



Review

Modulation of oncogenic transcription factors by bioactive natural products in breast cancer



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ABSTRACT

Carcinogenesis, a multi-step phenomenon, characterized by alterations at genetic level and affecting the main intracellular pathways controlling cell growth and development. There are growing number of evidences linking oncogenes to the induction of malignancies, especially breast cancer. Modulations of oncogenes lead to gain-of-function signals in the cells and contribute to the tumorigenic phenotype. These signals yield a large number of proteins that cause cell growth and inhibit apoptosis. Transcription factors such as STAT, p53, NF- κ B, c-JUN and FOXM1, are proteins that are conserved among species, accumulate in the nucleus, bind to DNA and regulate the specific genes targets. Oncogenic transcription factors resulting from the mutation or overexpression following aberrant gene expression relay the signals in the nucleus and disrupt the transcription pattern. Activation of oncogenic transcription factors is associated with control of cell cycle, apoptosis, migration and cell differentiation.

Among different cancer types, breast cancer is one of top ten cancers worldwide. There are different subtypes of breast cancer cell-lines such as non-aggressive MCF-7 and aggressive and metastatic MDA-MB-231 cells, which are identified with distinct molecular profile and different levels of oncogenic transcription factor. For instance, MDA-MB-231 carries mutated and overexpressed p53 with its abnormal, uncontrolled downstream signalling pathway that account for resistance to several anticancer drugs compared to MCF-7 cells with wild-type p53. Appropriate enough, inhibition of oncogenic transcription factors has become a potential target in discovery and development of anti-tumour drugs against breast cancer.

Plants produce diverse amount of organic metabolites. Universally, these metabolites with biological activities are known as “natural products”. The chemical structure and function of natural products have been studied since 1850s. Investigating these properties led to recognition of their molecular effects as anticancer drugs. Numerous natural products extracted from plants, fruits, mushrooms and mycelia, show potential inhibitory effects against several oncogenic transcription factors in breast cancer. Natural compounds that target oncogenic transcription factors have increased the number of candidate therapeutic agents. This review summarizes the current findings of natural products in targeting specific oncogenic transcription factors in breast cancer.

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1. Introduction

Breast cancer along with other malignancies are a result of iterative genetic alterations of normal cells. Non-genetic or epigenetic modifications in cancerous cells and normal cells that interact with tumour cells, such as vascular cells, stromal cells and immune cells, also contribute to the formation of the malignancies [1]. Breast cancer is one of highly prevalent malignancies among women, and is one of top ten cancer worldwide [2,3]. A growing knowledge about these alterations and their associated molecular signalling pathways, offer opportunities for therapeutic strategies. Most genetic alterations or genetic instability (GI) are only present in malignant cells. For instance, certain genes mutation are associated with high level of cancer risk, due to the malfunction of these gene products. Genes that are activated and contribute to emerge and development of malignancy are called oncogenes. Oncogenes may be involved in emerge or function of other genes that contribute in cell survival, proliferation, motility, mutation and drug resistance. In breast cancer, the specific loss of some genes or changes in number of copy of some other genes, appeared to cause transition from hyperplasia to ductal carcinoma *in situ* [4].

Transcription factors are proteins that bind to DNA to promote the gene expressions [5]. In particular, oncogenic transcription fac-

tors, those gene expression-promoters that their activity one way or another, leads to tumorigenesis, are divided into three groups in breast cancer: steroid receptors [6], resident nuclear transcription factors [7], and latent cytoplasmic factors [7]. Overexpression/over-activity/over-supply of these oncogenic transcription factors, leads to the survival of breast cancer cells [8,9]. Molecular signalling pathways that affected by these oncogenes, and those signalling pathway effected by first set of pathways, have complex interaction with each other. Due to this, the diagnostic and therapeutic achievements are progressing very slowly. Eventually, over the time gain of knowledge about oncogenes, their proteins and their functions, leaded therapeutic regimes, towards more selectivity and higher efficacy. However, the ideal therapy is not achieved yet due to our limited comprehension of molecular biology of cancer and crosstalk of cellular proteins that one way or another effect/interrupt on each other's contribution. Besides, effectiveness of each drug is limited, due to existence of other factors that may override the resistance, or the nature of targeted protein, targeted pathways or their functions may change over the time [10]. In this review, we focus on products, from natural sources that characterized to target oncogenic transcription factors in breast cancer. Natural products in general, afford not only selective benefits against cancer cells compared to normal cells, but also provide a template structure for the design

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