ELSEVIER

European Journal of Cancer 41 (2005) 2379–2380

European Journal of Cancer

www.ejconline.com

Editorial

Transcription factors in cancer

This special issue resulted from recent research progress in transcriptional regulation of cancer related genes. Oncogenic activation of transcription factors is a key event in the establishment and progression of human cancer. All cancer cells acquire similar sets of functional capacities such as: independence from mitogenic/proliferative regulatory signals; loss of sensitivity to "anti-growth" signals, evasion of apoptosis, neo-angiogenic conversion, release from senescence, and acquisition of invasiveness, and metastasis. Transcription factor proteins act as modulators of cell proliferation, and regulate the balance of apoptotic and anti-apoptotic gene activities as well as the controls for cell death. These factors bind to DNA and/or other proteins of the transcriptional machinery, directly leading to expression, and in some cases, to repression, of key genes involved in tumourigenesis. Much fascinating work and a number of promising *in vitro* methods for interdicting these mechanisms are described in this volume.

Rb was the first tumour suppressor identified through human genetic studies. Liang Zhu discusses the molecular mechanisms for Rb's repressive effects on E2Fs and other aspects of Rb that are not directly related to transcription regulation but do contribute significantly to Rb function.

A subset of sarcomas is characterised by recurrent chromosome translocations that generate novel fusion oncoproteins. These fusion transcription factors deregulate multiple biological pathways by altering the expression of downstream target genes, and effect a variety of altered cellular properties that contribute to the tumourigenic process, as is clearly discussed here by Frederick Barr.

Chromatin modifier enzymes represent an additional level of transcription regulation. Carlos Caldas focuses on such transcription activators and repressors that catalyze histones by acetylation, methylation, phosphorylation, ubiquitination and sumoylation – and how these enzymatic activities and post-translational modifications alter cellular homeostasis during tumourigenesis.

Intrinsic or acquired resistance to anticancer agents is a major obstacle to the success of chemotherapy. Kimitoshi Kohno describes how drug resistant cells arise in solid tumours and reviews what is known of the transcription factors that are involved in resistance to chemotherapeutic drugs, particularly with a focus on cisplatin.

David Hodge discusses the relationships between cancer and inflammation, and some of the molecular mechanisms involved in mediating the unintended consequences of host defenses like chronic inflammation and its contribution to tumour survival.

Oncogenic viral proteins deregulate signalling pathways pertaining to transcriptional regulation and cell cycle control, these detrimental effects are discussed by Kamel Khalili using the JCV virus as an example. Interference with transcription triggers a stress response leading to the induction of the tumour suppressor p53. If transcription is not restored within a certain time-frame, cells may undergo apoptosis. Mats Ljungman describes mechanisms by which obstruction of transcription induces apoptosis, which may involve: diminished levels of anti-apoptotic factors; inappropriate accumulation of proteins in the nucleus, or the increase of complications arising during replication.

The Fos family of transcription factors play significant roles in tumourigenesis and Karin Milde-Langosch summarises our current understanding of the functions of the AP-1 proteins c-Fos, FosB, Fra-1 and Fra-2 in carcinogenesis. Nuclear receptors are a family of ligand dependent transcription factors that have important roles in control of growth and differentiation in many cell types. Raphael Nemenoff focuses on the role of two members of this family, estrogen receptors and PPAR, in the initiation and progression of lung cancer, and describes the development of selective agonists for these receptors.

The HIV-1 long terminal repeat (LTR) is stringently controlled by T cell activation signals, and binds a variety of transcription factors whose activities are regulated downstream of the T cell receptor. As described by Ivan

0959-8049/$ - see front matter
doi:10.1016/j.ejca.2005.09.005

Sadowski, this system may be responsible for regulating promoter context by controlling chromatin organisation, thereby coordinating transcriptional activation by additional factors bound to the enhancer region.

Sp1 and other Krüppel-like factor proteins regulate expression of multiple genes in normal tissues and tumours. Stephen Safe describes critical roles for these factors in the growth and metastasis of many tumour types where they regulate cell cycle genes and vascular endothelial growth factor.

B-MYB, a transcription factor implicated in the regulation of the cell cycle, apoptosis and cancer is known to interact with important players of the cell cycle and transcription machinery, such as E2F and retinoblastoma proteins. Arturo Sala describes its essential transcriptional function in stem cell formation and mammalian development. VG Gorgoulis provides a brief but concise overview of E2F function and its putative role in the most common human tumour types.

ETS proteins are transcription factors that activate or repress the expression of genes that are involved in various critical biological processes, including cellular proliferation, differentiation, development, transformation and apoptosis. Watson and Seth highlight the current understanding of the ETS genes and their role in cancer.

Homeobox genes encode transcription factors that play essential roles in controlling cell growth and differentiation during embryonic development. Shaija Samuel and Honami Naora explain how homeobox genes are aberrantly expressed in a wide variety of solid tumours, and discuss how their deregulation enhances cell survival and proliferation and inhibits differentiation.

Azmi and Seth describe the role of a novel small ring finger protein RNF11, in cell surface receptor signalling and in transcription factor modulation by its interaction with Smad4 and ZBRK1. Important role of RNF11 is emphasized by demonstrating that it enhances the tumour suppressive effects of TGF-β and opposes the oncogenic signalling of the EGF receptor. The omnipotent Myc oncoprotein plays a pivotal role as a regulator of tumourigenesis in numerous human cancers of diverse origin. Linda Z. Penn and colleagues summarize recent advances in understanding the function of Myc as a transcription factor, with emphasis on key Myc:protein interactions and target gene regulation. Progress in drug development aimed at eliminating Myc is also a major focus of their review.

Understanding the molecular mechanisms of transcription factor actions in cancer will likely provide new possibilities for earlier detection, diagnosis and staging of this disease. As described in this issue a limited number of transcription factors are overactive in most human cancer cells, which makes them targets for the development of anticancer drugs. Thus targeting specific transcription factors by novel therapeutic agents promises to have a profound impact in combating many types of cancer.

Manipulation of transcription factor-regulated biological pathways will also directly impact these areas, leading to significant advances in the evaluation of clinical response to therapy, as well as to possible ways of prevention, and ultimately, novel treatment strategies.

I am grateful to each of the individual authors without whose contribution this special issue would not be possible and to our administrative assistants Sarah Jenkins and Laura Silver whose gentle persuasions kept us all moving along.

Arun Seth
University of Toronto, Sunnybrook and Women's College Health Sciences Centre, Laboratory of Molecular Pathology, Rm E-423B, 2075 Bayview Avenue, Toronto Ont., Canada M4N 3M5
E-mail address: arun.seth@utoronto.ca

Available online 21 October 2005