УДК [61+615.1] (043.2)
ББК 5+52.81
А 43
ISBN 978-985-21-1864-4

Shivaramaiah B.

THE EFFECT OF GERMLINE AND SOMATIC MUTATIONS IN BREAST CANCER

Tutor: PhD, associate professor Zhadan S.A.
Department of Pathological Physiology
Belarusian State Medical University, Minsk

The inheritance of an autosomal dominant allele has a predisposing factor in about 10% of all women with breast cancer. BRCA1 and BRCA2 are the hereditary susceptible genes, which has a high penetrance of germline and somatic mutations. Women who have a mutation in either of these genes have a cumulative lifetime risk of 60–80% and 20–40% for the development of breast and ovarian cancer. Therefore, there is a great need for new and effective measures for their management. Progress in our understanding of the normal biological function and regulation of BRCA1 and BRCA2 has helped us in knowing molecular basis of hereditary breast cancer, and provide a driving force for the development of diagnostic and therapeutic strategies.

BRCA1 and BRCA2 are tumour suppressor genes whose products function is to maintain the genome stability. They ensure that the genetic integrity of a cell is not compromised by any duplication or rearrangement of chromosomal DNA. The damage of the DNA by metabolic processes within cell or by extrinsic factors like radiation or chemicals can happen on daily basis so, it is important to maintain genome stability. Unrepaired DNA damage can lead to chromosomal instability which restricts the normal growth of the cell.

Genome integrity is a response involves the assembly of DNA-repair protein complexes which able to recognise and eliminate damage-induced lesions, and the synthesis of cell-cycle checkpoint those control proteins that provide a sufficient opportunity to repair damaged DNA. BRCA1 and BRCA2 does the fundamental role in coupling DNA damage-induced signals to downstream cellular responses, including damage repair and cell-cycle checkpoint activation.

BRCA1 and BRCA2 genes are likely to function ubiquitously in the maintenance of genome integrity. Inactivation of BRCA1 or BRCA2 generally leads to cancer of the breast or ovary.

The breast and the ovary are reproductive organs that rely on hormones, including oestrogen and progesterone, for growth, differentiation, and homeostasis. According to one theory, inactivation of BRCA1 and BRCA2 causes breast and ovary susceptible to tissue-specific effects of oestrogen-induced DNA damage. Thus, inactivating mutations in BRCA1 and BRCA2 could compromise the response of breast and ovarian epithelial cells to oestrogen-induced DNA damage, thereby resulting inefficient or error-prone DNA repair. Alternatively, BRCA1 might modulate hormone signalling pathways and control of cellular proliferation. BRCA1 represses the transcriptional activity of the oestrogen and progesterone receptors, and mutational inactivation of the gene. Therefore, promote epithelial cell proliferation through altered expression of hormone-responsive genes.

These two genes are not mutually exclusive and could suggest a combinatorial path to breast cancer, since they invoke BRCA1-mediated and BRCA2-mediated control at two distinct steps of tumorigenesis - initiation and progression. Thus, inappropriate expression of hormone-responsive genes could promote the proliferation of transformed cells arising through inefficient or error-prone repair of oestrogen-induced DNA damage. In this way, hereditary BRCA1 and BRCA2 mutations could cause breast and ovarian epithelial cells particularly susceptible to tumorigenesis through disturbing the distinct hormone-dependent pathways.