SciMedCentral

JSM Gastroenterology and Hepatology

Review Article

Let-7 microRNA as a Genetic Regulator of Colorectal Carcinogenesis Process: Principles and Queries

Nikolaos Margetis[1,2]* and Theodoros Mariolis-Sapsakos[3,4]

[1]*Department of Gastroenterology, Athens Euroclinic, Greece*
[2]*Molecular Carcinogenesis Group, University of Athens, Greece*
[3]*Department of Gastroenterology, Aghioi Anargyroi Hospital, Greece*
[4]*Laboratory of Anatomy, University of Athens, Greece*

***Corresponding author**
Nikolaos Margetis, Department of Gastroenterology, Athens Euroclinic, Gennimata 46 Street, Halandri, 15238, Athens, Greece, Tel: 30 211 700 54 76; 30 6945 592 568; Email: nmargetis@yahoo.gr

Submitted: 19 August 2017

Accepted: 18 September 2017

Published: 21 September 2017

Keywords

- Let-7; SNP; LCS6; K-ras mutation; Biomarker; Colorectal cancer

Abstract

Colorectal cancer (CRC) is the third most common cancer worldwide, whose mortality remains high, despite the huge amount of knowledge accumulated and the development of preventive strategies. Recent advances have demonstrated that small, non-coding RNA molecules (microRNAs), which inhibit or abrogate the translation of their mRNA-targets, are critical regulators across the full spectrum of stages of colorectal tumorigenesis process. The prototypical microRNA is let-7, with highly conserved sequence through species. Let-7 is found in ten mature isoforms, characterized by remarkable redundancy and abundance in colorectal epithelium. Let-7 is widely considered a tumor-suppressor, with scarce reports implying a concurrent oncogenic activity as well. K-ras oncogene, one of the most crucial genetic alterations in colorectal tumorigenesis, is a major target of let-7. The intact let-7 complementary sites (LCSs) in the 3' UTR of mRNA of K-ras are indispensable for the complete action of let-7 upon K-ras expression. LCS6 is viewed as the most important of these LCSs, and a SNP variant (T to G) inside this locus exerts more prognostic and predictive role in CRC, when combined with K-ras status and let-7 levels. Mature let-7 is down regulated in colorectal cancer tissue compared with its paired normal mucosa; nonetheless it is gradually up regulated through the successive stages of colorectal tumorigenesis process, playing a central role in all the accomplishment of all these intermediate stages. Its high levels are considered a favorable prognostic and predictive biomarker, whereas its low levels may confer to early diagnosis of colorectal cancer. As let-7 collaborates with other miRNAs, regulates crucial oncogenes (as K-ras and c-myc) and tumor-suppressing pathways (as Wnt/APC and p53) and is regulated by a plethora of its effectors, it might serve as an in vivo manipulator of patients suffering from colorectal cancer in the future.

INTRODUCTION

Colorectal cancer (CRC) is the third most common cancer in men and the second most common cancer in women globally [1]. It was the third most common cause of cancer-related deaths on the USA on 2014 [2]. The five distinct genotypes of CRC [3] arise from a combination of the fundamental pathways of genomic instability, i.e. chromosomal instability, microsatellite instability and CIMP pathway [4]. CRC is the prototype of the genetic multistep model, in which definite genetic alterations result in distinct histopathological changes [5,6]. Colorectal carcinogenesis is multifactorial, involving a complex interplay between genetic background, acquired genetic alterations and environmental factors [7], especially in the sporadic form of the disease, which accounts for the 75% of cases [8]. Epigenetic gene regulation is critical for the entire multistep colorectal carcinogenesis development [8-10]. microRNAs (miRNAs) clearly represent important epigenetic regulators throughout all steps of colorectal carcinogenesis process [10-13], both spatially and temporally [14]. miRNAs are 18-25 nucleotides long, non-coding RNAs with post transcriptional action, i.e. they repress the translation process of their mRNA-target [15]. The mature miRNA consists of two strands, guide strand (5p) and passenger strand (3p). In colon cancer cells both strands silence equally their mRNA-targets [16].

Let-7 family, the prototype miRNA, is the largest miRNA family studied [17]. It consists of ten mature members produced from 13 precursor sequences [18]. There are two designations in the let-7: the first (a letter, e.g. let-7a) shows that mature let-7s are of nearly -but not absolutely- identical sequences. The second (a number, e.g. let-7a-1) signifies that more than one, slightly different, precursors let-7 genes may generate an identical mature let-7 [18]. Genes encoding for let-7 are distributed through 9 different chromosomes [19]. Mature let-7 isoforms display functional redundancy [20], despite their slightly different (1-4 nucleotides) total sequence [21], since they display identical seed sequence, critical for target recognition [22].

Let-7's expression increases during late embryogenesis [23]. It is undetectable in embryonic stem cells. Its major role is to promote cell differentiation: its high expression is maintained in various adult differentiated cells [24] and tissues [25]. Therefore, let-7 is considered a marker of differentiation [26].

Let-7 down regulates numerous mRNA-targets by forming RISC (RNA-induced silencing complex) [15] and guiding it to

the 3 UnTranslated Region (3′ UTR) of the mRNA-target: partial complementarity represses, whereas high complementarity degrades mRNA [27]. Moreover, it establishes many regulatory circuits both in differentiated and dedifferentiated cells [11,12,17,19,27-29]. By these feedback loops let-7 both regulates its targets and is being regulated by several of them. Many of its targets are cell cycle regulators and strong oncoproteins [25]. Consequently, let-7 is widely considered to protect cells from undergoing neoplastic transformation and its role in carcinogenesis, which reflects a process inverse of embryogenesis, is well-established [24].

LET-7 TARGETS A PLETHORA OF MRNAS

Let-7 against oncogenes

The majority of mRNA-targets of let-7 are oncogene transcripts. Numerous targets of let-7 are verified in colorectal tumorigenesis process (Figure 1):

- The cyclins A, D1, D2 and D3 [17,25,30]
- Cyclin-dependent kinases (CDKs): CDK 2/4/6, which control G1 progress [25,30] and CDK 25A/34A, which regulate S/G2 transition [17,25,30]
- K-ras proto oncogene [31] and K-ras oncogene [32]
- The oncogene c-myc [17,19,25], which is up regulated in CRC [26]
- Protein AKT2, resulting in down regulation of the PI3K/AKT pathway activity [17]
- The High Motility Group A2 (HMGA2), a known stemness enhancer [33]
- IL-6 and STAT-3, which display a crucial role to the inflammation-derived cancerous transformation [17,28]
- The enzymes pyruvate dehydrogenase kinase and IFG1R,

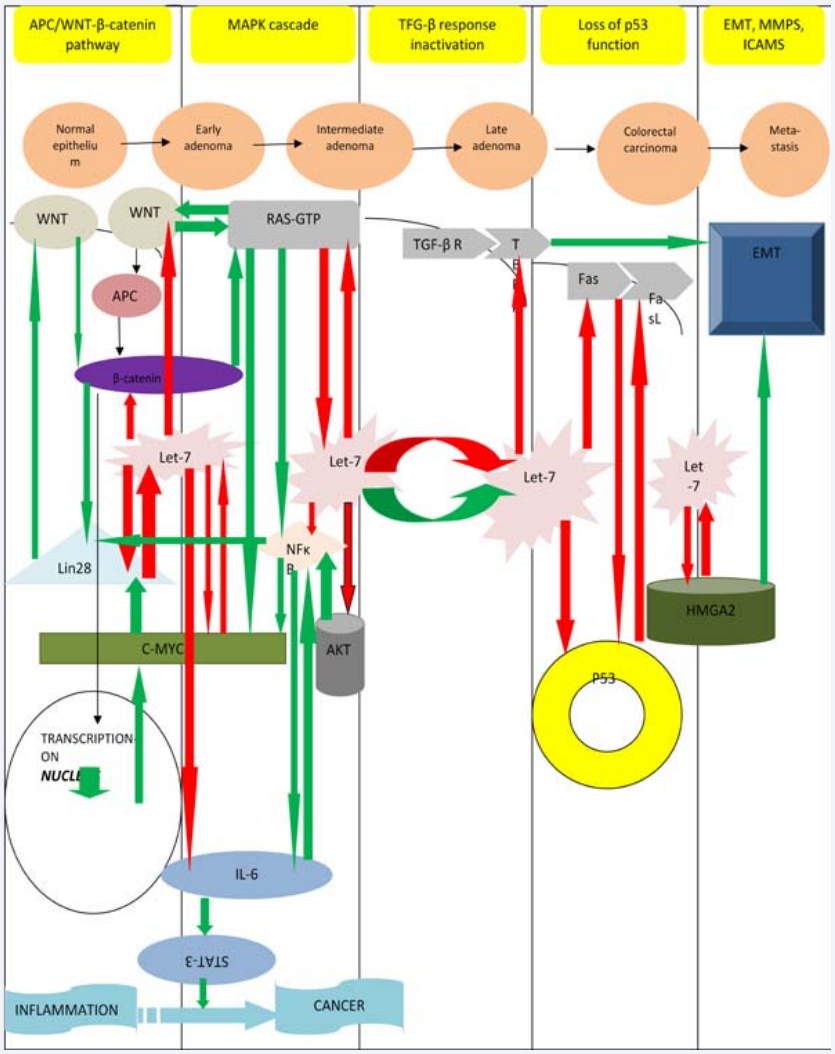

Figure 1 Let-7 contributes to the regulation of many crucial genetic alterations throughout the full spectrum of the intermediate changes of colorectal carcinogenesis process. Furthermore, it is regulated my many of its effectors, forming feedback loops. The arrows filled with red colour indicate inhibition of the target they direct; the arrows filled with green colour indicate promotion of the target they direct. Based on references 17, 19, 21, 25, 27, 28, 31-38, 40, 42-44, 54-63, 87, 89 and 91.

which are indispensable for energy provision in cancerous cell; therefore let7 prevents tumor spread [17]

- The anti apoptotic protein BCL-XL; thereby let-7 enhances apoptosis [17]
- IGF2BP1 (Igf2 mRNA binding protein 1), which promotes dissemination of colon cancer cells [34]
- LIN28 A/B, an RNA-binding protein, which promotes all hallmarks of cancer [17], enhances stemness and pluripotency [25,29], inhibits differentiation [34,35] and parallels colorectal cancer aggressiveness [20,25,29,34,35]. LIN28 activation by low let-7 levels cooperates with mutations in β-catenin (Ctnnb1) gene [35], enhancing the hyper activation of the Wnt/APC pathway. Opposite to this, LIN28 repression by high let-7 levels, hypo activates Wnt signaling, lowering nuclear β-catenin levels. Since β-catenin is a key component connecting the two major initiating oncogenic pathways in colorectal cancer (Wnt/APC and MAPK) [36], let-7 down regulates MAPK pathway both directly (down regulating K-ras) and indirectly (decreasing β-catenin levels) See Figure 1.

Let-7 against tumor-suppressors

The role of let-7 in colorectal tumorigenesis becomes complicated by five notifications, which move towards a quite opposite direction from the just mentioned data. 1st, high levels of let-7 limit the apoptotic barrier, by inhibiting the death receptor Fas (which induces apoptosis and progressively decreases in nearly half colorectal cancers [37]) and by down regulating the terminal effector of apoptosis caspase 3 [38]. 2nd, let-7 suppresses innate immune reactions against colorectal cancer by inhibition of Toll-like receptor 4 [39], by inhibition of NFκB pathway [17], by targeting Mtor RNA and by inhibiting Th17 differentiation [38]. 3rd, under genotoxic conditions, several members of let-7 family target the guardian of the genome, p53 protein [40]. 4th, let-7 inhibits transforming growth factor-β (TGF-β), factor known to halt proliferation [27]. Last, but not least, in normal colon the promoter of let7a-3 is methylated in a CpG island, resulting in let-7 precursor silence, whereas its epigenetic hypomethylation on colorectal cancer cell lines confers oncogenic functions [41]. The collective data imply that, under circumstances, let-7 is capable to exhibit oncogenic properties.

HOW IS THE REGULATOR REGULATED?

The interplay between let-7 and its effectors is complex; mounting evidence asserts that approximately all let-7 targets behave as its reciprocal regulators as well (Figure 1). Let-7 establishes a negative feedback regulatory loop with LIN28A/B [17,25,35], with HMGA2 [17] and with c-myc [17,19,37,42]. Last, as Wnt pathway activation increases β-catenin levels, it hyper activates LIN28 [35], thereby repressing let-7 expression. β-catenin up regulates LIN28 either directly [17] or indirectly, via activating MAPK pathway [36].

Considerable interplay exists between let-7 and other microRNAs throughout the successive stages of colorectal cancer progression [43]. This crosstalk is either towards the same direction (e.g. let-7 and mir-200 cooperate against stemness and cancer progression [26]) or towards an opposite direction (e.g. mir-107 destabilizes mature let-7 [25]).

Interestingly, let-7 regulates its own expression in dual manner. First, let-7 is positively auto regulated, i.e. the mature let-7 enhances its own biosynthesis [21], in order to potentiate its actions. Second, it is negatively auto regulated, if not used, as it drives its own degradation in case its mRNA-target is not silenced, through the use-it-or-lose-it mechanism [44].

Environmental factors influence let-7 expression as well. In rats, the carcinogen PhIP reduces colon levels of several let-7 isoforms, deregulating the axis let-7/c-myc/LIN28, whereas dietary spinach exerts a tumor-suppressive effect, partially by restoring let-7 levels [45]. Boswellic acid, a component of gum resin, displays antitumor effect in colorectal cell lines partially by up regulating let-7 levels (especially let7-i) and its effectors [46]. Opposite to this, polyamines are oncogenic in colon cells, due to let-7i depletion and the increase of LIN28 and HMGA2 [47]. Finally, tea polyphenoles, soy isoflavones and curcumin display tumor-protective effects in various cancer types by increasing let-7 levels [48]; future studies might show whether they are equally beneficial for colorectal cancer prevention.

LET-7/K-RAS INTERACTION IS IMPORTANT IN COLORECTAL TUMORIGENESIS

The interaction between let-7 and its major target, K-ras, deserves special merit. K-ras mutation is the most prevalent oncogenic driver mutation in CRC [49]. It is present in 15-78% of colorectal adenomas [50] and in 36-42% of colorectal carcinomas [51]. Moreover, it is a primitive mutation in colorectal carcinogenesis process, being the earliest driving force in a subset of cases [36].

Twelve years ago, Johnson and coworkers proved -in an experimental model- that native let-7 leads to less expression of RAS protein and that inhibition of let-7 may lead to derepression of RAS expression. They showed that this action is exerted through ten different LCSs (let-7 complementary sites), located in the 3′ UTR of K-ras mRNA [52]. This connection, absolutely necessary for the complete let-7 action, was confirmed by many other researchers [53,54]. In the following years, it was demonstrated that, in the setting of colorectal cancer, let-7 is capable to target mRNAs, this of the wild-type K-ras [44,54-63] and that of the mutated K-ras [32,54,56,58-63]. Let-7 silences K-ras mRNA only in case LC6 is intact, allowing complete complementarity. The incomplete complementarity permits K-ras-mRNA to survive, and thereby, K-ras is expressed, though in low levels.

Two LC6s have gained the interest of researchers in CRC, LCS1 and LCS6. A polymorphic variant (SNP) polymorphism in LCS1 (rs712, G to T substitution) ras recently been correlated with increased risk for CRC development [64,65], with initiation and progression of CRC in Chinese population and with worst prognosis [65].

By far, the best studied LCS in CRC is LCS6. A SNP in the rs61764370 chromosomal locus of LCS6, a germ-line functional variation of T to G substitution [32,44,54-63] has been studied extensively. LCS6 variant (G-allele) varies geographically

[66]: it is found in 12-15% of the European population and 6% worldwide [58]. The binding affinity of let-7 with K-ras is diminished in the polymorphic (GG or TG) carriers [63]. G-allele carriers, therefore, display diminished efficacy of let-7 upon K-ras. Despite its documented connection with increased risk for various cancer types [44], only one study suggested a probable positive relationship with CRC [56], whereas another study showed reduced risk for developing early CRC [58] and most well-studied research works do not support the positive correlation of G allele to CRC development [61]. G-allele carriers are proved to have lower levels of innate let-7, probably via the use-it-or-lose-it mechanism [44]. This remark has been demonstrated in cancers of different origin (colorectal, lung and breast) [44,63,67]. In this way, both antitumor mechanisms are combined (G-allele, low let-7) and G-allele is considered, therefore, an inheritable unfavorable player in the colorectal tumorigenesis process.

Nevertheless, this effect has been proved only in wild-type K-ras cancers. In spite the fact that SNP-LSC6 is a germline mutation, its presence is not identical along the discrete stages of colorectal tumorigenesis. There are indications that the incidence of variant SNP parallels the level of oncogenic activity: Graziano et al., proved a correlation between G-variant (germline mutation) and mt K-ras (somatic mutation) [56], Smits et al., showed a gradual increase of the G-allele throughout the successive stages of colorectal carcinogenesis [58], and Saridaki et al., suggested that this variant increases the possibility of acquiring B-RAF mutation, a MAP kinase downstream KRAS in the MAPK pathway [54]. These results, implying a possible clonal selection inside the growing neoplasm that favors more aggressive clones harboring both the hostle inheritable variant and the oncogenic acquired mutation, should be validated with multiple future studies in colorectal cancer development.

Many ongoing efforts search for a possible correlation between the G-variant in LCS6 and the prognosis of colorectal cancer patients or their response to therapy. The very recent works [32,54-63] are characterized by intense in homogeneity (concerning staging of CRC, K-ras status, B-RAF status, naïve patients or not, the modality of therapy, the kind of the treatment given, the type of chemotherapeutic and/or monoclonic antibody against EFGR, and the ethnicity of the participants), by the fact that let-7 levels were not measured (except from one study [32]), and by the small number of patients harboring G-allele; inevitably, they displayed contradictory results.

Notwithstanding the limitations of these studies, five notifications deserve our attention:

1st despite the presumed unfavorable effect of G-allele, several well-studied works proved that this SNP was associated with improved prognosis, both in naïve patients and in patients receiving anticancer therapy, either traditional (chemotherapy) or advanced (anti-EGFR antibodies) [54,55,58].

2nd G-allele was proved an insufficient predictor by itself, even in patients receiving anti-EGFR therapy [60].

3rd K-ras mutation was a stronger factor to determine the relationship between G-allele with survival, compared to the stage of colorectal cancer [59].

4th in the unique work, which analyzed the effect of G-variant in K-ras activity in colorectal cancer tissues, KRAS protein was found to decrease, opposite to the expected [44] and

5th a common conclusion of these studies was that the net result in prognosis and progress of the growing colorectal neoplasm depends on the interplay and interdependence among 3 factors: K-ras status, let-7 levels and the genotype of the LCS6. Neither this complex interaction nor the mutual effects of these factors between them and with many other players of colorectal tumorigenesis process were studied in these works.

To make complexity deeper, mutated Ras regulates let-7 levels via a feedback loop. Let-7 is negatively regulated by RAS protein via indirect route: by activation of NFκB, which activates LIN28 [28] and by up regulating the expression on LIN28 via MAPK activated c-myc expression [17]. Nonetheless, experimental findings are not consistent with the theoretical background. Vickers et al., showed, for instance, that mt K-ras CRC displays higher let-7 levels compared to wt K-ras CRC [68]. One possible explanation might be that clonal selection, which, as already mentioned, selects clones with the unfavorable G-allele in the K-ras mutated context, generates a counterweight to attenuate the forthcoming oncogenic effect.

LET-7 AND CANCER

Let-7 is broadly accepted as a bona fide tumor-suppressor miRNA [18,23,33,52], as it represses cell proliferation pathways [69]. Let-7 genes have been mapped to genetic regions frequently altered or deleted in cancers [14,70]. Let-7 prevents all capabilities, globally accepted as the hallmarks of cancer [71]. Low let-7 levels are, in contrast, tumor-promoting: they lead growing cells to sustain proliferative signaling (up regulating oncogenes), to evade growth suppressors (le**t**-7 inhibits epithelial-mesenchymal transition or EMT, since it inhibits HMGA2 [17] and TBF-β [27]), to resist cell death (action upon BCL-XL [72]), to promote replicative immortality and to induce angiogenesis (via up regulation of LIN28 [28,33]), to activate invasion and metastasis (low let-7 levels enhance EMT and increase LIN28) and to reprogram energy metabolism (low let-7 attenuates Warburg effect) [17].

Furthermore, let-7 depletion enhances both characteristics that help the acquisition of these capabilities. First, low let-7 provokes genomic instability, either directly, as it hyper activates critical oncogenes as K-ras [19] which cause DSBs (DNA double-strand breaks) and DNA damage response (DDR) [36] or indirectly, as the resulting hyper expression of LIN28 inhibits the repair of DSBs [17]. Second, low let-7 fosters tumor-promoting inflammation, by hyper activating MAPK pathway and by increasing IL-6 production [17,28,52].

LET-7 IN NORMAL AND NEOPLASTIC COLON

The predominant let-7 isoforms normally found in colonic epithelia are let-7-a, let-7-b [20] and let-7-c [73] whereas let-7-g and let-7-f are found in slightly increased levels [20]. Let-7 keeps differentiated cells in their differentiated state, and if this function fails, neoplastic conformation initiates [27]. Neoplastic transformation, a process similar to reversed embryogenesis, presupposes loss of let-7 even from the very early stages of the

process [26]. Indeed, the levels of various let-7 members are found down regulated in colorectal cancer tissues: this fact was valid for the isoforms let-7-a, let-7-b [20,74], let-7-c and let-7-f [74], whereas other researchers correlated reduced mature levels of let-7-a with CRC [75-77]. Moreover, the chromosomal locus of let-7-a1 (9q22.3) is frequently deleted in colon cancer [78]. To complete the image, Liu et al., demonstrated that the prevalent isoforms of let-7 inside colorectal cancer cell lines don't differ compared to the normally found prevalent ones (let-7a and let-7b) [79].

Nevertheless, neither normal colonic epithelia nor cancerous colorectal tissues exhibit homogeneity, regarding let-7 levels inside their different cell types. A gradual increase of let-7 levels is remarkable across the axis of the normal crypt, from the bottom of the crypt domain to the top of the villous domain [80]: normal colorectal stem cells in the basis of the crypt express low or undetectable let-7 levels [23,25,35,73], whereas normal differentiated colonic cells display increased let-7 levels [23]; the role of let-7 is to control crypt fission and repress cell cycle progression [73] preventing in this way the neoplastic initiation.

It is well-documented that CRC is a disease of stem cells [80,81]. Inside colorectal cancer tissue, the inhomogeneity of let-7 levels is more prominent. Cancer stem cells still contain lower levels of let-7; up regulation of let-7 regulates cell proliferation and stem cell transition to differentiated cancer cells [23]. In fact, let-7 is the strongest marker of the epithelial signature: its presence (along with E-cadherin expression) is a hallmark of differentiated epithelial cells (type I cells), its absence (along with vimentin presence) is a hallmark of dedifferentiated mesenchymal cells (type II cells) [82]. Therefore, low let-7 levels govern the dedifferentiation process, which is accomplished by EMT, a process that generates stem cells and leads to invasion and metastasis of cancer [26]. Conversely, high levels of let-7 govern differentiation and limit the aggressiveness of colorectal cancer: they are major guardian against stemness [26], invasion and metastasis [17].

Interestingly, the supportive stroma around colon cancer cells harbors high let-7 levels. Stroma consists of mesenchymal cells as well as immune inflammatory cells. Stromal inflammatory cells contain up to 4 times higher let-7 levels, compared to invasive cancer cells, conferring to diminished lymphocytic innate immunity against colorectal cancer cells and raising the aggressiveness of the tumor [39].This notification is consistent with several studies reporting increased let-7 levels in colorectal cancer tissues [16,83-85]. Nonetheless, it is broadly accepted by the vast majority of the scientific society, that low levels of let-7 are the responsible for directing colorectal cancer tissue to an aggressive state [21,26,86].

LET-7 REGULATES ALL INTERMEDIATE STAGES OF COLORECTAL TUMORIGENESIS

Let-7 genes have gained the interest of many researchers in colorectal carcinogenesis because of their abundance in colonic epithelium, their pro-differentiation effects [12] and their anti proliferative properties [69].

Mature let-7 levels are found down regulated in colorectal neoplastic tissues compared to the normal adjacent tissues both in premature and late stage of colorectal carcinogenesis process [87]. Two queries emerge. First, what is the nature of this down regulation? Apart from the already mentioned regulators, TP53, seems to play a key role. Wt TP53, commonly found in early stages, suppresses let7-a and let7-b directly (by binding to its promoter [88,89]) and indirectly (by inhibiting Fas [89]). Paradoxically, mutated TP53, commonly found in late stages of the process (4-26% of adenomas and 50-75% of carcinomas carry the mutation [90]), results in the same phenomenon, i.e. it lowers let-7 levels, via inhibiting its maturation process [87,91].

The second question may be related to the first. What are the consequences of this depletion? In the primitive stages of colorectal carcinogenesis (i.e. benign polyp formation), let-7 depletion results in oncogene hyper activation (e.g. K-ras, c-myc) and down regulation of LIN28; both increase genomic instability [17,36,92]. Nonetheless, cancer does not occur and the total process stops to the precancerous lesions (adenomas). In general, the road to cancer is halted, at least partially, because of the induction of the established barriers of cancer, i.e. apoptosis and oncogene-induced senescence [92,93]. Oncogene-induced senescence occurs mainly in early stage of colorectal cancer [58]. Furthermore, raised incidences of apoptosis and senescence have been documented in colorectal adenomas, coinciding with reduced proliferation activity [92]. It is well-known that low let-7 levels are capable to induce apoptosis [37,38,89]. Moreover, low let-7 levels induce oncogene-induced senescence globally [17] and, more specifically, in colorectal cancer context [54]. It seems, therefore that, inside the frame of wild-type TP53 and under the effect of the, commonly early found, K-ras mutation [36,94], low let-7 levels are beneficial in colorectal adenoma and, probably, in very early carcinoma stage. Probably, inside this setting one should integrate the contradiction that let-7 family members suppress immune innate tumor reaction [17,39]: low let-7 levels provide advantage by enhancing the innate immunity against cancer progression.

Contrast to this, in late stages of colorectal carcinogenesis process, upon the deleterious effects of mutated TP53, low let-7 may inhibit apoptosis [17,37,38]. Taking into consideration the stage-dependent nature of oncogene-induced senescence [58], the increased proliferation index and the low incidence of apoptosis and senescence found in advanced stages of colorectal tumorigenesis [92], one might imply that low let-7 levels are harmful in colorectal carcinoma stage.

Despite the fact that colorectal tumors develop due to loss of let-7 and other tumor-suppressors, Vickers et al., demonstrated that mature let-7-a levels parallels the progression of colorectal cancer; in case metastases occur, they proved that let7-a continues to up regulate [68]. Towards the same direction, Ruoxu and coworkers proved that higher levels of let-7-a and let-7-b might be associated with stage III/IV colorectal cancer patients [39]. This phenomenon may mirror the pressure of natural selection, or, alternatively, the unknown significance of tumor-promoting properties of let-7. Other researchers demonstrated the increased levels of let-7 in advanced colorectal cancer tissues [83-85], probably due to the contribution of the let-7-rich stroma to the estimation of let-7 levels.

Suppressed let-7 is involved in every single stage of the entire spectrum of patho physiological stages of colorectal cancer development [43], as it is illustrated in Figure 1. In the very early steps of the process, low let-7 cooperates with WNT pathway activation (β-catenin, c-myc) [17,19,35-37,42]. Following this, it represses EGFR signaling activation (RAS, AKT2) [17,35,54-63]. Next, it participates in the third stage, by repressing TGF-β response inactivation. In the fourth stage, low let-7 levels acquire onco genetically important interdependency on TP53 expression. At last, it inhibits EMT [17], promoting invasion and metastasis. Furthermore, it is noteworthy that low let-7 levels in the front-specific of liver colorectal metastases lead to more aggressive cancer and poor clinical outcomes compared to their respective high levels [95], a remark emphasizing the importance and the contribution of let-7 in metastatic colorectal disease.

LET-7 AS A BIOMARKER IN COLORECTAL CANCER

Let-7 is a very stable molecule that resists prolonged storage, exposure to high or low pH values or even boiling [10]. These characteristics are invaluable for its use as a biomarker. Nonetheless, the utility of let-7 as an important biomarker in clinical practice has not been documented yet. Limited reports confer contradictory data about the role of let-7 in early detection of CRC.

Few reports exist, for instance, regarding the value of let-7 levels in blood circulation for early diagnosis of CRC, and their primary data rather generate concerns than clarifications. Ghanbari and coworkers proved simultaneous decline of let-7a and let-7f in plasma and stool samples from patients with early-stage CRC [96]. Contrast to this finding, Wang et al., proved that let-7-g levels were significantly increased in the serum of CRC patients compared to control group [97] and Ogata-Kawata et al., demonstrated that let-7-a, alongside with other miRNAs, were up regulated in plasma of patients suffering from colorectal cancer and were down regulated after the surgical removal of the tumors [98]. Since many works searching for the potential role of circulating let-7 in CRC diagnosis are in evolution, it is reasonable to wait with great interest their results in the near future.

Efforts trying to correlate let-7 levels in colorectal cancer tissue with prognosis and survival did not provide straight-forward results, either. Nakajima et al., found that let-7g levels were not correlated to survival [99]. Opposite to this, Ju et al., demonstrated that let-7g levels correlated with the clinical outcome of CRC patients [100]. Low let-7a levels were weakly associated with microsatellite instability (MSI) and let-7-a levels were correlated either with microsatellite stability or with MSI-low tumors [99]. Despite this notification, CRC patients stage II with microsatellite stability (MSS) were more likely to exhibit clinical recurrence when let-7b and let-7d were up regulated [101]. Similarly, two studies correlated increased CRC tissue let-7 levels with bad prognosis, the first in metastasic disease [102] and the second in stage III/IV CRC patients [38]. Against these data, low let-7 at the invasion front of colorectal liver metastases were proved to reduce overall survival [95], increased let-7 levels have been correlated with improved prognosis in the unique study with metastatic mt K-ras CRC patients in which the investigators measured let-7 levels [32] and two well-studied works associated low let-7 levels with poor prognosis [20,32].

In early CRC stages, the G-variant genotype of LCS6, known to represss let-7 levels, has been associated with improved [58] or neutral [59] effect on patients' prognosis. As mentioned earlier, the correlation of the G-genotype to prognosis and survival of CRC patients needs further clarification [60].

Increased let-7 expression inside CRC is a positive predictive factor in advanced CRC stages, where adjuvant or advanced therapies are necessary. Increased let-7 levels were correlated to radio sensitivity [17,22,103]. Similarly, increased let-7 levels confer to sensitivity to various chemotherapeutic regimens. Let-7 family members as an entity were positively related to chemo sensitivity to chemotherapeutics [12,22]. Let-7-d levels were positively related to chemo sensitivity to chemotherapeutics [22], whereas let-7-g levels predicted chemo sensitivity to per os 5-FU chemotherapeutic S-1 [85,99,100]. Nonetheless, 2 concluded opposite data: the former showed that that over-expression of let-7-a reduces sensitivity to doxorubicin, paclitaxel or interferon-γ [22], the latter that low let-7 expression predicted improved response to folate-based chemotherapy.

Increased efficacy to anti-EFGR antibodies (cetuximab) was shown also in patients harboring high let-7 levels [55,32]. Nevertheless, the conclusions from these 2 studied cannot be grouped, since in the former cetuximab was given as monotherapy in metastatic wt K-ras CRC patients, whereas in the latter cetuximab was given in combination to irinotecan in metastatic mutated K-ras CRC patients. Analogously, low let-7-b and let-7-e levels, especially in cancer stem cells, are synonymous to resistance to cetuximab [99,104].

Accumulated data support, unfortunately, that the positive predictive marker (i.e. high let-7 levels) that might attract clinicians to select patients for therapy is attenuated because of the counteractive effect of the corresponding modality: colorectal tumors develop defensive mechanisms against treatment. Cetuximab was found to reduce the levels of let7-b and let-7e [104] and irradiation reduced the levels of let-7-a [103,105], let-7-b [105] and let-7-d [22]. Besides these, things may be more convoluted than apparently look: let-7d levels displayed bidirectional behavior (i.e. either up regulation or down regulation) in response to irradiation, depending on the genetic background of the irradiated cell population and on the dose and time after irradiation [22].

IS LET-7 A POTENTIAL TARGET IN COLORECTAL CANCER?

In theory, a useful strategy concerning miRNA-based therapy might prove to restore the levels of a tumor-suppressor miRNA by forced expression or to inhibit a miRNA with oncogenic capabilities (oncomir) via anti-sense oligonucleotides (ASOS), anti-miRNA oligonucleotides (AMOS), microRNA sponges or oncomir masking [27,106,107]. Regarding let-7 as a new therapeutic goal in CRC, scientists should overcome several hurdles.

First, it is difficult to decide whether to down regulate or up regulate let-7 in a given patient suffering from colorectal cancer. As let-7 is commonly playing an anti tumorigenic role in CRC and its high levels usually increase the sensitivity of the tumor to treatment modalities, it seems reasonable to increase its

expression levels. Restoration of high levels of let-7 expression inside a colorectal cancer reduces cell migration and invasion [20], inhibits growth [76] and decrease tumor proliferation in the setting of heterozygous APC loss [35]. Contrast to this, Geng increased the sensitivity of HT29 colon cancer cells to Fas-related apoptosis by conferring them a let-7 inhibitor [37]. Therefore, the let-7 signature of a given colorectal neoplasm might give the answer to the query imposed.

Second, as *in vivo* genetic studies (e.g. well-studied loss/gain research works, pharmacological analyses, clinical trials) of let-7 function are lacking [108,109], probably due to its abundance in colon and its redundancy [12], we are unaware about the isoform of let-7 that might be critical to be manipulated in a given colorectal neoplasm, we don't know which maturation isoform of let-7 biosynthetic cascade has to be delivered (pri-let-7, pre-let-7, mature duplex let-7, let-7-p5 or let-7-3p), and we have not clearly defined the stage of colorectal carcinogenesis process it should generate the optimal result.

Third, the inhomogeneity of let-7 levels inside a given tumor should attract special consideration. Currently, it seems not feasible to maintain target specificity, i.e. to direct down regulate let-7 specifically in tumor microenvironment or to up regulate let-7 exclusively inside the incipient cancerous cells [24,27,107].

Fourth, synthesis and purification of therapeutic let-7 is quite difficult and let-7 restoration methods are not yet satisfactory [27].

Fifth, the delivery method has not been elucidated yet. In order to restore let-7 levels *in situ*, a vector, like adeno-associated virus (AAV) over expressing let-7 must be conscripted. As other AAV-mediated recombinant miRNAs have caused death in mice, as a result of liver cytotoxicity, there is ethical obstacle to expand this practice in humans [27]. Other promising delivery experimental methods (high density lipoprotein conjugated siRNA, nanoparticle-based delivery systems, cationic liposome-mediated delivery of pri-let-7 and electroporation of synthetic let-7) might translate into therapeutic approaches for CRC in the near future [27,106].

The last goal to achieve is to overcome or diminish let-7's side-effects, as skin toxicity [32].

FUTURE LET-7/CRC CORRELATION: WEAK RELATIONSHIP OR STRONG BOND?

The traditional model of colorectal cancer development proposed by Fearon and Vogelstein [5,6] is changing its face day by day: the progress of the neoplasm seems to depend on post transcriptional regulation by miRNAs [10]. Let-7 is not an innocent bystander in the physical history of colorectal cancer. It is rather a strong regulator of every single intermediate stage of colorectal tumorigenesis procedure, and, probably, a dominant piece of the puzzle of the specific individualized signature of a given colorectal tumor. Several let-7 isoforms may prove sufficient diagnostic, prognostic or predictive biomarkers. Additionally, many novel therapeutic modalities are expected to influence the biogenesis and action of various let-7 isoforms. This fact might improve importantly the prognosis and the survival of colorectal cancer patients. However, in order to use let-7 as an *in vivo* manipulator, several obstacles, such as ineffective delivery strategies, should de surmounted. Finally, better understanding of let-7's biology and its multiple roles in normal colorectum as well as in malignant and premalignant colorectal neoplasms is indispensable, in order to exploit the possible preventing advantages of regulating let-7 in the very early stages of colorectal tumorigenesis process and the potential curative benefits of manipulating let-7 in patients suffering from colorectal cancer. Consequently, let-7 may prove the cornerstone of the personalized management of colorectal cancer in the near future.

REFERENCES

1. Arvelo F, Sojo F, Cotte C. Biology of colorectal cancer. Ecancermedicalscience. 2015; 9: 520.
2. Siegel R, Desantis C, Jemal A. Colorectal cancer statistics, 2014. CA Cancer J Clin. 2014; 64: 104-117.
3. Fearon ER, Carethers JM. Molecular subtyping of colorectal cancer: time to explore both intertumoral and intratumoral heterogeneity to evaluate patient outcome. Gastroenterology. 2015; 148: 10-13.
4. Bosman F, Yan P. Molecular pathology of colorectal cancer. Pol J Pathol. 2014; 65: 257-266.
5. Vogelstein B, Fearon ER, Hamilton SR, Kern SE, Preisinger AC, Leppert M, et al. Genetic alterations during colorectal-tumor development. N Engl J Med. 1988; 319: 525-532.
6. Fearon ER, Vogelstein B. A genetic model for colorectal tumorigenesis. Cell. 1990; 61: 759-767.
7. Worthley DL, Whitehall VL, Spring KJ, Leggett BA. Colorectal carcinogenesis: road maps to cancer. World J Gastroenterol. 2007; 13: 3784-3791.
8. Migliore L, Migheli F, Spisni R, Coppedè F. Genetics, cytogenetics, and epigenetics of colorectal cancer. J Biomed Biotechnol. 2011.
9. Grady WM, Carethers JM. Genomic and epigenetic instability in colorectal cancer pathogenesis. Gastroenterology. 2008; 135: 1079-1099.
10. Lizarbe MA, Calle-Espinosa J, Fernández-Lizarbe E, Fernández-Lizarbe S, Robles MÁ, Olmo N, et al. Colorectal Cancer: From the Genetic Model to Posttranscriptional Regulation by Noncoding RNAs. Biomed Res Int. 2017.
11. Rahmani F, Avan A, Hashemy SI, Hassanian SM, et al. Role of Wnt/β-catenin signaling regulatory microRNAs in the pathogenesis of colorectal cancer. J Cell Physiol. 2017.
12. Strubberg AM, Madison BB. MicroRNAs in the etiology of colorectal cancer: pathways and clinical implications. Dis Model Mech. 2017; 10: 197-214.
13. Guo Y, Bao Y, Yang W. Regulatory miRNAs in Colorectal Carcinogenesis and Metastasis. Int J Mol Sci. 2017; 18.
14. Agostini M, Pucciarelli S, Calore F, Bedin C, Enzo M, Nitti D. miRNAs in colon and rectal cancer: A consensus for their true clinical value. Clin Chim Acta. 2010; 411: 1181-1186.
15. Macfarlane LA, Murphy PR. MicroRNA: Biogenesis, Function and Role in Cancer. Curr Genomics. 2010; 11: 537-561.
16. Choo KB, Soon YL, Nguyen PN, Hiew MS, Huang CJ. MicroRNA-5p and -3p co-expression and cross-targeting in colon cancer cells. J Biomed Sci. 2014; 21: 95.
17. Wang T, Wang G, Hao D, Liu X, Wang D, Ning N, et al. Aberrant regulation of the LIN28A/LIN28B and let-7 loop in human malignant

tumors and its effects on the hallmarks of cancer. Mol Cancer. 2015; 14.

18. Roush S, Slack FJ. The let-7 family of microRNAs. Trends Cell Biol. 2008; 18: 505-516.

19. Wang Z, Lin S, Li JJ, Xu Z, Yao H, Zhu X, et al. MYC protein inhibits transcription of the microRNA cluster MC-let-7a-1~let-7d via noncanonical E-box. J Biol Chem. 2011; 286: 39703-39714.

20. King CE, Wang L, Winograd R, Madison BB, Mongroo PS, Johnstone CN, et al. LIN28B fosters colon cancer migration, invasion and transformation through let-7-dependent and independent mechanisms. Oncogene. 2011; 30: 4185-4193.

21. Pasquinelli AE. The primary target of let-7 microRNA. Biochem Soc Trans. 2013; 41: 821-824.

22. Kolenda T, Przybyła W, Teresiak A, Mackiewicz A, Lamperska KM. The mystery of let-7d- a small RNA with great power. Contemp Oncol (Pozn). 2014; 293-301.

23. Büssing I, Slack FJ, Grosshans H. let-7 microRNAs in development, stem cells and cancer. Trends Mol Med. 2008; 14: 400-409.

24. Boyerinas B, Park SM, Hau A, Murmann AE, Peter ME. The role of let-7 in cell differentiation and cancer. Endocr Relat Cancer. 2010; 17: 19-36.

25. Su JL, Chen PS, Johansson G, Kuo ML. Function and regulation of let-7 family microRNAs. Microrna. 2012; 1: 34-39.

26. Peter ME. Let-7 and miR-200 microRNAs: guardians against pluripotency and cancer progression. Cell Cycle. 2009; 8: 843-852.

27. Barh D, Malhotra R, Ravi B, Sindhurani P. MicroRNA let-7: an emerging next-generation cancer therapeutic. Curr Oncol. 2010; 17: 70-80.

28. Iliopoulos D, Hirsch HA, Struhl K. An epigenetic switch involving NF-kappaB, Lin28, Let-7 MicroRNA, and IL6 links inflammation to cell transformation. Cell. 2009; 139: 693-706.

29. Pang M, Wu G, Hou X, Hou N, Liang L, Jia G, et al. LIN28B promotes colon cancer migration and recurrence. PLoS One. 2014; 9.

30. Bueno MJ, Malumbres M. MicroRNAs and the cell cycle. Biochim Biophys Acta. 2011; 1812: 592-601.

31. Bueno MJ, Pérez de Castro I, Malumbres M. Control of cell proliferation pathways by microRNAs. Cell Cycle. 2008; 7: 3143-3148.

32. Ruzzo A, Graziano F, Vincenzi B, Canestrari E, Perrone G, Galluccio N, et al. High let-7a microRNA levels in KRAS-mutated colorectal carcinomas may rescue anti-EGFR therapy effects in patients with chemotherapy-refractory metastatic disease. Oncologist. 2012; 17: 823-829.

33. Lee YS, Dutta A. The tumor suppressor microRNA let-7 represses the HMGA2 oncogene. Genes Dev. 2007; 21: 1025-1030.

34. Hamilton KE, Noubissi FK, Katti PS, Hahn CM, Davey SR, Lundsmith ET, et al. IMP1 promotes tumor growth, dissemination and a tumor-initiating cell phenotype in colorectal cancer cell xenografts. Carcinogenesis. 2013; 34: 2647-2654.

35. Tu HC, Schwitalla S, Qian Z, LaPier GS, Yermalovich A, Ku YC, et al. LIN28 cooperates with WNT signaling to drive invasive intestinal and colorectal adenocarcinoma in mice and humans. Genes Dev. 29: 2015; 1074-1086.

36. Margetis N, Kouloukoussa M, Pavlou K, Vrakas S, Mariolis-Sapsakos T. K-ras Mutations as the Earliest Driving Force in a Subset of Colorectal Carcinomas. *In vivo*. 2017; 31: 527-542.

37. Geng L, Zhu B, Dai BH, Sui CJ, Xu F, Kan T, et al. A let-7/Fas double-negative feedback loop regulates human colon carcinoma cells sensitivity to Fas-related apoptosis. Biochem Biophys Res Commun. 2011; 408: 494-499.

38. Liu M, Chen H. The role of microRNAs in colorectal cancer. J Genet Genomics. 2010; 37: 347-358.

39. Dou R, Nishihara R, Cao Y, Hamada T, Mima K, Masuda A, et al. MicroRNA let-7, T Cells, and Patient Survival in Colorectal Cancer. Cancer Immunol Res. 2016; 4: 927-935.

40. Boominathan L. The tumor suppressors p53, p63, and p73 are regulators of microRNA processing complex. PLoS One. 2010; 5.

41. Brueckner B, Stresemann C, Kuner R, Mund C, Musch T, Meister M, et al. The human let-7a-3 locus contains an epigenetically regulated microRNA gene with oncogenic function. Cancer Res. 2007; 67: 1419-1423.

42. Chang TC, Zeitels LR, Hwang HW, Chivukula RR, Wentzel EA, Dews M, et al. Lin-28B transactivation is necessary for Myc-mediated let-7 repression and proliferation. Proc Natl Acad Sci USA. 2009; 106: 3384-3389.

43. Slaby O, Svoboda M, Michalek J, Vyzula R. MicroRNAs in colorectal cancer: translation of molecular biology into clinical application. Mol Cancer. 2009; 8.

44. Crowley EH, Arena S, Lamba S, Di Nicolantonio F, Bardelli A. Targeted knock-in of the polymorphism rs61764370 does not affect KRAS expression but reduces let-7 levels. Hum Mutat. 2014; 35: 208-214.

45. Parasramka MA, Dashwood WM, Wang R, Abdelli A, Bailey GS, Williams DE, et al. MicroRNA profiling of carcinogen-induced rat colon tumors and the influence of dietary spinach. Mol Nutr Food Res. 2012; 56: 1259-1269.

46. Takahashi M, Sung B, Shen Y, Hur K, Link A, Boland CR, et al. Boswellic acid exerts antitumor effects in colorectal cancer cells by modulating expression of the let-7 and miR-200 microRNA family. Carcinogenesis. 2012; 33: 2441-2449.

47. Paz EA, LaFleur B, Gerner EW. Polyamines are on co metabolites that regulate the LIN28/let-7 pathway in colorectal cancer cells. Mol Carcinog. 2014; 53: 96-106.

48. Shah MS, Davidson LA, Chapkin RS. Mechanistic insights into the role of microRNAs in cancer: influence of nutrient crosstalk. Front Genet. 2012; 3: 305.

49. Le Rolle AF, Chiu TK, Zeng Z, Shia J, Weiser MR, Paty PB, et al. Oncogenic KRAS activates an embryonic stem cell-like program in human colon cancer initiation. Oncotarget. 2016; 7: 2159-2174.

50. Yadamsuren EA, Nagy S, Pajor L, Lacza A, Bogner B. Characteristics of advanced- and non advanced sporadic polypoid colorectal adenomas: correlation to KRAS mutations. Pathol Oncol Res. 2012; 18: 1077-1084.

51. Morkel M, Riemer P, Bläker H, Sers C. Similar but different: distinct roles for KRAS and BRAF oncogenes in colorectal cancer development and therapy resistance. Oncotarget. 2015; 6: 20785-20800.

52. Johnson SM, Grosshans H, Shingara J, Byrom M, Jarvis R, Cheng A, et al. RAS is regulated by the let-7 microRNA family. Cell. 2005; 120: 635-647.

53. Chin LJ, Ratner E, Leng S, Zhai R, Nallur S, Babar I, et al. A SNP in a let-7 microRNA complementary site in the KRAS 3' untranslated region increases non-small cell lung cancer risk. Cancer Res. 2008; 68: 8535-8540.

54. Saridaki Z, Weidhaas JB, Lenz HJ, Laurent-Puig P, Jacobs B, De Schutter J, et al. A let-7 microRNA-binding site polymorphism in KRAS predicts improved outcome in patients with metastatic colorectal cancer

treated with salvage cetuximab/panitumumab monotherapy. Clin Cancer Res. 2014; 20: 4499-4510.

55. Zhang W, Winder T, Ning Y, Pohl A, Yang D, Kahn M, et al. A let-7 microRNA-binding site polymorphism in 3'-untranslated region of KRAS gene predicts response in wild-type KRAS patients with metastatic colorectal cancer treated with cetuximab monotherapy. Ann Oncol. 2011; 22: 104-109.

56. Graziano F, Canestrari E, Loupakis F, Ruzzo A, Galluccio N, Santini D, et al. Genetic modulation of the Let-7 microRNA binding to KRAS 3'-untranslated region and survival of metastatic colorectal cancer patients treated with salvage cetuximab-irinotecan. Pharmacogenomics J. 2010; 10: 458-464.

57. Sebio A, Paré L, Páez D, Salazar J, González A, Sala N, et al. The LCS6 polymorphism in the binding site of let-7 microRNA to the KRAS 3'-untranslated region: its role in the efficacy of anti-EGFR-based therapy in metastatic colorectal cancer patients. Pharmacogenet Genomics. 2013; 23: 142-147.

58. Smits KM, Paranjape T, Nallur S, Wouters KA, Weijenberg MP, Schouten LJ , et al. A let-7 microRNA SNP in the KRAS 3'UTR is prognostic in early-stage colorectal cancer. Clin Cancer Res. 2011; 17: 7723-7731.

59. Ryan BM, Robles AI, Harris CC. KRAS-LCS6 genotype as a prognostic marker in early-stage CRC:letter. Clin Cancer Res. 2012; 18: 3487-3488.

60. Langevin SM, Christensen BC. Let-7 microRNA-binding-site polymorphism in the 3'UTR of KRAS and colorectal cancer outcome: a systematic review and meta-analysis. Cancer Med. 2014; 3: 1385-1395.

61. Kjersem JB, Ikdahl T, Guren T, Skovlund E, Sorbye H, Hamfjord J, et al. Let-7 miRNA-binding site polymorphism in the KRAS 3'UTR; colorectal cancer screening population prevalence and influence on clinical outcome in patients with metastatic colorectal cancer treated with 5-fluorouracil and oxaliplatin +/- cetuximab. BMC Cancer. 2012; 12: 534.

62. Sha D, Lee AM, Shi Q, Alberts SR, Sargent DJ, Sinicrope FA, et al. Association study of the let-7 miRNA-complementary site variant in the 3' untranslated region of the KRAS gene in stage III colon cancer (NCCTG N0147 Clinical Trial). Clin Cancer Res. 2014; 20: 3319-3327.

63. Sclafani F, Chau I, Cunningham D, Peckitt C, Lampis A, Hahne JC, et al. Prognostic role of the LCS6 KRAS variant in locally advanced rectal cancer: results of the EXPERT-C trial. Ann Oncol. 2015; 26: 1936-1941.

64. Pan XM, Sun RF, Li ZH, Guo XM, Zhang Z, Qin HJ, et al. A let-7 KRAS rs712 polymorphism increases colorectal cancer risk. Tumour Biol. 2014; 35: 831-835.

65. Jiang QH, Peng HX, Zhang Y, Tian P, Xi ZL, Chen H. rs712 polymorphism within let-7 microRNA-binding site might be involved in the initiation and progression of colorectal cancer in Chinese population. Onco Targets Ther. 2015; 8: 3041-3045.

66. Uvirova M, Simova J, Kubova B, Dvorackova N, Tomaskova H, Sedivcova M, et al. Comparison of the prevalence of KRAS-LCS6 polymorphism (rs61764370) within different tumour types (colorectal, breast, non-small cell lung cancer and brain tumours). A study of the Czech population. Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub. 2015; 159: 466-471.

67. Paranjape T, Heneghan H, Lindner R, Keane FK, Hoffman A, Hollestelle A, et al. A 3'-untranslated region KRAS variant and triple-negative breast cancer: a case-control and genetic analysis. Lancet Oncol. 2011; 12: 377-386.

68. Vickers MM, Bar J, Gorn-Hondermann I, Yarom N, Daneshmand M, Hanson JE, et al. Stage-dependent differential expression of microRNAs in colorectal cancer: potential role as markers of metastatic disease. Clin Exp Metastasis. 2012; 29: 123-132.

69. Johnson CD, Esquela-Kerscher A, Stefani G, Byrom M, Kelnar K, Ovcharenko D, et al. The let-7 microRNA represses cell proliferation pathways in human cells. Cancer Res. 2007; 67: 7713-7722.

70. Calin GA, Sevignani C, Dumitru CD, Hyslop T, Noch E, Yendamuri S, et al. Human microRNA genes are frequently located at fragile sites and genomic regions involved in cancers. Proc Natl Acad Sci USA. 2005; 101: 2999-3004.

71. Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. Cell. 2011; 144: 646-674.

72. Tian N, Han Z, Li Z, Zhou M, Fan C. Lin28/let-7/Bcl-xL pathway: the underlying mechanism of drug resistance in Hep3B cells. Oncol Rep. 2014; 32: 1050-1056.

73. Madison BB, Liu Q, Zhong X, Hahn CM, Lin N, Emmett MJ, et al. LIN28B promotes growth and tumorigenesis of the intestinal epithelium via Let-7. Genes Dev. 2013; 20: 2233-2245.

74. Michael MZ, O' Connor SM, van Holst Pellekaan NG, Young GP, James RJ. Reduced accumulation of specific microRNAs in colorectal neoplasia. Mol Cancer Res. 2003; 1: 882-891.

75. Volinia S, Calin GA, Liu CG, Ambs S, Cimmino A, Petrocca F, et al. A microRNA expression signature of human solid tumors defines cancer gene targets. Proc Natl Acad Sci USA. 2006; 103: 2257-2261.

76. Akao Y, Nakagawa Y, Naoe T. let-7 microRNA functions as a potential growth suppressor in human colon cancer cells. Biol Pharm Bull. 2006; 29: 903-906.

77. Fang WJ, Lin CZ, Zhang HH, Qian J, Zhong L, Xu N. Detection of let-7a microRNA by real-time PCR in colorectal cancer: a single-centre experience from China. J Int Med Res. 2007; 35: 716-723.

78. Wiesner GL, Daley D, Lewis S, Ticknor C, Platzer P, Lutterbaugh J, et al. A subset of familial colorectal neoplasia kindreds linked to chromosome 9q22.2-31.2. Proc Natl Acad Sci U S A. 2003; 100: 12961-12965.

79. Liu H, D'Andrade P, Fulmer-Smentek S, Lorenzi P, Kohn KW, Weinstein JN, et al. mRNA and microRNA expression profiles of the NCI-60 integrated with drug activities. Mol Cancer Ther. 2010; 9: 1080-1091.

80. Cui S, Chang PY. Current understanding concerning intestinal stem cells. World J Gastroenterol. 2016; 22: 7099-7110.

81. Zeki SS, Graham TA, Wright NA. Stem cells and their implications for colorectal cancer. Nat Rev Gastroenterol Hepatol. 2011; 8: 90-100.

82. Shell S, Park SM, Radjabi AR, Schickel R, Kistner EO, Jewell DA, et al. Let-7 expression defines two differentiation stages of cancer. Proc Natl Acad Sci USA. 2007; 104: 11400-11405.

83. Nam S, Kim B, Shin S, Lee S. MiRGator: an integrated system for functional annotation of microRNAs. Nucleic Acids Res. 2008; 36: 159-164.

84. Xi Y, Shalgi R, Fodstad O, Pilpel Y, Ju J. Differentially regulated micro-RNAs and actively translated messenger RNA transcripts by tumor suppressor p53 in colon cancer. Clin Cancer Res. 2006; 12: 2014-2024.

85. Nakajima G, Hayashi K, Xi Y, Kudo K, Uchida K, Takasaki K, et al. Non-coding MicroRNAs hsa-let-7g and hsa-miR-181b are Associated with Chemoresponse to S-1 in Colon Cancer. Cancer Genomics Proteomics. 2006; 3: 317-324.

86. Ji J1, Wang XW. A Yin-Yang balancing act of the lin28/let-7 link in tumorigenesis. J Hepatol. 2010; 53: 974-975.

87. Lee JY, Kim HJ, Yoon NA, Lee WH, Min YJ, Ko BK, et al. Tumor suppressor p53 plays a key role in induction of both tristetraprolin and let-7 in

human cancer cells. Nucleic Acids Res. 2013; 41: 5614-5625.

88. Saleh AD, Savage JE, Cao L, Soule BP, Ly D, DeGraff W, et al. Cellular stress induced alterations in microRNA let-7a and let-7b expression are dependent on p53. PLoS One. 2011; 6: 24429.

89. Hau A, Ceppi P, Peter ME. CD95 is part of a let-7/p53/miR-34 regulatory network. PLoS One. 2012; 7: 49636.

90. Pino MS, Chung DC. The chromosomal instability pathway in colon cancer. Gastroenterology. 2010; 138: 2059-2072.

91. Finnegan EF, Pasquinelli AE. MicroRNA biogenesis: regulating the regulators. Crit Rev Biochem Mol Biol. 2013; 48: 51-68.

92. Halazonetis TD, Gorgoulis VG, Bartek J. An oncogene-induced DNA damage model for cancer development. Science. 2008; 319: 1352-1355.

93. Gorgoulis VG, Halazonetis TD. Oncogene-induced senescence: the bright and dark side of the response. Curr Opin Cell Biol. 2010; 22: 816-827.

94. Ronai Z. ras oncogene detection in pre-neoplastic lesions: possible applications for diagnosis and prevention. Oncol Res. 1992; 4: 45-48.

95. Kahlert C, Klupp F, Brand K, Lasitschka F, Diederichs S, Kirchberg J, et al. Invasion front-specific expression and prognostic significance of microRNA in colorectal liver metastases. Cancer Sci. 2011; 102: 1799-1807.

96. Ghanbari R, Mosakhani N, Sarhadi VK, Armengol G, Nouraee N, Mohammadkhani A, et al. Simultaneous Underexpression of let-7a-5p and let-7f-5p microRNAs in Plasma and Stool Samples from Early Stage Colorectal Carcinoma. Biomark Cancer. 2016; 7: 39-48.

97. Wang J, Huang SK, Zhao M, Yang M, Zhong JL, Gu YY, et al. Identification of a circulating microRNA signature for colorectal cancer detection. PLoS One. 2014; 9.

98. Ogata-Kawata H1, Izumiya M2, Kurioka D3, Honma Y4, Yamada Y4, Furuta K5 , et al. Circulating exosomal microRNAs as biomarkers of colon cancer. PLoS One. 2014; 9: e92921.

99. Dong Y, Wu WK, Wu CW, Sung JJ, Yu J, Ng SS. MicroRNA dysregulation in colorectal cancer: a clinical perspective. Br J Cancer. 2011; 104: 893-898.

100. Ju J. miRNAs as biomarkers in colorectal cancer diagnosis and prognosis. Bioanalysis. 2010; 2: 901-906.

101. Schepeler T, Reinert JT, Ostenfeld MS, Christensen LL, Silahtaroglu AN, Dyrskjøt L, et al. Diagnostic and prognostic microRNAs in stage II colon cancer. Cancer Res. 2008; 68: 6416-6424.

102. Mosakhani N, Lahti L, Borze I, Karjalainen-Lindsberg ML, Sundström J, Ristamäki R, et al. MicroRNA profiling predicts survival in anti-EGFR treated chemorefractory metastatic colorectal cancer patients with wild-type KRAS and BRAF. Cancer Genet. 2012; 205: 545-551.

103. Oh JS, Kim JJ, Byun JY, Kim IA. Lin28-let7 modulates radiosensitivity of human cancer cells with activation of K-Ras. Int J Radiat Oncol Biol Phys. 2010; 76: 5-8.

104. Ragusa M, Statello L, Maugeri M, Majorana A, Barbagallo D, Salito L, et al. Specific alterations of the microRNA transcriptome and global network structure in colorectal cancer after treatment with MAPK/ERK inhibitors. J Mol Med (Berl). 2012; 90: 1421-1438.

105. Saleh AD, Savage JE, Cao L, Soule BP, Ly D, DeGraff W, et al. Cellular stress induced alterations in microRNA let-7a and let-7b expression are dependent on p53. PLoS One. 2011; 6.

106. Rupaimoole R, Han HD, Lopez-Berestein G, Sood AK. MicroRNA therapeutics: principles, expectations, and challenges. Chin J Cancer. 2011; 30: 368-370.

107. Li C, Feng Y, Coukos G, Zhang L. Therapeutic microRNA strategies in human cancer. AAPS J. 2009; 11: 747-757.

108. Christopher AF, Kaur RP, Kaur G, Kaur A, Gupta V, Bansal P. MicroRNA therapeutics: Discovering novel targets and developing specific therapy. Perspect Clin Res. 2016; 7: 68-74.

109. Schee K, Fodstad Ø, Flatmark K. MicroRNAs as biomarkers in colorectal cancer. Am J Pathol. 2010; 177: 1592-1599.

Cite this article

Margetis N, Mariolis-Sapsakos T (2017) Let-7 microRNA as a Genetic Regulator of Colorectal Carcinogenesis Process: Principles and Queries. JSM Gastroenterol Hepatol 5(3): 1086.