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Cancer biology and genomics: translating discoveries, transforming pathology

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Abstract

Advances in our understanding of cancer biology and discoveries emerging from cancer genomics are being translated into real clinical benefits for patients with cancer. The 2011 *Journal of Pathology* Annual Review Issue provides a snapshot of recent rapid progress on multiple fronts in the war on cancer or, more precisely, the wars on cancers. Indeed, perhaps the most notable recent shift is reflected by the sharp increase in understanding the biology of multiple specific cancers and using these new insights to inform rationally targeted therapies, with often striking successes. These recent developments, as reviewed in this issue, show how the long-term investments in basic cancer research are finally beginning to bear fruit.

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Over the past decade, we have finally witnessed how advances in our understanding of cancer biology and discoveries emerging from cancer genomics can be translated into real clinical benefits for patients with cancer. Clinical oncology is being transformed, along with the practice of tumour pathology. The 2011 *Journal of Pathology* Annual Review Issue (ARI) is an opportunity to assess this ongoing transformation. Ideally, an annual review issue functions as a snapshot of the timeliest topics in a given area. This year marks the third *Journal of Pathology* ARI on Cancer since 1999. A perusal of the two prior ARIs on Cancer [1,2] provides an interesting perspective on trends in cancer research, both anticipated and unanticipated, with various predictions, some quite prescient, others completely unrealized.

Notably, three areas that have assumed a central role in cancer research but were nascent or essentially undiscovered in 1999 are: (a) kinase mutational activation and targeted inhibition; (b) microRNAs and the tool of RNA interference as a human biological phenomenon and as an experimental tool; and (c) massively parallel sequencing. Mutational activation of kinase signalling as a therapeutic target has assumed an importance well beyond that expected from the initial successes in 'niche' settings such as chronic myelogenous leukaemia [3] and gastrointestinal stromal tumours (GISTs) [4,5]. Indeed, the generalizability of this cancer paradigm was not really evident until the discovery in 2002 of *BRAF* mutations in

melanomas [6] and many other common cancers and the concept was further 'democratized' with the discovery in 2004 of *EGFR* mutations in a subset of lung adenocarcinomas [7–9]. The dramatic responses to EGFR inhibitors in these lung cancers [10], to ALK kinase inhibitor in lung cancers with *ALK* fusions [11] and, most recently, to BRAF inhibitor in *BRAF*-mutant melanomas [12], have transformed clinical oncology. The striking advances achieved by kinase targeting in lung cancer, melanoma, GIST and other cancers are the subjects of detailed reviews in this issue [13–16]. These advances are also transforming the practice of pathology, as we face an ever-increasing need for tumour genotyping, given the relationships between type of mutation in the target gene and response to therapy. Accordingly, departments of pathology are increasingly being asked to become 'departments of comprehensive tumour characterization'. At the same time, as more and more genes need to be screened clinically, technological developments in massively parallel sequencing have drastically reduced the costs of comprehensive sequencing. These two intersecting trajectories suggest that, sooner than we expect, it may become more cost-efficient and expeditious to prospectively obtain whole-genome, or at least whole-exome, sequencing data on every patient's tumour, a scenario analysed in more depth elsewhere in the present issue [17], than to do multiple single gene studies on each tumour specimen.

At the time of the 1999 ARI, microRNAs as a part of human cell biology and RNA interference as an experimental tool were still undiscovered but the field was about to explode. The profound impact of this paradigm-shifting discovery was recognized in 2006, when the Nobel Prize in Physiology or Medicine was awarded jointly to Andrew Z Fire and Craig C Mello. The field is now sufficiently mature that a thorough review of the role of microRNAs in human cancer, as contained in the present ARI [18], can provide a comprehensive perspective on this complex topic.

The only topic to be covered in all three Cancer ARIs (1999, 2005, 2011) is p53, attesting to its crucial role in so many human cancers and in so many cellular processes in cancer biology [19–22]. Mouse models of cancer, the subject of reviews in both 1999 and 2005 [23–25], are not featured as a separate review this time, perhaps reflecting their transition into a commonplace tool in cancer biology, but they do figure prominently in the thoughtful review by Berger and Pandolfi of the challenging area of haploinsufficient tumour suppressor genes [26], as well as in the update provided by Lozano and colleagues [21] on how mouse models are helping us understand why p53 activation can lead to different cell fates, namely cell death, cell cycle arrest or senescence, in different settings.

As the biology (or biologies?) of specific cancers have become more fleshed out and therapeutically relevant, reviews are more often focused on individual cancers. In 1999, only one review focused on a single cancer (lung cancer) [27]. In 2005, there were two such reviews (breast cancer, gastrointestinal lymphoma) [28,29]. In the present issue, approximately half of the review articles are disease-specific [13,14,16,30–34]. This signals both the growth in our biological understanding of certain cancers and an increased awareness of the diversity (but genetic specificity) of human cancer. Pathologists have long been keenly aware of the variety and heterogeneity of human cancers, an aspect that was historically less appreciated by basic researchers working on ‘cancer’ or carcinogenesis as a single process rather than multiple diseases. Nonetheless, there are also many important problems in cancer that cut across histological types and they continue to be the focus of intense study. In the present ARI, the general problems of metastasis [35], the role of the tumour microenvironment [36,37], TGF β signalling [38] and cancer stem cells [39] are examined in great detail. Understanding these general processes better as common denominators for many cancers may lead to potentially more broadly applicable, but nonetheless biologically precisely targeted therapies.

For cancer researchers, pathologists and oncologists, it is indeed reassuring to see progress in understanding the basic biology of cancers of several types leading to clinically relevant rational therapies. Real clinical impact in a wide range of tumours is within sight but the optimism generated by kinase targeting in CML, GIST, lung cancer, melanoma, is tempered

by the regular emergence of secondary resistance, making long-term cures still elusive in most of these cancers. Clearly, we have penetrated the defences of the enemy but the battle is far from over. The articles in the present issue may reflect the next steps taken in unravelling this complex problem and form an inspiring basis for ongoing progress in the many ‘wars on cancers’.

Author contributions

Both authors contributed to writing and editing the manuscript.

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