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Guest editorial/preface

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(K)RAS is the most frequently mutated human oncogene in cancer. This mantra appears as an intro in all the articles published about in the past decades. If this is the case, this mutated oncogene is the most important target for personalized medicine. Compared with these facts, our molecular, biochemical, and cell biological picture of the mutated KRAS are compatible with the twentieth century but not with twenty-first. Similar to other oncogenes, there are several mutation hotspots in KRAS which differentially occur in various cancer types due to differences in various carcinogenic effects. It is also a paradigm that the mutation of KRAS in cells which have a "quasi-normal" genetic background does not behave as oncogene but rather as an oncosuppressor, a master manipulator of senescence, and is responsible for various RASopathies, (non-cancerous malformations). Accordingly, mutant KRAS could develop into oncogene only if the genetic background is appropriate and the pattern of co-mutated oncogenes and oncosuppressors is permissive. Again, similar to other mutated oncogenes, various mutant alleles result in diverse functional changes in the KRAS protein: accordingly, a KRAS mutant cancer/tumor does not exist due to functional diversity. Textbook mantra also is the declaration that mutant KRAS loose its charismatic GTPase activity, which is not exactly what happens in various allelic variants, but rather a diverse alteration of sensitivity to activators and inhibitors and changes in efficacy stimulating effectors. As a consequence, mutant KRAS can be a master driver or only a minidriver in various cancers. It is also a textbook dogma that mutant KRAS loose its dependence on prenylation/membrane anchor for functional activity: various allelic variants may still remain dependent on this epigenetic modification. All these factors gain outstanding importance in the new era of "druggable KRAS" when irreversible small molecular inhibitors emerged to treat KRAS mutant malignancies. The clinical challenge is enormous: pancreatic cancer, a rather chemoresistant disease, is a typical KRAS mutant disease without target therapy options. The KRAS mutant lung or colorectal cancers even behave differently as compared with their wildtype counterparts clinically when conventional or target or immunotherapies applied. And now the first clinical trials are ahead with G12C-mutated KRAS-driven colorectal and lung cancers, the moment of truth arrived: the very same irreversible inhibitor has a very different efficacy in the two diseases. The editors dedicated this issue of "Cancer and Metastasis Reviews" to mutant KRAS to portray a different picture of this oncogene to better understand the challenges we face when we are going into war against this enemy. This issue is dedicated to my previous mentors, professor Alan Hall and Chris Marshall, who were pioneers in this field of RAS research who were not allowed to live the time when basic science turns into real translational research.

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