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International Immunopharmacology 5 (2005) 1113–1130

International Immunopharmacology

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Mini review

The molecular mechanisms of oesophageal cancer

M.L. McCabe, Z. Dlamini*

School of Molecular and Cell Biology, Faculty of Science, University of the Witwatersrand, P/Bag 3, Johannesburg, 2050, South Africa

Received 27 September 2004; received in revised form 19 November 2004; accepted 29 November 2004

Abstract

Apoptosis is a process of programmed cell death, which is as essential as cell growth, for the maintenance of homeostasis. When these processes loose integration such as cancer, then uncontrolled cell growth occurs. Cancer of the oesophagus ranks as the ninth most common malignancy in the world, and recent evidence shows that its incidence is increasing. Prognosis of this disease is poor, with an overall 5-year survival rate of less than 10%. Unraveling the mechanisms or developing animal models for oesophageal carcinoma have thus far not been successful. It is believed that oesophageal cancer has an intricate molecular mechanism of evading apoptosis by the down-regulation of Bax, up-regulation of Bcl-2, Bcl-xl and Survivin, mutation of p53 and alteration in Fas expression. A great deal of research has been performed in order to determine the key genes that initiate and promote the growth of oesophageal cancer. This review focuses on apoptosis and candidate genes linked to the development of oesophageal cancer, which it is hoped may provide diagnostic and therapeutic tools, and potential therapeutic strategies for the management of this carcinoma.

Keywords: Human oesophageal cancer; Molecular genetics; Apoptosis signalling pathway; Genomics; Oesophageal cancer therapeutics

Abbreviations: AINs, Apoptosis inducing nucleosides; Apaf-1, Apoptosis activating factor 1; APC, Adenomatous polyposis coli; BAAC, Barrets Oesophagus associated adenocarcinoma; BE, Barret's Esophagus; Bcl-2, B-cell lymphoma mutant 2; Bcl-xl, B-cell lymphoma extra long; CDDP, Cisplatin; CDK, Cyclin dependent kinase; COX-2, Cyclooxygenase 2; CSNK, Casein kinase; CTSB, Cathepsin B; DcR3, Decoy receptor member 3; DISC, Death inducing signalling complex; DLC1, Deleted in lung cancer 1; EMR, Endoscopic mucosal resection; FasL, Fas receptor ligand; GASC1, Gene amplified in squamous cell carcinoma 1; iNOS, Inducible nitric oxide synthase; Lef, Lymphoid enhancer binding factor; LOH, Loss of heterozygosity; LOI, Loss of imprinting; MMP-7, Matrix metalloproteinase-7; MT, Metallothionein; MTX, Methotrextate; ODC, Ornithine decarboxylase; OeAc, Adenocarcinoma; OeSc, Squamous carcinoma; p53, Protein with molecular weight ~53 kDa; p63, Protein with molecular weight ~63 kDa; p73, Protein with molecular weight ~73 kDa; PARP, Poly-ADP-ribose polymerase; PCNA, Proliferating cell nuclear antigen; PDT, Photodynamic therapy; pRb, Retinoblastoma protein; Rb, Restinoblastoma; Tcf, T cell specific transcription factor; TNF-β, Tumour necrosis factor-β; TSGs, Tumour suppressor genes; WWOX, WW domain containing oxireductase.

* Corresponding author. Tel.: +27 11 7176366; fax: +27 11 7176351.
E-mail address: dlamini@gecko.biol.wits.ac.za (Z. Dlamini).

1567-5769/$ - see front matter © 2004 Published by Elsevier B.V.
doi:10.1016/j.intimp.2004.11.017

1. Oesophageal cancer

1.1. Prevalence

Cancer of the oesophagus ranks as the ninth most common malignancy worldwide and recent evidence shows that its incidence is rising [1]. Prognosis of this disease is poor with an overall 5-year survival rate of less than 10%. There are two major types of oesophageal cancer: squamous carcinoma and adenocarcinoma. The incidence of oesophageal adenocarcinoma is increasing, and is most prevalent in the USA [2].

Universally, oesophageal cancer is more common in men than in women, with decreasing sex ratios in higher-risk areas and vice versa for lower-risk areas. Incidence rate for oesophageal cancer increases with age, with the lowest occurring at age 30 and the highest at age 70. The highest mortality rates are found in China accounting for 26.5% in males and 19.7% in females [3]. Oesophageal cancer in South Africa is the second most common cancer among all South African men combined and the most common cancer in black males. Regions of South Africa, like the Transkei, have recorded rise in incidence of oesophageal cancer from 16 per 100,000 before 1970 to over 40 per 100,000 thereafter [4]. To date, high incidence areas (expressed as crude incidence per 100,000) include: China (21 per 100,000), South America (13 per 100,000), Western Europe (11 per 100,000), South Africa (10 per 100,000), Japan (9 per 100,000) and the former Soviet Union (8 per 100,000) (Pearson et al., 2002) [5].

1.2. Etiology

Oesophageal cancer is a multifactorial disease; no single agent has been identified thus far as the cause of oesophageal cancer. Smoked food has a high content of nitrosoamines and nitrites [6]. Methyl alkyl nitrosamines appear to be specific inducers of carcinoma of the oesophagus, regardless of its route of administration. Smoking is also believed to play a role in oesophageal carcinogenesis. Alcohol is also a major etiological factor in oesophageal cancer. Fungal toxins and spices are believed to have a positive correlation with oesophageal cancer. It is suspected that home brewed beers and other spirits prepared in African countries cause oesophageal cancer due to contamination with mycotoxins occurring during preparation. The fungus, *Fusarium moniliforme*, is believed to play a role in the toxicity of maize, and when consumed, these mycotoxins are believed to play a role in the development of cancer. Human papilloma virus (HPV) serotypes 16 and 18 have also been found to be associated with the development of the disease. Barret's Oesophagus (BE) has also been found to be a risk factor for adenocarcinoma of the oesophagus. BE a metaplastic change of the oesophageal epithelium from squamous to columnar mucosa, which is associated with repeated episodes of chronic gastro-oesophageal reflux (GORD) [7]. It has been shown that 86% of primary oesophageal adenocarcinomas originate from BE [8].

1.3. Molecular genetics of oesophageal cancer

As oesophageal carcinogenesis is poorly understood, much research is being carried out to understand the precise mechanisms causing the metaplasia–dysplasia sequence of oesophageal carcinoma at a molecular level [9]. It is known that tumour suppressor genes, oncogenes, and apoptotic genes are involved in the initiation and development of oesophageal cancer, but to date no gene directly related to oesophageal cancer has been identified [10].

Many candidate genes and their role in the development of oesophageal cancer are still to be revealed before a human oesophageal carcinogenesis model can be developed. Key tumour related genes and their specific role played in the development of oesophageal cancer are discussed in more detail.

1.4. Apoptosis—genetic regulation of oesophageal cancer

Each living cell undergoes cell cycle regulation where an essential assessment mechanism occurs to determine the status of the cell, whether it is healthy enough to proceed to the next stage of cycle or whether it should commit suicide.

Apoptosis is generally defined as a programmed cell death that eliminates unwanted cells and is essential for the homeostatic maintenance of an organism. Like cell proliferation, cell death needs to take place in order for normal development to take place. It has been found that elevated levels of