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On biomarkers and pathways in rectal cancer: What's the target?

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Abstract

In spite of tremendous progresses in surgical and chemo-radiotherapeutic regimens, rectal cancer still suffers from high relapse and mortality rates, and metastatic disease is incurable. Here we assess some of the most recent and validated biomarkers and potential targets studied in rectal cancer, and provide comments to a recent monographic topic covering several aspects of colorectal cancer, published in *Current Cancer Drug Targets*.

Key words: Rectal cancer; Colorectal surgery; Chemotherapy; Targeted molecular therapy; Biological markers

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COMMENTARY ON HOT ARTICLES

The management of rectal adenocarcinoma has undergone tremendous improvements in the last decade, especially through the advancement of surgical techniques combined with a better defined timing of medical treatment. Still, rectal adenocarcinoma affects about 140 000 new patients each year in Europe, and has a 5-year overall survival of 54%[1]. Currently, standard treatment for stage Ⅱ and Ⅲ rectal cancer includes pre-operative (neo-adjuvant) treatment with 5-fluorouracyl or capecitabine, in combination with ionizing radiation (IR) therapy[1]. The introduction of biological drugs targeting receptor kinases like epidermal growth factor receptor (EGFR) (cetuximab, panitumumab[2,3]), or their ligands, like vascular endothelial growth factor (VEGF) (bevacizumab[4]), has shown promising results. Nonetheless, DNA damaging agents like capecitabine and IR have maintained their roles as the single, most effective modalities of treatment in locally advanced rectal cancer, together with surgery.

In spite of the above mentioned advancements, a large fraction of the patients who undergo regimens containing these agents does not respond to their action, strongly suggesting that rectal tumors can harbor resistance mechanisms *ab initio*, or are able to acquire them in the course of therapy. Microarray studies have been used in the effort of creating classifiers and predictors to treatment response, but the results are scarcely consistent and have not been validated extensively[5,6]. Small datasets, different technical and statistical approaches, and inhomogeneous treatment modalities might have contributed to suboptimal results in data interpretation. Among the best

studied molecular markers of rectal cancer (p53[7], p21[8], Bax and Mib[9], p27[10], thymidylate synthase[11], EGFR[12] or VEGFR[13]) few have shown to hold some promise in rectal cancer prognostic assessment before standard regimens, and their advantage over conventional pathological staging procedures to predict outcome has not yet been validated in large, prospective studies.

Identifying new biomarkers in rectal cancer management could be advantageous for several reasons: (1) the a priori knowledge of tumor resistance to neoadjuvant treatment would spare patients useless and potentially toxic pharmacologic agents, and could lead to the choice of different strategies (*e.g.*, immediate or more radical surgical intervention or shorter courses of adjuvant chemotherapy in complete responders to neoadjuvant treatment); (2) understanding the molecular alterations which constitute the ground of rectal cancer may allow the use of new biologically targeted agents, in combination with surgical resection; and (3) last but not least, the cost/effectiveness ratio of proposed management strategies could be better assessed, in a time when the economic burden of the health care system is steadily growing toward unmanageable dimensions.

The increasingly appreciated complexity of colorectal cancer systems biology is well addressed by the recently published monographic topic, published in *Current Cancer Drug Targets* (*CCDT*)[14-19]. Here, the contributing Authors deal with two of the mainstays of the new "smart weaponries" in colorectal cancer treatment: the EGFR pathway[15] and VEGF signaling[14]. Moreover, two new "hot topics" are covered: the concept of synthetic lethality[18] and the translational potential of mathematical simulations of signaling networks involved in the neoplastic process[19]. Synthetic lethality refers to the ideal situation where the inactivation of one protein product or another does not affect cancer viability, whereas the combined deficiency of both proteins is deadly for the cancer cell[20,21]. The first successful application of this model has been observed in the treatment of breast cancer 1 gene (*BRCA1*)-deficient breast cancer with poly (ADP-ribose) polymerase (PARP) inhibitors[22,23]. The difficulty of finding new synthetic lethal interactions lies in the combinatorial complexity of identifying pairs of protein products showing such properties. While high throughput silencing RNA based screenings may be of help in this field[24], a deepened understanding of how molecular networks interact with each other and dynamically react to internal and external stimuli[25] (such as chemotherapy, IR or targeted agents) is of the essence to generate plausible hypotheses before testing them in "real life". This last issue is well addressed by Parodi[16] in the aforementioned topic.

Finally, an "old dog with potentially new tricks" is also presented in the above referenced *CCDT* issue: targeting DNA damage repair pathways and cell cycle checkpoints in colorectal cancer[17]. While the Reader could reasonably object that such targets are nothing else than those aimed at for the last fifty years by conventional chemotherapy, an essential and relatively overlooked concept is highlighted: since cancer is ontologically characterized, among other features, by genomic instability and mutations[26], intrinsic deficits must exist in tumors which hamper their ability to repair their own genetic information. As a consequence, cancer cells should be more prone than healthy tissues to be killed by DNA damaging agents. It is therefore likely that, with a better knowledge of "what's wrong", physicians could be able to predict "what would be right" in individual cases. Again, PARP inhibition in breast cancer with *BRCA1* germline alterations has been the proof of principle, but it would be simplistic to assume that no other DNA damage repair genes are altered in somatic tumors, hence showing similar properties. This, in turn, leads directly back to one of the main questions in the management of rectal cancer, *i.e.*, why do some cases exhibit exquisite sensitivity to neoadjuvant chemo-radiation, whereas others appear to be completely resistant?

In conclusion, the recent topic appeared in *CCDT* is an interesting and comprehensive reading, that covers several essential aspects of what is currently known about colorectal cancer, and provides the Reader with an updated overview of its biology and of the future roads that may potentially lead to the complete cure of most patients affected by rectal cancer. The greatest endeavor of research in rectal cancer remains that of combining big, well-conducted prospective clinical trials with large breadth ancillary biologic studies. Only this synergism between basic and clinical analytic efforts will lead to the discovery and validation of new biomarkers with a real impact in everyday oncological and surgical practice.

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