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Mini Review

Modern Strategies in Cancer Study: Drug Repositioning in Colorectal Cancer Treatment

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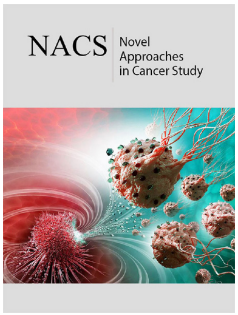

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Abstract

Colorectal cancer is one of the most fatal cancers in the world because most of cases are diagnosed in advanced stages, when the development of resistance to chemotherapy is more frequent. To face this situation, new drugs and drug combinations would be necessary. Drug discovery is a very costly process; although efforts in drug discovery have been amplified in recent decades the success rate of approved FDA drugs continues being low. In response to this situation the repositioning of drugs proposes to delve into the genetic, epigenetic and metabolic differences to discover new targets and redirect drugs already approved to the treatment of other diseases and conditions. In this minireview we discuss the main avenues in which repositioning can occur and we cite some examples of repositioning drugs in colorectal cancer treatment that are being tested in clinical trials in the last years.

Keywords: Colorectal cancer; Drug repositioning; Clinical trials

Abbreviations: CRC: Colorectal Cancer; DCA: Dichloroacetate; DHEA: Dehidroepiandrosterona; EGFR: Epidermal Growth Factor Receptor; EMT: Epithelial-Mesenchymal Transition; FDA: Food and Drug Administration; GEO: Gene Expression Omnibus; NCBI: National Center for Biotechnology Information; 5-FU: 5-Fluorouracil

Introduction

Colorectal cancer (CRC) is the third most commonly diagnosed cancer in males and the second in females, with 1.8 million new cases and almost 861,000 deaths in 2018 [1]. CRC is often diagnosed at advanced stages, when the probability of development of distal or local recurrence due to chemotherapy resistance is more elevated [2,3]. The common protocol for CRC treatment consists in a primary surgical resection of the tumor, followed by radiotherapy and/or adjuvant chemotherapy. Since the 1950s, 5-fluorouracil (5-FU) remains the mainstay of chemotherapy [4,5]. In the recent years other drugs have been developed and used in combination with 5-FU such as oxaliplatin, irinotecan and capecitabine [6]. The use of new monoclonal antibodies such as Bevacizumab and Cetuximab has also allowed great advances in therapies [7]. However, almost half of patients with advanced CRC are resistant to chemotherapies based on 5-FU [8]. To counter this situation new strategies are being implemented; these include improved early diagnosis (down-staging), discovery of reliable predictive biomarkers and development of novel drugs/drug combinations.

The development of a new drug is a process that can take 10-15 years; the number of drugs approved by the FDA (Food and Drug Administration) has been declining since 1995 and investment in drug development has been gradually increasing, indicating that the cost of new drug development will continue to grow [9-11]. In this context, repurposing of drugs has emerged as an alternative to the classical pipeline of drug development and there has been increasing interest in analyzing anti-cancer activity of non-cancer drugs already FDA approved. The two main advantages of this strategy are the knowledge of the pharmacokinetics and toxicity of the drugs and their low costs and accessibility, since they are mostly generic [12]. In addition, repositioning of drugs is a strategy of special importance in low- and middle-income countries, where the conventional therapies are not economically accessible to the population in general due to their high costs [13,14].

Drug repositioning can take advantage of both computational and experimental methods. There are two main approaches in the selection of drugs to reposition: the first consists

in propose a drug as possible anticarcinogenic based on prior information about it, such as the knowledge of its molecular target or the identification of its effects during the treatment of a clinical subpopulation that shows a lower incidence of certain disease. This approach is also called text mining-based since it is based on the literary and observational search of the mode of action and effect of the candidate drug and often the selection is follow by *in vitro* screening techniques. An example of this type is metformin, the postulation of this drug as a possible reposition drug arose as a result of a study of cancer incidence in patients with type II diabetes [15]. In this study it was observed that a group of diabetic patients treated chronically with metformin had a lower cancer incidence and cancer-related mortality. The drug was tested *in vitro* in cell lines of different types of cancer, including CRC, and due to favorable results also in animal models [16]. Preclinical studies determined that metformin affects cellular metabolism and suppresses oncogenic signaling pathways, such as receptor tyrosine kinase, PI3K/Akt, and mTOR pathway [17]. Metformin has been tested in combination with other compounds, showing synergistic action whit EGFR inhibitors and other repositioning drugs such as propranolol [18]. Currently, our group is testing the combination of metformin and propranolol on *in vitro* and *in vivo* models of CRC, where we observed a decrease in cell proliferation and tumor growth, and the inhibition of metastasis related events associated with an effect on epithelial-mesenchymal transitions through the modification of E-cadherin and B-catenin levels (unpublished data). Metformin is actually in phase II to be approved by the FDA for CRC treatment (Table 1).

Within this same approach, other drugs were postulated to be repositioned based on their molecular target; an example is chloroquine, a drug used in the treatment of malaria. Chloroquine was proposed as a possible anticancer drug due to previous knowledge about its effects on parasite autophagy processes. It is known that chloroquine diffuses easily into lysosomes is protonated and loses its ability to diffuse out of the vesicle. In malaria, chloroquine invades the lysosomes of the parasite and of enzymes such as phospholipase A2, hindering the breakdown of proteins and affecting cell signaling pathways [19]. The anticancer effects of chloroquine were corroborated in more than one type of cancer including CRC [20], leukemia [21] and breast cancer [22]. This drug is in phase II of preclinical studies for breast cancer treatment (NCT01446016) and *in vitro* stage for CRC treatment [23]. Other examples of repositioning drugs in CRC treatment whit this approach are dehidroepiandrosterona (DHEA) [24], orlistat [25], pantoprazole [26], DCA [27] and raloxifene [28], all these are in *in vitro* stage.

A second alternative approach for the search of putative drugs to be repositioned takes advantage of bioinformatic methods. During the past decade, the development of new technologies to study gene expression and the advances in sequencing machinery, such as microarrays and the whole transcriptome shotgun sequencing (RNA-seq), have allowed the emergence of gene expression databases (most of which are freely available) putting a large amount of information at the disposal of the scientific community. Some databases, like Gene Expression Omnibus (GEO) at the National Center for Biotechnology Information (NCBI) [29], Array Express [30] and EMBL-EBI Expression Atlas [31] are repositories of a great variety of gene expression studies including genetic expression of cell lines to human tissues, all of them under the most varied experimental conditions. The analysis of this new information has led to great advances in the acquisition of biological and chemical data pertaining to alteration of pathways in diseases, alteration in protein structures, drug-target interactions, mechanism of drug actions, disease-specific and drug-induced gene expression signatures [32-34]. In silico drug repositioning is an approach that takes advantage of this situation to relocate drugs using computational strategies [34]. A large amount of drugs to be repositioned have been proposed based on this approach, some of them for CRC treatment are itraconazole [17], tanshinone IIA [35], and fluspirilene [36], all these still are in *in vitro* tests stage, while others are already being tested in humans CRC as rapamycin and celecoxib (Table 1).

Table 1: Some repositioning drugs in clinical trial stage for CRC treatment.

Drug	Original Indication	Target in CRC	CT phase	NCT Example	N° of CT Testing Drug
Aflibercept	Wet macular degeneration treatment (DMAE)	VEGF pathway inhibitor	Approved (2015)	NCT01669720 NCT02181556	17
Aspirin	Treatment of pain, fever and inflammation	TLR4 expression inhibitor COX-2 inhibitor Increase TGF-β1 secretion	III	NCT02394769 NCT02467582 NCT02647099	27
Celecoxib	Treat pain and inflammation of osteoarthritis, rheumatoid arthritis, ankylosing spondylitis, acute pain in adults, painful menstruation	COX-2 selective inhibitor	III	NCT00005094 NCT03645187	27

Cyclosporine	Immunosuppressant used to avoid rejection of transplants	Wnt/calcium pathway modulator	II	NCT00003950	3
Doxycycline	Antibiotic used in bacteria and parasites treatment	Inhibitor of mitochondrial biogenesis	III	NCT02201381	1
Etodolac	Non-steroidal anti-inflammatory drug (NSAID)	COX-2 inhibitor	III	NCT00888797	1
Everolimus	Immunosuppressant used to avoid rejection of transplants	PI3K/mTOR pathway inhibitor	II	NCT00390364 NCT01154335 NCT01149434	22
Indomethacin	Nonsteroidal anti-inflammatory drug (NSAID)	Non-selective COX inhibitor	I	NCT01719926	1
Lamivudine	HIV and Hepatitis B treatment	Under study. Is known to affect p53 metastatic CCR impairing cancer cells mutant grow	II	NCT03144804	1
Mebendazole	Broad-spectrum anti-helminthic benzimidazole	Under study. Some known activities: a) Microtubule disrupting agent by BCL2 phosphorylation b) XIAP inhibitor c) VEGFR-2, PDGFRA and PDGFRB inhibitor	III	NCT02201381	1
Metformin	Diabetes type 2 treatment	mTOR pathway and IGF1R protein inhibitor	III	NCT01930864 NCT03359681 NCT03359681	10
Nelfinavir	Antiretroviral of the family of protease inhibitors. HIV-1 and HIV-2 treatment	PI3K pathway inhibitor	II	NCT00704600	1
Niclosamide	Intestinal parasite infections treatment	a) Calcium-binding protein A4 inhibitor b) Wnt/β-catenin, mTORC1, STAT3, NF-κB and Notch signaling pathways modulator	II	NCT02519582	2
Nintedanib	Idiopathic pulmonary fibrosis treatment	a) Triple angiokinase VEGF receptors inhibitor b) Platelet-derived growth factor receptor-α/β inhibitor c) Fibroblast growth factor receptors inhibitors d) FLT3, Lck and Lyn inhibitor	III	NCT02780700 NCT02149108	5
Pentamidine	Antimicrobial used to treat a African trypanosomiasis, leishmaniasis, babesiosis, and pneumocystis pneumonia	PRL phosphatases inhibitor	II	NCT00809796 NCT01378143	2
Phenylbutyrate	Treatment of urea cycle disorders	a) Inactivation of NF-kappaB b) Histone deacetylase inhibitor (HCADi)	II	NCT00002796	1

Propranolol	β-blocker use for hypertension treatment	Under study. Some know activities: a) Lipins PAP activity inhibitor b) Affect β-adrenergic pathway	III	NCT00888797	1
Rapamycin	Immunosuppressant to prevent organ transplant rejection	mTOR inhibitor	II	NCT03439462	3
Simvastatin	Cholesterol treatment	HMG-CoA inhibitor	II	NCT02026583	4
Trifluridine	Anti-herpesvirus, antiviral drug, used primarily on the eye	Thymidine phosphorylase inhibitor	III	NCT02848443 NCT03274882	15
Valproate	Epilepsy, bipolar disorder and migraine headaches treatment	HDAC inhibitor	II	NCT01898104	2

CT: Clinical Trial

NCT: Clinical Trial Number

Conclusion

Drug repositioning is becoming one of the fundamental pillars of personalized medicine; aim to improve the productivity of current drug discovery pipelines. The recent advances in next- generation sequencing technologies are enabling personalized genomic studies which in turn provide insight into the heterogeneity between patients within a disease and, in the case of cancer, even within a same type of tumor. The identification of new important molecular pathways and their respective pharmacological targets have potential therapeutic utility in drug repositioning. The knowledge derived from these kinds of approaches will result particularly useful for those patients that have developed pharmacological resistance to conventional treatment and/or suffer from tumors with reduced therapeutical options, especially in low- and middle-income countries.

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Conflict of Interest

The authors declare that they have no competing interest.

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