Chapter 16
Krüppel-like Factors in Cancers

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Abstract Krüppel-like factors (KLFs) are zinc finger-containing transcription factors that play important roles in diverse physiological and pathophysiological processes. A major function of many KLFs is to regulate cell growth, proliferation, and differentiation. It is therefore not surprising that some of the KLFs are involved in tumorigenesis of various organs and tissues. This chapter reviews the pathobiological roles of KLFs in several cancers, including those of the gastrointestinal tract, breast, skin, and pancreas. Understanding the functions of KLFs in cancers may help gain insight into the pathogenesis of cancers and provide novel therapeutic approaches to their treatment.

Introduction

Krüppel-like factors (KLFs) belong to the family of zinc finger-containing transcription factors that share homology to the Drosophila melanogaster gap gene product, Krüppel (Bieker 2001; Black et al 2001; Dang et al 2000b; Kaczynski et al 2003; Lomberk and Urrutia 2005; Philipsen and Suske 1999). Since identification and isolation of the prototypic mammalian KLF—KLF1 or erythroid Krüppel-like factor (EKLF)—a decade and half ago (Bieker 1996; Miller and Bieker 1993), there has been an explosion of research devoted to the identification, isolation, and characterization of many additional KLF family members. To date, there are approximately 17 identified mammalian KLFs (excluding the Sp1 and Sp1-related proteins) (Kaczynski et al. 2003). Together, these KLFs have been shown to exert important regulatory functions in numerous biological and physiological processes.

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Expression or activities of the KLFs are also frequently perturbed in pathological events. One of the main roles of many of the KLFs is their involvement in the regulation of cell growth, proliferation, differentiation, and development. As such, KLF expression and activities are often abnormal in neoplastic processes including cancers. Here we review the roles played by representative KLFs in several tumors including those of the gastrointestinal tract, breast, skin, and pancreas. The functions of KLFs in cancers of the liver, prostate, and ovaries are described elsewhere in this book (see Chapters 11 and 17).

Colorectal Cancer

Colorectal cancer is a common form of cancer and one of the leading causes of cancer mortality, with more than 655,000 deaths per year worldwide (Cancer. World Health Organization, February 2006). Clinical and epidemiological evidence indicates that colorectal cancer is preceded by a benign precursor lesion, an adenoma (Levin et al. 2008). Much progress has been made in understanding the genetics and pathogenesis of colorectal cancer at a molecular level (de la Chapelle 2004; Rustgi 2007). However, recent studies point to the complex, heterogeneous nature of colorectal cancer, which involves close to 200 genes that are mutated at a significant frequency (Sjoblom et al. 2006; Wood et al. 2007).

KLF4

Several KLFs have been implicated in the pathogenesis of colorectal cancer (Ghaleb and Yang 2008; Wei et al. 2006). Among these, KLF4 is the most extensively studied. KLF4 (also called gut-enriched Krüppel-like factor or GKLF) was initially identified as a gene whose expression is enriched in epithelial tissues, including the intestine and epidermis (Garrett-Sinha et al. 1996; Shields et al. 1996). In vivo studies in transgenic mice that are null for the Klf4 alleles indicate that KLF4 is required for the terminal differentiation of goblet cells in the colon and for the barrier function of the skin in neonates (Katz et al. 2002; Segre et al. 1999). Studies also indicate that expression of KLF4 is primarily located in the postmitotic, differentiated cells of epithelial tissues (Garrett-Sinha et al. 1996; McConnell et al. 2007; Shie et al. 2000b; Shields et al. 1996). This growth arrest-specific pattern of expression is also observed in cultured cells in vitro (Shields et al. 1996). Consequently, ectopic expression of KLF4 in cultured cells results in growth arrest (Chen et al. 2001; Shields et al. 1996). Additional conditions that are known to cause growth arrest in cultured colonic epithelial cells—such as DNA damage and treatment with interferon-γ, sodium butyrate, or 15-deoxy-Δ(12,14) prostaglandin J2 (15d-PGJ2)—all lead to the induction of KLF4 expression (Chen et al. 2000, 2004; Shen and Tseng 2005; Yoon et al. 2003; Yoon and Yang 2004; Zhang et al. 2000).