Published in final edited form as:

Semin Cancer Biol. 2019 February ; 54: iii–iv. doi:10.1016/j.semcancer.2018.08.005.

Some chinks in RAS armor

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RAS proteins (KRAS, NRAS, and HRAS) act as molecular switches that upon activation drive several key cellular processes such as cell growth, proliferation and survival [1]. In normal cells, RAS activity is under tight control by the precise cycling of the active RAS-GTP to inactive RAS-GDP [1]. Nevertheless, the genes encoding for RAS protein isoforms are found mutated or altered in a significant proportion of tumors [2]. Mutant RAS remains in a permanently activated state (GTP-bound) leading to uncontrolled cell growth and tumor formation. This is quite well known for more than 30–40 years and considerable dollar investments have been directed to develop drugs that can directly block RAS, or inhibit its activators as well as interfere with its downstream effectors [3]. However, to date there is no drug that could effectively block RAS signaling in the clinic. The problem lies in the RAS structure itself that lacks any potential drug-binding site that could fit in a small molecule drug. Similarly, drugs against targets within the RAS pathway (upstream or downstream) have not been very effectual clinically. These hurdles have led researchers to believe that the RAS armor is impenetrable [4].

In the last several years, there has been a renewed interest in the area of RAS research. Partly attributed to the National Cancer Institute's RAS Initiative, the field has seen a spurt in new discoveries. Significant new reagents and resources have also emerged and are aiding RAS drug discovery. I have organized this thematic issue in Seminars in Cancer Biology to keep the research community abreast with these latest developments. An attempt to cover the breadth and depth of this all-important topic has been made.

The first set of reviews highlight the importance of RAS and associated signaling in cancer. The thematic issue begins with the review from Khan and colleagues highlighting the role of RAS in regulating oncogenic signaling in various malignancies (1). In the second article, Imperial et al., review the PANCAN/PANCAN genome analysis showing global alterations of the RAS-RAF-MEK-ERK signaling in cancer (2). This is followed by an article from Seema Shah and colleagues on RAS cooperating protein RAP1 (3). In this review, the authors show how RAP1 performs RAS related functions by activating ERK and could plausibly become an important therapeutic avenue within this complex pathway. In the next article Chetan Rane and Audry Minden discuss the role of RAS downstream signaling mediator and Rho GTPase effectors p21 activated kinases in cancer and highlight some emerging small molecule drugs (4).

The thematic issue switches gear and the next several articles focus on the RAS signaling interactions within the tumor microenvironment. In this area, a review from Enrique Rozengurt and Guido Eibl emphasizes the unique communication between RAS and YAP in the high fat microenvironment (5). This review highlights how obesity and inflammatory signaling can trigger RAS activity and provides critical and actionable avenues within this interaction. In the next article Saswati Karmaker and colleagues, provide a perspective on the interactions of RAS with non-coding RNA signaling (6). This review especially focusses on pancreatic ductal adenocarcinoma and describes the key role of several RAS regulated microRNAs in therapy resistance. Following this, an article from Debabrata Mukopadhyay's lab reviews the interaction between RAS and TGF- β signaling in cancer (7). Their review describes how neuropilin-1 promotes RAS-TGF- β interaction and projects it to be actionable therapeutic axis.

The next several reviews focus on the challenges associated with targeting RAS. Oscar Aguilera and colleagues describe the role of altered metabolism (Warburg Effect) in RAS mediated chemoresistance (8). Here some interesting insights are provided that substantiate the use of natural products such as ascorbate to overcome altered metabolism and RAS related chemoresistance. Following this, Marin Ramos et al., give an overview of the post-translational mechanisms that regulate RAS and provide insight into how these can be targeted using new agents (9). In the next article Minsig Choi's group presents a detailed review on the clinical challenges in using RAS pathway targeted agents in pancreatic cancer that is recognized to carry high frequency of KRAS mutations (10).

RAS membrane anchoring is critical for its cellular functions. To cover this area, the interactions of RAS with cellular membrane and its therapeutic implications are discussed in three different articles. Two reviews from Ruth Nussinov's group focus on oncogenic KRAS mobility in the membrane and RAS membrane clustering (11, 12). In another article, Lawrence Goldfinger and colleagues provide a detailed overview of the new advances in the area of membrane targeting in RAS (13). Article from our group (Sexton et al.,) looks into the extracellular exosome signaling of RAS and its therapeutic implications (14).

The final set of articles focus on therapeutic strategies targeting RAS and associated pathways. John OBryan's and colleagues provide a very detailed account of the several different types of small molecule strategies targeting RAS and discuss the associated challenges (15). Their review discusses the pros and cons of the most emerging small molecule drugs in this area. Peptide based RAS therapeutics is highlighted in an article from Helen Mott's group (16). The scale of the complexity of the RAS signaling requires equally complex solutions. It is realized that reductionist biology may not be able to decipher the intricacies of RAS. Rather, holistic/systems level approaches are needed to understand the redundancies in the RAS pathway. This may help in the design of effective drugs targeting the most important biological node of this master oncogenic regulator. An article from Boris Kholodenko highlights the importance of holistic computational systems biology in the understanding of RAS signaling (17). Finally, this thematic issue concludes with an article from Dominic Esposito's group presenting the new research tools developed at the NCI RAS Labs. The readers would appreciate the importance of these new reagents and how these could aid the community in their research on RAS (18).

This thematic issue carries more than a 1000 updated references that would certainly find their way into the library of avid RAS researchers. It is hoped that these reviews will bolster new ideas and accelerate the development of clinically viable RAS therapeutics and create meaningful dents in the by far impenetrable RAS armor.

List of articles:

1. Khan et al., Ras-mediated oncogenic signaling pathways in human malignancies.
2. Imperial et al., Comprehensive Pancancer Genomic Analysis Reveal (RTK)-RAS-RAF-MEK as a key dysregulated pathway in cancer: its clinical implications.
3. Shah et al., Ras and Rap1: A Tale of Two GTPases.
4. Rane et al., p21 activated kinase signaling in cancer.
5. Rozengurt et al., KRAS, YAP, and obesity in pancreatic cancer: a signaling network with multiple loops.
6. Kamakar et al., MicroRNA Regulation of K-Ras in Pancreatic Cancer and Opportunities for Therapeutic Intervention.
7. Vivekanandhan et al., Genetic status of KRAS influences Transforming Growth Factor-beta (TGF β) signaling: an insight into Neuropilin-1 (NRP1) mediated tumorigenesis.
8. Serna-Blasco et al., Targeting the RAS-dependent chemoresistance: the Warburg connection.
9. Marin Ramos et al., Blocking Ras inhibition as an antitumor strategy.
10. Bien et al., Challenges in Ras therapeutics in pancreatic cancer.
11. Tsai et al., Oncogenic KRas mobility in the membrane and signaling response.
12. Tsai et al., Is Nanoclustering essential for all oncogenic KRas pathways? Can it explain why wild-type KRas can inhibit its oncogenic variant?
13. Michael et al., Concepts and advances in cancer therapeutic vulnerabilities in RAS membrane targeting.
14. Sexton et al., (to be accepted). Ras and Exosome Signaling.
15. Smith et al., Direct Inhibition of RAS: Quest for the Holy Grail?
16. Owen et al., Bioblockades join the assault on small G protein signaling.
17. Erickson et al., New insights into RAS biology reinvigorate interest in mathematical modeling of RAS signaling.
18. Stephen et al., New weapons to penetrate the armor: novel reagents and assays developed at the NCI RAS Initiative to enable discovery of RAS therapeutics.

Acknowledgement

Work in the lab of Asfar S. Azmi is supported by NCI R37 CA21542702.

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