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Towards the era of precision medicine in metastatic colorectal cancer

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Colorectal cancer (CRC) represents a heterogeneous group of dynamic biological phenomena with differing sets of genetic events, accompanying immune responses and influences of exogenous factors, providing a challenge for personalised therapeutic approaches.[1] These personalised treatments most often involve kinase inhibitors or monoclonal antibodies that target specific alterations known to drive the proliferation and survival of cancer cells.[2] In this scenario, the epidermal growth factor receptor (EGFR) family plays a key role in tumour growth and progression, but its use is limited by the presence of pre-existing innate resistance mechanisms or by the ability of cancer cells to acquire resistance to therapy.[2 3] *RAS* mutation status is the only negative predictive biomarker in the management of CRC. Additional molecular features associated with resistance to anti-EGFR therapy in many preclinical studies, including PIK3CA mutation, phosphatase and tensin homologue loss, *BRAF* mutation, human epidermal growth factor receptor 2 (HER2) and secondary *EGFR* mutations, have been studied, but no one has been incorporated routinely in clinical practice.[2 3] Intriguingly, all these alterations seem converge to reactivate the principal downstream effector of the EGFR pathway: MAPK-extracellular signal-regulated kinase (ERK), whose EGFR independent overactivation allows the tumour to survive in the presence of anti-EGFR drugs.[2 3]

In particular, recently, *HER2* amplification has been suggested as both an intrinsic, as well as an acquired mechanism of resistance to anti-EGFR therapies and consequently as a predictive biomarker of response to drugs targeting HER2.[4 5] Furthermore, these data have been debated recently.[6] *HER2*-amplified clones might be expanded under the selective pressure of anti-EGFR therapy, leading to disease progression. In this regard, *HER2* amplification is more likely to confer acquired anti-EGFR therapy resistance. On the contrary, as a primary resistance mechanism, no robust data are available to exclude the use of anti-EGFR therapies in this subgroup of patients. HER2 testing should be done after development of anti-EGFR resistance, suggesting the need for a new biopsy. Liquid biopsy could be a valid alternative. In fact, growing use of ctDNA testing has allowed for prediction of the loss of resistance mechanisms, an important determinant of potential future therapeutic options.[7]

In addition, *BRAF V600E* mutation has emerged as an important genetic, prognostic and therapeutic factor for patients with metastatic CRC, identifying a subgroup of patients who derive modest benefit from standard treatments and have extremely poor prognosis.[8]

Clinical trials on double and triple drug combinations for the blockage of the MAPK pathway have shown progressive improvement in the treatment of these patients.[9 10] Additional inhibition of the ERKs, in combination with current targeted therapies, could be the next step for further blockage of the MAPK pathway reactivation.[11] Improvements on the targeted therapies could also be useful for treatments of patients with atypical *BRAF* mutations. There are small percentages of patients with the whole BRAF mutant CRC, but studies are needed for the understanding of these mutations and their therapeutic implications. In addition, exploration of additional critical targets that can be combined with the current treatment regimens would be necessary for the further inhibition of tumourigenesis. Finally, further understanding of the interplay between the *BRAF V600E* mutation and associated tumour biology will lead to further treatment advances in the years to come.

The four consensus molecular subtype (CMS) groups represent the current best description of CRC heterogeneity at the gene-expression level, but further refinement in disease classification, with intra-CMS subgroups and better characterisation of samples with mixed phenotypes, is likely to

emerge in the future.[12] Comprehensive correlative analyses with well-defined genomic and epigenomic CRC features enable deeper understanding of the biological characteristics of each CMS.[12]

Despite its potential clinical utility for outcome prediction or immune-targeted therapy development, CMS classification implementation in clinical practice is challenging due to several factors, including the methods used.

Recently, multiple approaches have been used to identify novel targets, including single-cell genomics/transcriptomics, CRISPR(-Cas9 and interaction mapping.[13] These approaches have opened new avenues towards individualised therapeutic response prediction. However, until today, classification approaches remain insufficient for identifying specific avenues of oncogenic dependency on a patient-by-patient or tumour-by-tumour basis.

Therefore, systems that faithfully predict drug activity in a patient's tumour and enable high-throughput drug testing facilitating identification of cancer therapeutic targets and drug development are needed.

A novel integrative classification system that links molecular features to targeted drugs, re-examining previous successes and failures, is crucial for the future of precision medicine in CRC.

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