Eliana et al., Intern Med 2013, 3:1
DOI: 10.4172/2165-8048.1000120

Internal Medicine: Open Access

Review Article Open Access

Colorectal Cancer: A Pathology of the Colon-Rectum and A Disease of the Genome

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Abstract

Despite the well-established links between signalling and transcriptional activity, little is known about how transcriptional activators are regulated after tumorigenesis is triggered. An obvious mechanism to limit the expression time of an activator is to destroy it via the ubiquitin-proteasome pathway. Ideally, activator turnover should be tied to its efficiency in driving transcription. The F-box protein, FBXW7, is an E3 ubiquitin ligase molecule which targets multiple transcriptional activators and oncoproteins for degradation. FBXW7 mutations occur in nearly 10-15% of human colorectal cancer, making it the fourth most commonly mutated gene after TP53, RAS, and Adenomatous Polyposis Coli (APC). Elucidating its mechanism of action is very important but also difficult as it is likely to influence many pathways due to its role as an E3 ubiquitin ligase in proteasome degradation. Here we attempted to summarize the current state of understanding on this topic.

Keywords: CRC; P53; APC; FBXW7

Introduction to Colorectal Cancer

Colorectal carcinogenesis constitutes a major public health issue worldwide. It is a protracted process, probably spanning 10-15 years, and manifests in a stepwise fashion. In 95% of cases it starts as a collection of adenomatous polyps in the epithelial lining of the colon/rectum to eventually transform into an invasive adenocarcinoma. According to Cancer Research UK, data calculated in July 2011 estimates a CRC lifetime risk in men and women of 1 in 14 and 1 in 19 respectively.

CRC is now the third most common cancer in the UK, 75% of which is sporadic and 25% associated with inherited susceptibility, and the fourth most common cause of cancer mortality worldwide [1].

The significant contribution of CRC to cancer morbidity is attributed to a combination of genetic and environmental factors. The FAP [Familial Adenomatous Polyposis (APC gene)] and HNPCC (Hereditary Non-Polyposis CRC) hereditary syndromes are two dominantly inherited conditions most commonly associated with CRC. Lifestyle choices such as cigarette smoking, alcohol consumption, reduced physical activity and a "western" (high fat and low fibre intake) diet are key, and preventable, candidates of colorectal carcinogenesis. As in most solid tumours, increasing age increases the risk to carcinogenesis whilst at the same time cancer in elderly tends to be less aggressive than in the younger [1,2]. The fundamental and current approach to CRC treatment is the surgical excision of the primary tumour, success of which is based on the stage of cancer. The stage of the disease fundamentally relates to cancer prognosis and is therefore used to guide the choice of treatment [3]. The TNM (Tumour-Node-Metastasis) classification of clinicopathological staging remains the cornerstone of prognostication and treatment selection (replacing the Dukes classification system) (Figure 1). Adjuvant treatment currently consists of 5-FU (5 Fluorouracil), Oxaliplatin and Irinotecan but has expanded to include targeted therapies, the choice of which are tailored to the needs of the individual patient [4]. Targeted therapy, as to be discussed below, provides promising grounds, and is of particular relevance, to CRC therapeutics.

Colorectal cancer, like all cancer, is a disease rooting in the genes of human cells. At a time where biology provides prognostic information critically impacting clinical oncology, sophisticated investigation of cancer cell pathology at the preclinical level is vital. This literature review directs its focus onto the molecular aspect of CRC and in particular, expands onto two major culprits of the disease, namely P53 and FBXW7. Understanding of the molecular principles underlying

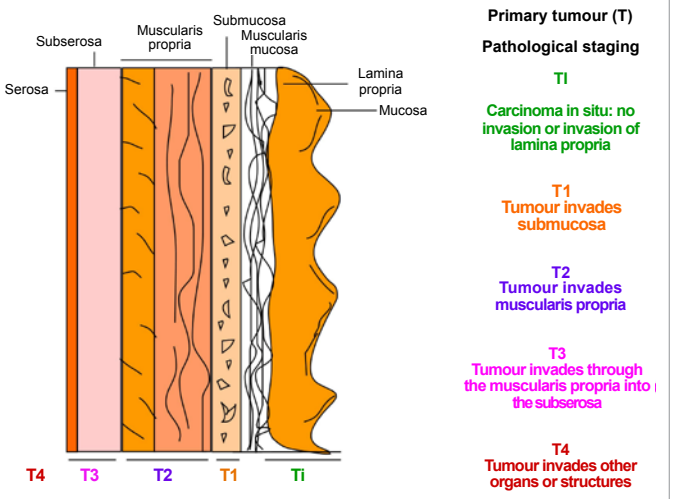

Figure 1: Schematic representation of a cross section through the bowel wall illustrating the primary tumour (T) section of the TNM classification. T describes how far the primary tumour has grown into the wall of the intestine or nearby areas. N describes the extent of spread to regional lymph nodes. M indicates whether the cancer has metastasized to other organs. [Adapted from Colorectal Cancer, 2nd edition, Taylor et al. 2002 (Taylor Irving 2002)].

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Received January 19, 2013; **Accepted** March 07, 2013; **Published** March 14, 2013

Citation: Eliana K, Federica L, Roya BJ, Abdolrahman NS (2013) Colorectal Cancer: A Pathology of the Colon-Rectum and A Disease of the Genome. Intern Med 3: 120. doi:10.4172/2165-8048.1000120

the processes of tumourigenicity in CRC is essential to expand the armamentarium of pharmacotherapeutic treatments available and improve its clinical prospect.

The genomic landscape of CRC

Genomic instability within the intestine can be attributed to environmental factors (exposure to carcinogens), spontaneous mutations, inherited gene defects or chronic inflammation [1]. These conditions contribute to a damage-inflicting microenvironment in the gut and augment the risk of bowel cancer by inducing mutations in oncogenes, tumour suppressor genes and DNA stability genes. Whereas gene mutations can be silent or benign, these three classes of genes, regulate homeostatic cell cycle progression and mutations in them will augment the risk to neoplastic growth [5,6].

Colorectal carcinogenesis relies on the progressive accumulation of genetic mutations, epigenetic changes and defects in DNA repair system [1,7,8]. Wood et al. [9] in their research article "The Genomic Landscapes of Human Breast and Colorectal Cancers" suggest that individual tumours accumulate approximately 80-90 mutations and only 15% of those contribute to neoplasia. Differences within mutated genes between tumours are likely the basis of wide variations in CRC tumour behaviour and responsiveness.

Regarding the genomic landscape of CRC the APC, K-Ras, P53 and FBXW7 genes represent the major mountains implicated in tumourigenesis [9]. The classic multistep, polyp-cancer theory of CRC agrees with the progressive accumulation of somatic mutations and proposes a multi-step path to malignancy (Figure 2). Bi-allelic deactivation of APC tumour suppressor is thought to be one of the earliest and most crucial events in colorectal carcinogenesis [7]. The APC mutation and its defective involvement in the WNT pathway appear to trigger tumour formation, however, additional mutations are required for tumour development. Subsequent accumulation of genetic mutations in oncogenes, tumour suppressor or stability genes such as KRas, DCC and p53 [1,7,10] (Figure 2), enable the intestinal cells to acquire properties conferring competitive advantage to their survival and abnormal proliferation. These novel acquired capabilities are summed up as the hallmarks of cancer and consist of: self sufficiency in growth signals, insensitivity to death signals, evasion of apoptosis, angiogenesis, limitless replicative potential, genomic instability and invasion and metastasis properties [11].

Patient prognosis in CRC is fundamentally related to the disease stage which guides the choice of therapy to be administered [3]. The different mutations are thought to reflect the different stages of tumour development during the transition of normal mucosa to polyp and subsequent cancer [10]. Understanding the molecular mechanisms in the development of CRC will therefore shed new light in the diagnosis, prognosis and treatment of the disease.

Cancer in absence of safeguard tumour suppressors P53 and FBXW7 are two widely known tumour suppressor genes heavily implicated in CRC. Defective tumour suppressors are unable to halt cell growth and subsequently augment the risk to neoplastic growth [11].

P53

The gene, the protein and the cancer P53 tumour suppressor gene, along with p73 and p63, constitute the highly conserved p53 family of transcription factors. P53 stretches 20 Kb long, consists of 11 exons and 10 introns and maps to human chromosomal region 17p13 [12-14]. It encodes for a 53 kDa phospho-protein which contains 393 amino acids and exists as an arrangement of functional domains which conform into a tetrameric structure upon p53 activation. p53 protein (Figure 3), consists of two amino (N)-terminal trans-activation domains involved in the recruitment of basal transcriptional machinery, a proline rich domain, a central DNA binding core domain by which it binds to target genes, a tetramerization domain and a carboxy (C)-terminal regulatory domain [15,16].

P53 protein acts as a tumour suppressor protein which exerts its anti-oncogenic properties by acting as transcriptional activator/repressor of genes involved in negative/positive regulation of cell cycle progression such as p21, NOXA, GADD45, BAX (up-regulated) and BCL-2, BCL-X, cyclin B1 (down-regulated), respectively [14,15]. Under physiological stress free conditions p53 is present in low levels but will become stabilised and accumulate in the cell in response to stress signals [17]. Cellular stress such as DNA damage, hypoxia and abnormal oncogenic events induce the quantitative up-regulation of p53 giving an overall increase in the p53 protein level [14]. Most importantly, cellular stress enables the extensive post-translational modification of p53 which gets activated to exert cell cycle arrest/pro-apoptotic activities and prevent propagation of damaged DNA [17].

Referring to its ability to conserve cellular stability, p53 has

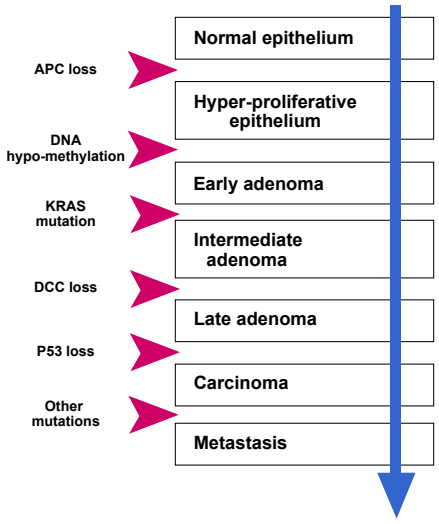

Figure 2: CRC develops over time, starting with the transformation of normal colonic epithelium to an adenomatous intermediate which on subsequent somatic mutations progresses into invasive adenocarcinoma. This multi step progress to malignancy is driven by the stepwise accumulation of genetic mutations in oncogenes (KRAS), tumour suppressor (APC, DCC, P53) or stability genes which enables the mutated intestinal cells to acquire properties conferring competitive advantage to their survival and abnormal proliferation. These novel acquired capabilities are summed up as the hallmarks of cancer and consist of: self sufficiency in growth signals, insensitivity to death signals, evasion of apoptosis, angiogenesis, limitless replicative potential, genomic instability and invasion and metastasis properties.

Figure 3: Schematic representation of p53 protein structure highlighting the two amino (N)-terminal trans-activation domains (TAD1&2), the proline-rich domain (PRD), the DNA binding core domain, the tetramerization domain (TET) and the carboxyl (C)-terminal nucleic acid binding region (BASIC). The (N)-terminal of p53 is highly implicated in post translational modifications, such as phosphorylation and acetylation, which stabilize the protein and increase specificity to its target (Hainaut 2007).

been described as the "guardian of the genome". Any mutation in this "guardian angel gene" will in turn lead to genomic instability, uncontrolled cellular proliferation and ultimately tumourigenesis [15]. In fact, p53 malfunction is said to be implicated in more than 50% of cancers entitling p53 as a superstar tumour suppressor and one of the most important proteins in preventing human cancer [18].

P53 phospshorylation: safeguard upon cellular stress

The authority p53 has over cell fate determination is reflected in the ability of P53 to induce cell cycle arrest and cell death (apoptosis) (Figure 4). Such ability needs to be tightly modulated as inappropriate activation of the tumour suppressor will interrupt normal cell proliferation. The highly evolved homeostatic system in humans controls p53 activity by maintaining low basal levels of the protein under normal conditions.

Upon cellular stress, post-translational modifications such as acetylation, methylation, sumoylation and phosphorylation switch p53 from a latent to an active form and prolong its half life from minutes to hours.

P53 accumulation and post-translational modifications can reflect the type and magnitude of cellular stress, making p53 a useful biomarker in carcinogenesis and chemoprevention efficacy. Phosphorylation has been regarded as the most commonly reported p53 protein modification in mammalian cells and is thought to affect about twenty serine/threonine residues concentrated within the end terminals of the protein [17]. It constitutes a complicated cascade with the same residue site able to get phosphorylated by several kinases, distinct kinases able to phosphorylate several residues and different forms of stress able to give different patterns of phosphorylation [13].

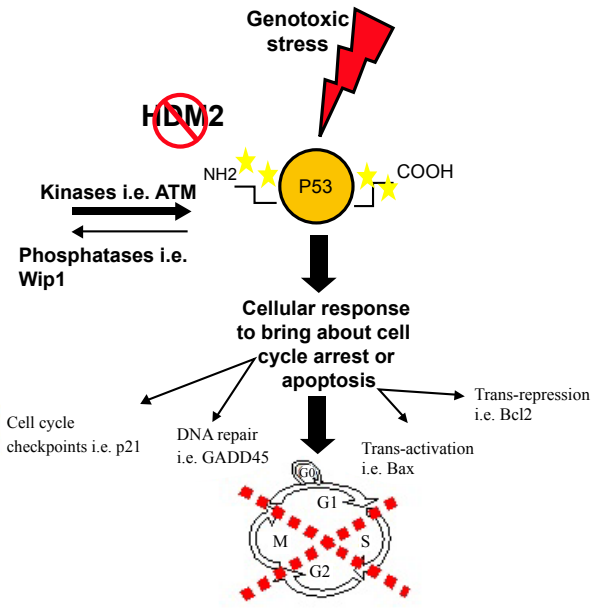

Figure 4: Schematic diagram illustrating p53 protein activation mediated by stress induced phosphorylation. According to the classical model of p53 activation, cellular damage (hypoxia, oncogenic over-expression, DNA damage, heat shock etc) enables phosphorylation of p53 by DNA-damage induced kinases. Phosphorylation stabilizes the protein in the nucleus which in turn binds to DNA and recruits transcriptional machinery. Trans-regulation of downstream targets, such as activation of pro-apoptotic proteins (BAX) or cell cycle arrest cyclins (p21) and repression of anti-apoptotic proteins (Bcl2), brings about protective cellular responses such as cell cycle arrest and apoptosis. In this way, p53 counteracts the pro-tumourigenic effects of genotoxic stress. [Inspired from Modes of p53 regulation, Jan-Philip Kruse and Wei Gu, Cell 137, May 15, 2009 with modifications].

More than 10 kinases are implicated in the p53 phosphorylation [18]. Amongst the most extensively studied phosphorylation sites is Serine15 (S15) contained within the trans-activation domain of the amino (N)- terminal [19]. Classic literature approach supports that S15 is phosphorylated as a result of stress mediated post-translational modifications of p53 by DNA-damage induced kinases most relevant of which are ATM, ATR and DNA PK [13,19,20]. Consequent to S15 phosphorylation, which is one of the earliest and most important events following genotoxic stress, p53 is released from its physiological repression and becomes stabilised in the nucleus to act as a transcriptional activator for tumour suppression [18].

The fundamental role of p53 as a cellular caretaker requires the protein to be under complex control mechanisms that orchestrate p53 activity in the cell cycle. HDM2 (Human Double Minute 2)- E3 ligase is involved in the maintenance of low p53 levels during cell homeostasis by targeting p53 for degradation. Stress induced (N)-terminal phosphorylation at S15, disrupts the negative regulation of HDM2 and allows p53 stabilization [21,22]. On the other hand, phosphorylation of p53 (S15) can be reversed once the cellular damage is over. Wip1 and PP-1 phosphatases were identified to be responsible for removal of S15 phosphorylation [23]. According to Zhang et al. [19] a knock in mutation of Serine 18 (S18) in murine p53, equivalent to S15 in human p53, reduced p53 stabilization in the nucleus and almost completely abolished activation of target genes. Moreover, substitution of S15 and S20 with aspartic acid residues, which mimicked the behaviour of a phosphorylated serine, activated p53 in the nucleus. Such activation is in agreement with elevated levels of p53 found in transformed cell lines and human tumour tissues as compared to non transformed cells [18].

FBXW7: A tumour suppressor implicated in CRC

Loss of FBXW7 has been proposed to cause chromosomal instability implicated in many cancers and is best described in CRC [24,25]. FBXW7 mutations are found in 10% of CRC tumours making it the 4th most frequently mutated gene after p53, K-Ras and APC. Research identified FBXW7 mRNA to be lower in human CRC tissues and low FBXW7 to correlate with worse prognosis relating to the five year survival postsurgery [26,27]. FBXW7 exhibits haploinsufficiency (a mutation in one allele is enough to express mutant phenotype even in the presence of a wild type allele) [27]. In their majority, mutations are mono-allelic with bi-allelic deactivation enhancing the phenomenon [26]. Sancho et al. [27] and Babaei-Jadidi et al. [28] report that FBXW7 deletion in the gut alters the differentiation and proliferation status of a subset of proliferative progenitors.

The Ubiquitin Proteosome System (UPS)

Maintenance of cellular homeostasis by the tight regulation of protein behaviour, which in turn directs cellular behaviour, is essential for the normal functioning of cells and acts as a safeguard against transformation [29-31]. Protein turnover is a dynamic process, and cellular protein homeostasis (proteostasis) requires a balance between protein synthesis and degradation. Removal of protein abundance is crucial for the proper step-wise progression of cell division, DNA repair, differentiation and growth [29,30,32,33]. Consequently, a faulty proteolytic system can alter cell fate, cause cellular transformation and bring about pathogenesis. The Ubiquitin Proteasome System (UPS) is a multi-subunit proteolytic pathway which uses ubiquitin (Ub), a small

molecule of 76 amino acids, to tag protein substrates for degradation [30,34]. Aberrant destruction of tumour suppressor proteins or limited degradation of oncoproteins are common scenarios associated with defective proteolysis. A functioning UPS is therefore regarded as a shield against deregulation of internal homeostasis, preventing development of shattering diseases such as cancer [30,33-35].

The UPS pathway (Figure 5), comprises a series of multiple sequential enzymatic steps, involving E1 Ub-activating enzymes, E2 Ub-conjugating enzymes, E3 Ubligases and the 26S proteosome, a cellular factory specialized in proteolysis of Ubtagged proteins [29,31]. E3 Ub-ligases control target specificity of the proteins to be degraded and therefore are key players to the UPS. The SCF (complex of SKP1-CULL-F-box protein) complexes form one of the two major families of E3 ubiquitin ligases (the other being APC/C) involved in degradation of cell cycle machinery and are mainly involved in the regulation of late G1 to early M phase [33,36-39].

SCFFBXW7: Suppressing carcinogenesis

Named after its components (Figures 5 and 6), the SCF complex comprises a three subunit invariable core consisting of SKP1, CULL and RBX1 to be completed by a forth, variable component of the F-box family of proteins- e.g. FBXW7 [36,37,39].

Mammalian FBXW7 (also known as Fbw7, Sel-10, hCdc4, or hAgo) forms the phospho-epitope-specific substrate recognition component

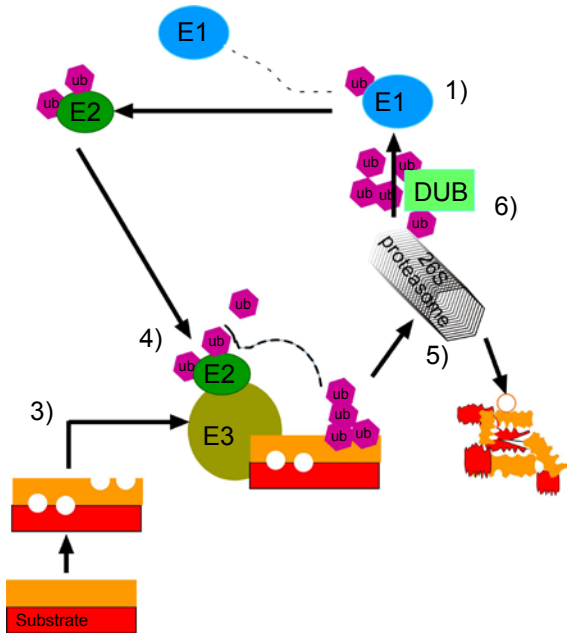

Figure 5: Schematic diagram illustrating the multi-step enzymatic pathway of the UPS (Nath and Shadan 2009)

1) To start with, Ub is covalently activated by E1-Ub activating enzyme
2) Activated Ub is then transferred to an E2-Ub conjugating enzyme
3) In the meantime, E3-Ub ligase enzyme recognises and interacts with phosphorylated (in the majority of cases) substrate
4) E3-Ub ligase mediates transfer of Ub tag from E2 enzyme to substrate to give a covalently bonded polyubiquitinated chain
5) Polyubiquitinated chain acts as cellular signal for irreversible destruction of tagged protein by 26S proteosome system to give functionless oligomers
6) Deubiquitinating (DUB) enzyme breaks down polyubiquitinated chain to monoubiquitins which are recycled for continuation of the UPS cycle.

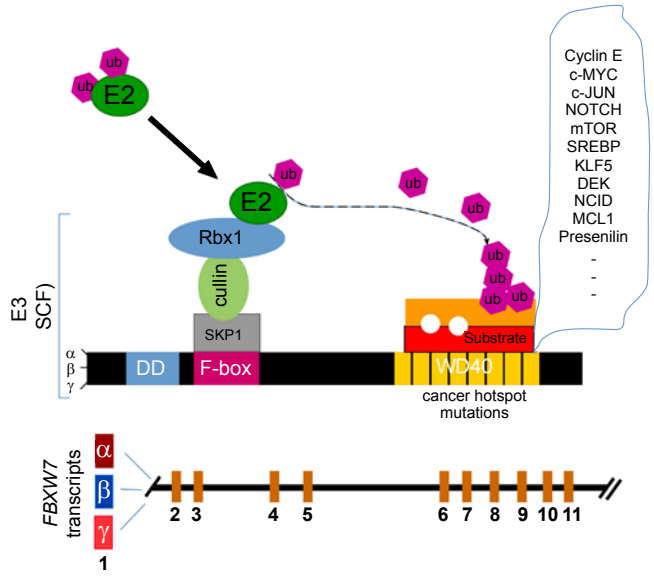

Figure 6: Schematic representation of the human *FBXW7* gene and the SCF^{FBXW7}-E3 ligase complex. *FBXW7* stretches on chromosomal region 4q.31.3 and encodes for 3 isoforms which share 10 common exons and differ in their first isoform-specific exon. All isoforms are functionally identical and form the substrate recognition component of the SCF complex. The FBXW7 protein consists of 627 amino acids and contains 3 main domains: a dimerization doman (DD), an F-box domain and a stretch of eight WD40 repeats domain. (Kemp, et al. [25]; Nakayama and Nakayama (2006) [35]. FBXW7 bridges the interaction between the substrates and the core SCF component mediating ubiquitin tranfer from E2 to the target protein. The F-box domain enables recruitment of the SCF complex via interaction with SKP1, and the WD40 complex mediates interaction with the phosphorylated substrates. (Nakayama and Nakayama (2006); Hoeller and Dikic [29]; Babaei-Jadidi, Li et al. (2011) [28]). FBXW7 substrates consist of oncoproteins implicated in human tumorigenesis such as growth promoters and EMT inducers as listed above.

of the complex [40]. Once substrates get phosphorylated within their conserved CPD (Cdc4 phospho-degron) motif (commonly due to the action of GSK-3β), FBXW7 recognises them for ubiquitination and subsequent degradation [33,36,40,41].

The contribution of SCFFBXW7 in cellular harmony is reflected in the choice of substrates FBXW7 targets for degradation. These include key regulatory proteins of cell division and growth, such as cyclin E, c-Myc, c-Jun, HIF1, of which the ability to drive cell cycle progression, unless tightly controlled, could lead to tumorigenic behaviour [34]. Not surprisingly, most FBXW7 substrates identified (Figure 6) are known to be dominant oncogenes implicated in a wide range of human neoplasms.

Such critical involvement in tumour suppression and cell fate determination means that any perturbation in FBXW7 function or modulation will disturb normal cell behaviour.

FBXW7: the gene, the protein and the cancer

The first member of the evolutionary conserved FBXW7 gene family was found to regulate the disposal of Cyclin-Dependent Kinase (CDK) inhibitor Sic1 in budding yeast and was called Cdc4 [40,42]. Further investigation for the identification of the human orthologue, identified FBXW7 gene (also known as FBW7, CDC4, Sel10, Ago) on the human chromosomal region 4q31.3 (200 kDa) [32,43,44].

FBXW7 gene encodes for three protein transcripts: FBXW7α, FBXW7β, FBXW7γ [40,45]. These share ten common exons and

differ only at their N-termini by a single isoform-specific first exon [28,40,43]. Although functionally identical, isoform-specific transcriptional control allows the distinct sub-cellular and tissue distribution of the transcripts. FBXW7α localises in the nucleus and is found ubiquitously in tissue, FBXW7β localises in the ER/cytoplasm and is found predominantly in brain and testis and FBXW7γ localizes in the nucleolus and is found in heart and skeletal muscle [33,43,46].

FBXW7 protein is a member of the F-box family which consists of approximately 70 proteins in humans [32,35]. These proteins share a common F-box primary motif and most often include additional secondary motifs, the most common of which are WD or leucine rich repeats [41]. The human FBXW7 protein basically denotes an F-box protein with 8- WD repeats. These key domains enable FBXW7 to carry out its function by enabling protein-protein interaction. The F-box domain recruits the SCF complex through its direct contact with the adaptor SKP1 [47]. The WD40 domain harbours phosphodegron binding pockets which mediate interaction with the phosphorylated substrates. In this way, FBXW7 bridges the interaction between the substrate and the core SCF component mediating ubiquitin tranfer from E2 to the target protein for degradation. Loss of FBXW7 will subsequently result in elevated levels of its substrates (mainly proto-oncogenes) and may lead to oncogenesis. Three main lines of evidence suggest FBXW7 as a putative tumour supressor in human tumourigenesis:

1) The oncogenic potential of its putative substrates

2) Deletion of FBXW7 gene in human malignancies (30%)

3) The ability to drive tumorigenesis in FBXW7 knockout mice and cultured cell lines [28,27,32].

On average, 6% of tumours exhibit FBXW7 mutations, with higher frequencies observed in individual malignancies, such as cholangiomas (35%), T-cell acute lymphocytic leukemia (31%), endometrium (9%) and colon (9%) [33,40,44]. The WD40 domain responsible for the interaction of FBXW7 with the phospho-CPDsubstrate is a mutational hotspot for carcinogenesis [25].

Directing Crc therapy

It is now established that cancer is more than a batch of rapidly proliferating cells and more is required than the mere use of empirical cytotoxic agents in its treatment. Inter-tumoural and even intra-tumoural heterogeneity render the non-targeted use of adjuvant chemotherapy much less effective than intended. The undesirable side effects (hair thinning, skin reactions, mouth sores etc.) and the low response rates brought about by a treatment common to all patients, substantially decrease the quality of life for cancer sufferers [48].

Pritchard and Grady [4] states that personalised medicine is now "a clinical reality" and that it will form the "next major advance" in CRC therapeutics. Targeted therapy is particularly applicable to CRC because of the heterogeneity in chemotherapy response among the individual cancers and even among the different disease stages, the undesirable treatment toxicities and the cost of care [3,4,48]. Molecular characterization of tumours allows the use of prognostic biomarkers to predict individual tumour behaviour and subsequently define a more rational therapeutic approach tailored to the needs of each patient (targeted therapy) [3]. Molecular markers are currently used in the routine care of CRC to indicate which patients are at high risk of recurrence and who would benefit from adjuvant chemotherapy after surgery [3,4]. The application of molecular biomarkers, such as the K-Ras and microsattelite instability, is used for the targeted administration of cetuximab [1] and 5-FU/Irinotecan [4] respectively.

Recently a body of literature revealed an intimate correlation of FBXW7 loss and drug response, with FBXW7 mutations promoting resistance to certain therapeutic drugs while increasing sensitivity in others. The Wertz group has recently reported that FBXW7-wild type colon cancer cells demonstrated greater sensitivity to the chemotherapeutic agent Taxol than their FBXW7-null counterparts [49]. Furthermore, inhibition of tumour growth by the novel anticancer drug ABT 737 was shown to be compromised after loss of FBXW7 due to failure of degradation of the Mc11 oncogene in the absence of FBXW7. Reconstitution of FBXW7 was in turn found to restore sensitivity to the chemotherapeutic agent [50]. Likewise, sensitivity to the anti-cancer chemotherapy drug vincristine was shown to be impaired in FBXW7-deficient ovarian and colon cancer lines in the Mcl1-mediated fashion. Subsequently, restoration of FBXW7 status restored sensitivity [50]. All together, this body of literature suggests that profiling the FBXW7 status of tumours could be exploited in predicting response to chemotherapeutic agents. Since FBXW7 loss in linked to drug resistance and tumour aggressiveness, application of FBXW7 gene therapy and reconstitution of FBXW7 could be used to increase drug responsiveness and/or drive aggressive tumours to dormancy [51]. Manipulation of FBXW7 status could offer a promising treatment strategy in predicting and exploiting chemotherapeutic response and can eventually become an integrated part of the clinical management of CRC.

Conclusions and Remarks

All in all, this literature review attempts to emphasize the importance of thorough molecular understanding in cancer research. Sophisticated investigations at the pre-clinical level are essential to eventually deliver the best possible treatment options in the clinical setting under evidence-based medicine. It advocates the theory of the "lab bench to bedside approach" in which cancer research is driven by its clinical significance, with the ultimate aim to contribute to the successful management of the cancer sufferer. Molecular characterization of tumours and exploitation of cancer biomarkers make the option of "personalised/targeted therapy" a clinical reality. Even though the field of molecular therapeutics is still in its infancy, it is expanding rapidly and is expected to provide the way forward to cancer diagnosis and treatment.

Acknowledgements

Such a privilege to thank the fantastic fundraising efforts of Charlotte Sims and her family in memory of Daz Sims to support the work in our laboratory. Cancer Genetics and Stem Cell group at the Division of PreClinical Oncology supported by the Medical Research Council (MRC), Cancer Research UK and the University of Nottingham.

Reference

1. Annie Y, Richard H, David K (2011) ABC of Colorectal Cancer. (2ndedn) Blackwell Publishing Ltd.
2. Scholefield JH (2000) Challenges in colorectal cancer (2ndedn). Blackwell Science Ltd.
3. Funaioli C, Pinto C, Mutri V, Di Fabio F, Ceccarelli C, et al. (2006) Does Biomolecular Characterization of Stage II/III Colorectal Cancer Have Any Prognostic Value? Clin Colorectal Cancer 6: 38-45.
4. Pritchard CC, Grady WM (2011) Colorectal cancer molecular biology moves into clinical practice. Gut 60: 116-129.
5. Sjöblom T, Jones S, Wood LD, Parsons DW, Lin J, et al. (2006) The Consensus Coding Sequences of Human Breast and Colorectal Cancers. Science 314: 268-274.

6. Vogelstein B, Kinzler KW (2004) Cancer genes and the pathways they control. Nat Med 10: 789-799.
7. Chung DC (2000) The genetic basis of colorectal cancer: insights into critical pathways of tumorigenesis. Gastroenterology 119: 854-865.
8. Zhang J, Roberts TM, Shivdasani RA (2011) Targeting PI3K Signaling as a Therapeutic Approach for Colorectal Cancer. Gastroenterology 141: 50-61.
9. Wood LD, Parsons DW, Jones S, Lin J, Sjobolm T, et al. (2007) The Genomic Landscapes of Human Breast and Colorectal Cancers. Science 318: 1108-1113.
10. Elaine S (2005) Colorectal Cancer (1stedn) Whurr Publishers Ltd USA.
11. Hanahan D, Weinberg RA (2011) The Hallmarks of Cancer: the next generation. Cell 144: 646-674.
12. May P, May E (1999) Twenty years of p53 research: structural and functional aspects of the p53 protein. Oncogene 18: 7621-7636.
13. Matsumoto M, Furihata M, Ohtsuki Y (2006) Posttranslational phosphorylation of mutant p53 protein in tumor development. Med Mol Morphol 39: 79-87.
14. Bai L, Zhu WG (2006) p53: Structure, Function and Therapeutic Applications. Journal of Cancer Molecules 2: 141-153.
15. Dai C, Gu W (2010) p53 post-translational modification: deregulated in tumorigenesis. Trends Mol Med 16: 528-536.
16. Brady CA, Attardi LD (2010) p53 at a glance. J Cell Sci 123: 2527-2532.
17. Olsson A, Manzl C, Strasser A, Villunger A (2007) How important are post-translational modifications in p53 for selectivity in target-gene transcription and tumour suppression? Cell Death Differ 14: 1561-1575.
18. Minamoto T, Buschmann T, Habelhah H, Matusevich E, Tahara H, et al. (2001) Distinct pattern of p53 phosphorylation in human tumors. Oncogene 20: 3341-3347.
19. Zhang Y, Xiong Y (2001) A p53 Amino-Terminal Nuclear Export Signal Inhibited by DNA Damage-Induced Phosphorylation. Science 292: 1910-1915.
20. Kruse JP, Gu W (2009) Modes of p53 Regulation. Cell 137: 609-622.
21. Muller PAJ, Vousden KH, Norman JC (2011) p53 and its mutants in tumor cell migration and invasion. J Cell Biol 192: 209-218.
22. Sluss H.K, Heather Armata, Judy Gallent, Stephen N.Jones (2004) Phosphorylation of Serine 18 Regulates Distinct p53 Functions in Mice. Molecular and Cellular Biology 24: 976-984.
23. Ling S, Lin WS (2011) EDD Inhibits ATM-mediated Phosphorylation of p53. J Biol Chem 286: 14972-14982.
24. Rajagopalan H, Jallepalli PV, Rago C, Velculescu VE, Kinzler KW, et al. (2004) Inactivation of hCDC4 can cause chromosomal instability. Nature 428: 77-81.
25. Kemp Z, Rowan A, chambers W, Wortham N, Halford S, et al. (2005) CDC4 Mutations Occur in a Subset of Colorectal Cancersbut Are Not Predicted to Cause Loss of Function and Are Not Associated with Chromosomal Instability. Cancer Res 65: 11361-11366.
26. Iwatsuki M, Mimori K,Ishii H, Yokobori T, Takatsuno Y, et al. (2010) Loss of FBXW7, a cell cycle regulating gene, in colorectal cancer: Clinical significance. Int J Cancer 126: 1828-1837.
27. Sancho R, Jandke A, Davis H, Diefenbacher ME, Tomlinson I, et al. (2010) F-box and WD Repeat Domain-Containing 7 Regulates Intestinal Cell Lineage Commitment and Is a Haploinsufficient Tumor Suppressor. Gastroenterology 139: 929-941.
28. Babaei-Jadidi R, Li N, Saadeddin A, Spencer-Dene B, Jandke A et al. (2011) FBXW7 influences murine intestinal homeostasis and cancer, targeting Notch, Jun, and DEK for degradation. J Exp Med 208: 295-312.
29. Hoeller D, Dikic I (2009) Targeting the ubiquitin system in cancer therapy. Nature 458: 438-444.
30. Nath D, Shadan S (2009) The ubiquitin system. Nature 458: 421-467.
31. Bartek J, Lukas J (2001) Order from Destruction. Science 294: 66-67.
32. Akhoondi S, Sun D, von der Lehr N, Apostolidou S, Klotz K, et al. (2007) FBXW7/hCDC4 Is a General Tumor Suppressor in Human Cancer. Cancer Res 67: 9006-9012.
33. Tan Y, Sangfelt O, Spruck C (2008) The Fbxw7/hCdc4 tumor suppressor in human cancer. Cancer lett 271: 1-12.
34. Crusio KM, King B, Reavie LB, Aifantis I (2010) The ubiquitous nature of cancer: the role of the SCFFbw7 complex in development and transformation. Oncogene 29: 4865-4873.
35. Nakayama KI, Nakayama K (2006) Ubiquitin ligases: cell-cycle control andcancer. Nat Rev Cancer 6: 369-381.
36. Nakayama KI, Nakayama K (2005) Regulation of the cell cycle by SCF-type ubiquitin ligases. Semin Cell Dev Biol 16: 323-333.
37. Fujii Y, Yada M, Nishiyama M, Kamura T, Takahashi H, et al. (2006) Fbxw7 contributes to tumor suppression by targeting multiple proteins for ubiquitin-dependent degradation. Cancer Sci 97: 729-736.
38. Skaar JR, Pagano M (2009) Control of cell growth by the SCF and APC/C ubiquitin ligases. Curr Opin Cell Biol 21: 816-824.
39. Zheng N, Schulman BA, Song L, Miller JJ, Jeffrey PD, et al. (2002) Structure of the Cul1-Rbx1-Skp1-F boxSkp2 SCF ubiquitin ligase complex. Nature 416: 703-709.
40. Welcker M, Clurman BE (2008) FBW7 ubiquitin ligase: a tumour suppressor at the crossroads of cell division, growth and differentiation. Nat Rev Cancer 8: 83-93.
41. Ang XL, Wade Harper J (2005) SCF-mediated protein degradation and cell cycle control. Oncogene 24: 2860-2870.
42. Hartwell LH, Culotti J, Reid B (1970) Genetic Control of the Cell-Division Cycle in Yeast, I. Detection of Mutants. Proc Natl Acad Sci USA 66: 352-359.
43. Matsumoto A, Tateishi Y, Onoyama I, Okita Y, Nakayama K, et al. (2011) Fbxw7 beta resides in the endoplasmic reticulum membrane and protects cells from oxidative stress. Cancer Sci 102: 749-755.
44. Perry JM, Linheng L (2008) Self-renewal versus transformation: Fbxw7 deletion leads tostem cell activation and leukemogenesis. Genes Dev 22: 1107-1109.
45. Koepp DM, Schaefer LK, Ye X, Keyomarsi K, Chu C, et al. (2001) Phosphorylation-Dependent Ubiquitination of Cyclin E by the SCFFbw7 Ubiquitin Ligase. Science 294: 173-177.
46. Matsumoto A, Onoyama I, Nakayama KI (2006) Expression of mouse Fbxw7 isoforms is regulated in a cell cycle- or p53-dependent manner. Biochem Biophys Res Commun 350: 114-119.
47. Kipreos ET, Pagano M (2000) The F-box protein family. Genome Biol 1 reviews3002.
48. Hamilton SR (2008) Targeted therapy of cancer: new roles for pathologists in colorectal cancer. Mod Pathol 21: S23-S30.
49. Wertz IE, Kusam S, Lam C, Okamoto T, Sandoval W, et al. (2011) Sensitivity to antitubulin chemotherapeutics is regulated by MCL1 and FBW7. Nature 471: 110–114.
50. Inuzuka H, Shaik S, Onoyama I, Gao D, Tseng A, et al. (2011) SCF(FBW7) regulates cellular apoptosis by targeting MCL1 for ubiquitylation and destruction. Nature 471: 104–109.
51. Wang Z, Fukushima H, Gao D, Inuzuka H, Wan L, et al. (2011) The two faces of FBW7 in cancer drug resistance. Bioessays 33: 851-859.