Summary

Colorectal cancer is the fourth most common cancer worldwide and the fourth most common cause of cancer mortality, with approximately 529,000 deaths annually (1). The concept of molecular targeting in colorectal cancer is not new. After all, 5-fluorouracil (5-FU), the standard bearer of “old school” treatment and continued mainstay of colon cancer systemic therapy, was developed as a “targeted” agent. In this case, the primary target is thymidylate synthase, a key enzyme in DNA synthesis, and the mechanism of action is competitive inhibition by a false substrate. Whereas 5-FU is clearly targeted, it lacks specificity, and the therapeutic window is therefore narrow. In the past decade, advances in understanding of the biology of colorectal cancer as well as the technology of drug development have permitted the identification of new targets and inhibitory pharmaceuticals with high specificity and favorable toxicity profiles. It is this specificity with regard to both target and tissue that characterizes the current generation of targeted therapeutics.

In contrast to other tumors that are driven by a single transforming molecular event, colorectal cancers are characterized by their genetic diversity. This diversity presents challenges for treatment and suggests that molecular profiling of individual patients and tumors will ultimately be required if we are to optimize the matching of patients and treatments. In this chapter, we will review the landscape of colorectal cancer treatment, with a focus on the most promising molecular targets in development. The cancer cell as well as surrounding stroma will be considered. In addition, we will review mechanisms of colorectal cancer pathogenesis and their implications for therapeutic intervention.

Key Words: Colorectal cancer; colon cancer; epidermal growth factor receptor (EGFR); vascular endothelial growth factor.
1. THE COLORECTAL CANCER CELL AS TARGET

A great deal has been learned about those features that distinguish colorectal cancer cells from normal tissues, and a variety of efforts are under way to exploit these characteristics (see Fig. 1). We will begin with a discussion of cell surface targets and subsequently consider downstream intracellular events.

1.1. Surface Targets

1.1.1. Epidermal Growth Factor Receptor

Identification of the epidermal growth factor receptor (EGFR) as a therapeutic target has provided the first proof of concept that a highly specific molecularly targeted therapy can be of clinical benefit in patients with colorectal cancer. The EGFR is a 170-kDa transmembrane cell surface glycoprotein and was the first receptor protein to be recognized as a tyrosine-specific protein kinase (2). This receptor consists of an extracellular portion that serves as a glycosylated ligand-binding domain, a transmembrane region, and an intracellular carboxy-terminal domain with tyrosine kinase (TK).

![Fig. 1. The cancer cell as a target. EGF, epidermal growth factor; EGFR, epidermal growth factor receptor; IGF, insulin-like growth factor; IGFR, insulin-like growth factor receptor; mTOR, mammalian target of rapamycin; MEK, mitogen-activated protein kinase; ERK, extracellular signal-regulated protein kinase; PDGF, platelet-derived growth factor; PDGFR, platelet derived growth factor receptor; PI3K, phosphatidylinositol 3-kinase; PIP3, phosphatidylinositol (3,4,5) triphosphate; PTEN, phosphatase and tensin homologue deleted on chromosome ten; STAT, signal transducers and activators of transcription; TRAIL-R, tumor necrosis factor-related apoptosis-inducing ligand receptor; uPA, urokinase plasminogen activator; uPAR, urokinase plasminogen activator receptor.](image-url)