitation of the newly emerging large datasets, generated by pan-genomic analyses, for conceptual thinking about the various types of genomic instability that occur in human malignancies.

Tetraploidy and aneuploidy, the latter often following the former during malignant transformation, are other frequently observed forms of genetic instability in cancer cells. This class of chromosomal aberrations is discussed by Aylon and Oren (2011), and presented from a p53-centric view. The p53 tumor suppressor is a central player in the DNA damage response network including cell-cycle checkpoints, and its activity leads to elimination of tetraploid cells by induced cell death or senescence, depending on cell type and biological context. Mechanistic insights into the origin of tetraploidization, the involvement of p53 and its upstream regulators and downstream effectors, are also the subject of this essay. Indeed, p53 (and its closely related cousin p73) operate hand in hand with other tumor suppressors that also contribute to cell-cycle checkpoints, and Aylon and Oren illustrate this functional cooperation for both G1/S and the spindle checkpoint. Consideration of cancer-promoting defects in key cell-cycle checkpoint components that facilitate tetraploidy and aneuploidy by establishing 'an atmosphere of tolerance' for such gross genomic instability concludes this insightful article.

The theme of aneuploidy is also discussed in the contribution by Krämer et al. (2011), in this case in the context of centrosomal aberrations, their causes and consequences. Centrosome amplification occurs commonly in diverse types of human tumors, through mechanisms such as cytokinesis failure or centrosome overduplication, and it is closely linked to chromosomal instability and tumorigenesis. The review by Krämer and colleagues focuses primarily on the puzzling ability of cancer cells to survive the deregulated mitoses with the hazardous scenario of too many centrosomes, an ability that allows cancer cells to continue proliferation with unstable genomes despite the potential of fatal errors during chromosome segregation. The answer to the puzzle seems to lie in a mechanism called 'centrosome clustering' that allows cells to transiently organize the aberrant supernumerary centrosomes into bipolar mitotic spindles and thereby undergo a relatively 'normal' cell division (Krämer et al., 2011). The authors provide a survey of recent mechanistic insights into the molecular and cellular basis of centrosome clustering, the impact of this phenomenon on genetic instability, tumorigenesis, potential role in asymmetric divisions of stem cells, and links with DNA damage signaling proteins that reside directly on centrosomes. Finally, the authors discuss translational implications of centrosome clustering as an emerging target for drug discovery, and approaches to exploit this centrosomal aberration in cancer treatment.

Widespread alteration of gene expression programmes is one of the prominent features of the global cellular response to genotoxic stress. In addition, critical components of the transcriptional machinery itself are frequently subverted in virtually all types of malignancies. This important topic at the interface of transcriptional regulation, cancer, and response to DNA damage (the latter exemplified by effects of ionizing radiation) is discussed by Shiloh and colleagues (Rashi-Elkeles et al., 2011). The authors generated a vast amount of data on altered gene expression profiles in multiple cellular models, and then mined their own dataset, together with several analogous datasets from other studies, to obtain a global view of the transcriptomic changes that take place after exposure to radiation. The analysis revealed a pivotal involvement of p53-regulated genes, including identification of multiple novel p53 targets, and demonstrated the power of combined bioinformatics, computational and experimental approaches in contemporary systems biology research, applied to the fields of DNA damage, genome stability and cancer.

One of the most rapidly evolving, and cancer-relevant areas of research on genetic stability concerns modifications and remodeling of chromatin structure in response to DNA damage. Genome maintenance requires such dynamic changes of chromatin in order to allow better access of DNA damage sensors, mediators and repair proteins to lesions in genomic DNA that is normally hidden and packaged into a complex and rather inaccessible higher order nucleosomal structure. At the same time, re-structuring of chromatin is critical during processes such as gene transcription, DNA replication and chromosome condensation preceding mitotic division, processes that are commonly deregulated during tumorigenesis. An overview of the critical types of posttranslational protein modifications, including phosphorylation, ubiquitylation, sumoylation, acetylation and methylation, as well as the reversal of these processes on histones and other chromatin and DDR-related proteins, and pathophysiological relevance of these events, is the subject of the article by Luijsterburg and van Attikum (2011). The authors summarize the recently gained insights into functional links between the DNA damage signaling kinases ATM, ATR, Chk1 and Chk2 and the wide range of enzymes that carry out a myriad of chromatin protein modifications, including multiple ATP-dependent remodeling complexes. Furthermore, this timely review also explains the respective roles of such enzymes within the genome surveillance machinery, and provides thoughts on the current open issues at the interface of chromatin modulation, DNA integrity, and cancer.

The strategy of targeting the DNA damage response machinery through inhibition of DDR kinases such as ATM,

ATR or Chk1, in the hope of achieving treatments that are more selectively toxic to cancer cells, is a topical issue reviewed by Fernandez-Capetillo and colleagues (Toledo et al., 2011). The authors provide a thorough overview of literature in this area, and discuss arguments for such higher differential toxicity of checkpoint kinase inhibition in cancer cells, compared to proliferating normal cells. Apart from the commonly accepted view that the lack of p53 function in cancer, resulting in the inactivation of G1 checkpoint and hence higher demand on the G2 checkpoint that depends on ATR-Chk1 signaling, Toledo et al. (2011) add another explanation for the effects of Chk1/ATR inhibition, and propose that the toxicity of checkpoint kinase inhibitors may reflect the fact that these compounds generate supra-threshold loads of replication stress, which 'cooperate' with the less restrictive S-phase entry found in p53-deficient cells. The authors furthermore suggest that the toxicity of DDR kinase inhibitors might not be restricted to p53-deficient cells, but could be applicable more broadly, consistent with the endogenous, oncogene-driven replication stress (Toledo et al., 2011) recently reported for a wide range of human tumors (Bartkova et al., 2005; Gorgoulis et al., 2005; Bartek et al., 2007). This very informative review should further stimulate interest in translational exploitation of the concept of enhanced replication stress in cancer, and hopefully help develop effective cancer treatments.

Glioblastomas, one of the most aggressive and deadly forms of cancer, represent a type of tumor with rampant genetic instability and high degree of spontaneous DNA damage (Bartkova et al., 2010). At the same time, these tumors are commonly resistant to radiotherapy and chemotherapy, and this appears to be, at least in part, due to the so-called tumor initiating cells (or glioma stem cells) a subset of cancer cells that are more resistant to genotoxic treatments and likely responsible for recurrent growth and overall treatment failure of these malignancies. It is therefore appropriate that Mannino and Chalmers selected the topic of glioblastoma stem cells and their resistance to radiation as a biological system to present in this collection of essays on genetic instability (Mannino and Chalmers, 2011). Based on their own work and review of the large body of published evidence, the authors propose that the radioresistance of glioma stem cells does not only reflect the intrinsic properties of these cells, but it is a result of interactions between the cancer stem cells and their microenvironment, the latter itself being affected by DNA damage in various ways. While focusing on glioblastomas, the thoughtful discussion about the cross talk between tumor initiating cells and their surrounding niche has broader implications for both our understanding of cancer biology, and potential innovative treatment strategies to target the cancer stem cells.

Probably the best example of a therapeutic potential among the emerging DDR-targeted drugs are the PARP inhibitors (Bryant et al., 2005; Farmer et al., 2005), now under scrutiny in numerous clinical trials, at various phases and for diverse types of malignancies. Despite their successful performance in preclinical studies and the initial phase I clinical trials (Fong et al., 2009), and the ensuing hopes and attention they created within the biomedical research community, the mechanisms that underlie the synthetic lethal effect of PARPi in BRCA1/BRCA2-defective tumors remains incompletely understood. In a thought-provoking analysis of current views on this important topic, Thomas Helleday presents evidence to support several mechanistic models that may explain the pronounced synthetic lethality of PARP inhibitors and BRCA1/2 deficiency (Helleday, 2011). The essay touches on issues of PARP involvement in base excision repair, its role at stalled replication forks, hyperactivation of PARP in cancer cells defective in homologous recombination repair, as well as the ability of the currently used compounds to inhibit several members of the PARP family (Helleday, 2011). Importantly, as a proof of principle and pioneering example of this therapeutic strategy, better understanding of the biological impact of PARP inhibitors is likely to facilitate discovery and development of additional synthetic lethal combinations and drugs applicable in personalized treatment of cancer.

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