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The role of the PI3K pathway in colorectal cancer

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Contents

Abstract

In the last decade treatment for colorectal cancer (CRC) has evolved with the addition of contemporary chemotherapy drugs and targeted therapies. Despite this progress, our drug armamentarium is by no means complete and modern molecular biology techniques have led to the identification of a number of 'druggable' targets. One of the most important current drug targets is the phosphatidyl-inositol 3-kinase (PI3K) pathway, which is frequently deregulated in patients with CRC. In vitro and in vivo data strongly support the clinical development of compounds affecting signal transduction via the PI3K pathway. In this review we outline the role of PI3K in the development and progression of CRC and discuss data from current and ongoing clinical trials targeting this pathway. In addition we make suggestions toward the optimization of future research in order to derive the maximum benefit for patients with CRC.

Keywords: Colorectal; PI3K; PIK3CA; Predictive; Biomarkers

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1. Introduction

Colorectal carcinoma (CRC) is the third most common malignancy diagnosed worldwide and the second most common cause of cancer-related death in the Western population [1,2]. Early detection of pre-malignant and cancerous lesions, together with more effective surgical and pharmacological therapies have led to a decrease in the incidence and mortality of CRC [2]. 5-Fluorouracil (5FU), either used as bolus or as continuous infusion, was for many decades the only approved drug for patients with metastatic disease [3]. Irinotecan and subsequently oxaliplatin were licensed after they were found to significantly prolong the OS from 12 months (5FU alone) to approximately 20 months when used in combination with 5FU [4,5]. Bevacizumab, a humanised IgG1 monoclonal antibody against vascular endothelial growth factor A (VEGF-A) and subsequently cetuximab and panitumumab – monoclonal antibodies that inhibit the downstream activation of the epithelial growth factor receptor (EGFR) – were the first targeted agents to be licensed in patients with metastatic CRC [6–10]. Aflibercept, a fusion protein against vascular endothelial growth factor is now approved as second line treatment and more recently, regorafenib became the first small molecule tyrosine kinase inhibitor to demonstrate a survival advantage in patients who have progressed through standard therapies [11,12].

Phosphatidyl-inositol 3-kinase (PI3K) was first discovered more than 20 years ago and its central role in several cellular functions, critical for oncogenesis and cancer progression, is well described [13,14]. Alterations that lead to increased PI3K signaling are among the most common changes found in human cancers [15]. In the present manuscript we describe the role of the PI3K pathway in carcinogenesis and its significance in early and late stage CRC. In addition we outline clinical data regarding compounds currently in development and highlight the challenges associated with their use.

2. An overview of the PI3K pathway (Fig. 1)

PI3K is an intracellular lipid kinase which has an important role in cell function and cancer development [15]. There are three classes of PI3Ks which are distinguished by differences in structure and function. The type most implicated in human cancer is Class Ia which is comprised of a regulatory (p85) and catalytic (p110) subunit (Fig. 2) [16]. A more detailed schema of the functional domains of the PI3K protein can be found in the excellent review by Vanhaesebroeck and colleagues [17]. Three genes, namely *PIK3R1*, *PIK3R2* and *PIK3R3* encode for the different isoforms of the p85 regulatory subunit, whereas the catalytic subunits p110α, p110β and p110γ are products of *PIK3CA*, *PIK3CB* and *PIK3CD* respectively [14,18]. Somatic mutations that are known to induce activation of the PI3K are commonly found on *PIK3CA* and *PIK3CB* in cancer cells [19].

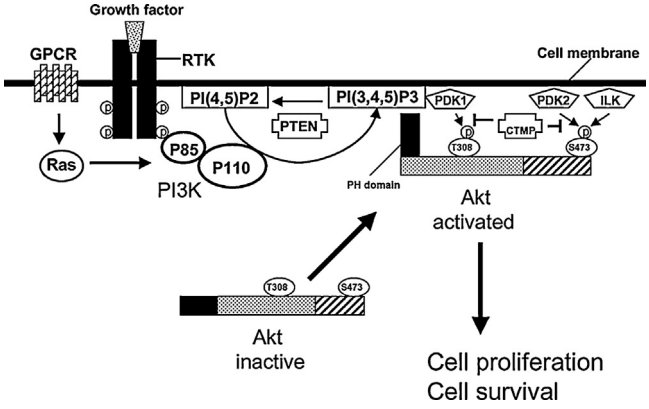

Fig. 1. Scematic diagram of the PI3K signalling cascade. Activation of receptor tyrosine kinases (RTK's) results in the activation of PI3K via the release of the inhibitory effects of the p85 subunit on the p110 subunit. Alternative activation of PI3K can occur via activated Ras. PI3K converts PIP2 to PIP3 that subsequently activates AKT via PDK1. Activated AKT results in cell proliferation and cell survival. PTEN, a tumor suppressor molecule, downregulates the PI3K pathway by dephosphorylating PIP3 to PIP2.

Activation of the PI3K can also occur either with extra cellular stimuli, via receptor tyrosine kinases (RTK) or by stimulation from activated Ras, a molecule with a central role in the growth of CRC [20]. Once p85 is bound to phosphotyrosine residues located in the intracellular part of RTK, the inhibitory effect of p85 to p110 is relieved and PI3K is activated [20]. PI3K phosphorylates phosphatidylinositol 4,5 biphosphate (PIP2) to phosphatidylinositol 3,4,5 triphosphate (PIP3) and subsequently the accumulation of PIP3 at the membrane leads to the recruitment of AKT and its subsequent phosphorylation by PDK1 and mTORC2 [21]. Some of the ways that the activated AKT promotes cell growth and survival are (i) inhibition of proapoptotic proteins of the bcl-2 family, (ii) enhanced degredation of p53 (a proapoptotic molecule), via increased cytoplasmic availability of mdm2, (iii) increased transcription of antiapoptotic genes by affecting the transcription factor NF-kB [20,22]. Another important effect of activated AKT is stimulating the mammalian target of rapamycin (mTOR) group of proteins, which in turn increase protein synthesis by activating mTORC1 and mTORC2 [14]. Finally, the key down-regulator of the PI3K pathway is the phosphatase and tensin homologue protein (PTEN), a tumor suppressor molecule, which dephosphorylates PIP3 to PIP2 [20]. Low activity of PTEN is usually due to truncated proteins – a product of somatic mutations – or epigenetic silencing often by promoter hypermethylation [20]. PTEN deficient cells are dependent on *PIK3CB* and its protein-product p110β to activate PI3K, providing the rational for developing targeted therapies against PIK3CB in patients with PTEN downregulated tumors [23].

3. From benign to malignant: the role of PI3K

CRC results from precursor lesions that have important differences in both morphology and at the molecular level.

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