

**UNIVERSITI TEKNOLOGI MARA**

***IN SILICO* ANALYSIS OF TUMOR SUPPRESSOR  
*SMAD4* GENE**

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## ABSTRACT

*Smad4* gene is an essential signal transducer of the transforming growth factor  $\beta$  (TGF- $\beta$ ) signaling pathway and has been identified as a tumor suppressor, being mutated in approximately 30% of colorectal cancers. The human *Smad4* gene encodes a 552 amino acid coding sequence, which contains 11 exons and located in chromosome 18q21. Lacking in the signature phosphorylation site in its C terminus, *Smad4* is unable to associate with TGF- $\beta$ R complex. In the nucleus, *Smad4* binds to specific short sequences of DNA directly or indirectly and regulate transcription of the targeted genes, leading to the regulation of cellular proliferation. *Smad4* protein has two regions that contain highly conserved amino-terminal and carboxyl-terminal, known as Mad homology 1 (MH1) and Mad homology 2 (MH2). Germline mutations in the *Smad4* gene have been detected in nearly 25 to 60% of the cases analyzed and 90% of the mutations located in the MH2 region. In CRC, *Smad4* gene mutations are found in carcinomas and increased frequencies of metastatic CRC, and these mutations cannot be detected in premalignant stages. *In silico* identification and characterization of *Smad4* provide preliminary information on the structure and function of the gene in human. In addition, comparative modeling is becoming a useful technique in the field of bioinformatics because the knowledge of the three-dimensional structure of protein would be an invaluable aid to understand the details of a particular protein. The predicted three-dimensional model may be further used in characterizing the interest protein in wet laboratory. The methods in this study can be used to get more information about biosystem by identifying and characterization of other genes and biomolecules.

# CHAPTER 1

## INTRODUCTION

### 1.1 Overview

*Smad4* gene is an essential signal transducer of the transforming growth factor  $\beta$  (TGF- $\beta$ ) signaling pathway and has been identified as a tumor suppressor, being mutated in approximately 30% of colorectal cancers (De Bosscher *et. al.*, 2004). Inactivation of *Smad4* gene seems to occur late during tumor progression when tumors acquire invasive and metastatic properties. Metastases are the major cause of death from cancer. Cancer is a leading cause of death worldwide, accounted for 7.8 million deaths or 13% of all deaths around the world. About 80% of all cancer deaths occurred in low and middle income countries, and these numbers are estimated to increase with an approximately 12 billion deaths in 2030. The most frequent types of cancer worldwide are among male; lung, stomach, liver, colorectal, esophagus and prostate, while among female; breast, lung, stomach, colorectal and cervical. Overall colon cancer mortality each year is 677,000 deaths and about 30% of these deaths can be prevented (WHO 2008).