Editorial

New hopes in the fight against cancer: a special issue on targeted anti-cancer drug discovery and cell signaling

Since the declaration of war on cancer more than 40 years ago, progresses on cancer treatment outcomes have been slow and limited for most part, despite major investments in research and development. However, the realization that cancer is an extremely complex and heterogeneous mixture of diseases, coupled with technological advances in cancer genomics, proteomics, and metabolomics, has led to the development of novel and more effective treatment approaches in recent years. In fact, the approvals of multiple new classes of targeted therapies, particularly anti-cancer immune therapy agents in recent months, may have signaled the arrival of a new era in our fights with cancer. With the expansion of anti-cancer therapeutics toolbox, it is now possible to design individualized treatments to match the genetic makeups of the patients and their tumors. It is fair to say that there is no better time than now for cancer research. This special issue showcases 11 up-to-date reviews written by experts in their corresponding fields covering the major forefronts of targeted cancer drug discovery research.

As the most mutated oncogene in human cancers and one of the first oncogenes discovered, rat sarcoma viral oncogene homolog (RAS) is the 800-pound gorilla. Despite more than three decades of extensive research and development efforts, attempts to develop therapeutics targeting RAS have not been successful, which leads to the perception that RAS is ‘undruggable’. Driven by a better understanding of RAS signaling networks and the advent of novel chemical biology approaches, the RAS research field is undergoing a renaissance. Therefore, it is not surprising that we have four review articles covering different aspects of recent developments in targeting this ‘undruggable’ cancer villain. The extreme high affinity for ligand and similarity of the ligand binding sites among large numbers of small GTPases pose major challenges to develop direct RAS inhibitors. Innovative and unconventional approaches are required to overcome this major barrier. While McCarthy et al. [1] discuss recent progresses in applying structure-based computational approaches to search for novel allosteric ligand binding sites on the soluble and membrane-bound RAS, Deng and colleagues [2] review different strategies, including an intriguing and alternative concept of hyperactivating KRAS by activators, currently being explored to target cancer activating KRAS in non-small-cell lung cancer (NSCLC). On the other hand, Lv et al. [3] examine the potential of targeting the metabolic reprogramming driven by oncogenic RAS. Whether these novel approaches and concepts will lead to the ultimate discovery of a ‘silver bullet’ remains to be seen. Considering that RAS mutant-driven cancers are heterogeneous because of the presence of distinct mutant alleles and co-activation in other cancer-related genes, it is unlikely that one universal RAS inhibitor will be effective for all RAS mutant-driven cancers. Effective treatments will require the stratification of RAS mutant tumors and personalized combination therapies targeting co-mutations through precision medicine, which is the emphasis of a review by Fang [4].

One class of cancer-related genes that are known to crosstalk with oncogenic RAS in cancers and may be targeted for combination therapy are the HER (EGFR/ErbB) receptor family, particularly HER3. In a review by Zhang and colleagues [5], recent efforts in the development of HER3-based anti-cancer monoclonal antibodies, as well as progresses in biomarker discovery for anti-HER3 therapies, are expertly discussed. Unlike HER3, a cell surface receptor, retinoid X receptor-alpha (RXRα) is a member of the nuclear receptor superfamiy and a proven cancer therapeutic target. However, how RXRα regulates cancer cell growth and how RXRα modulators suppress tumorigenesis is poorly understood. Zhang et al. [6] account the characterization of N-terminally-truncated tRXRα (tRXRα) in cancer cells and discuss new and improved strategies for the development of anti-cancer therapeutics targeting tRXRα.

In addition to well-established cancer drug targets, this special issue also contains articles covering the validation of several emerging anti-cancer targets and related drug discovery researches. One such effort summarizes the recent advances in our understanding of the roles that autophagy participates in cancer metastasis and cancer drug resistance and deliberates the potentials of modulating autophagy in anti-cancer therapy [7]. Similarly, Almahariq et al. [8] recap the contributions of the exchange protein directly activated by cAMP (EPAC1) in cancer development by focusing on EPAC1’s roles in cancer metastasis, metabolism, and immune-modulation, as well as the advantage of a multimechanistic anti-cancer approach using small molecule EPAC1 inhibitors. Another interesting target, reviewed by Xu et al. [9], is the thymine DNA glycosylase (TDG), an important enzyme that is involved in the DNA repair, methylation, and transcription regulation. The expression patterns of TDG are altered in several types of cancers, particularly in gastric cancer, which is the focus of another review by Xie and colleagues [10]. In their article, the classification, treatment option, molecular mechanisms for drug resistance, and future directions in gastric cancer biology and drug targets are discussed in detail. It is now well recognized that epigenetic regulation is another important facet of cancer development. Indeed, oncogenic mutations and epigenetic dysregulations go hand in hand in fueling the vicious cycles of cancer initiation and progression [11]. The excellent review by Wang and colleagues [12] summarizes the key players important for epigenetic regulation, their cancer associations, and recent advancement in developing pharmacological agents targeting epigenetic controls in cancers.

Acknowledgements

I thank all the authors for their fine contributions to this special issue. I would like to express my gratitude to all the reviewers for their excellent and constructive review comments. I hope that our readers will
enjoy reading all the aforementioned articles and find this special issue helpful for their future research.

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