IGF-1 and BRCA1 signalling pathways in familial cancer

Haim Werner, Ilan Bruchim

The insulin-like growth factor (IGF) system has a direct effect on cellular proliferation and survival, and interacts with genetic and environmental factors implicated in causing cancer. Experimental, clinical, and epidemiological evidence show that the IGF signalling pathways are important mediators in the biochemical and molecular chain of events that lead from a phenotypically normal cell to one harbouring neoplastic traits. BRCA1 and BRCA2 have an important role in the development of hereditary and sporadic breast and ovarian cancer. Recent evidence suggests that risk of cancer conferred by BRCA mutations can be modified by genetic and environmental factors, including ambient concentrations of IGF-1 and polymorphisms in IGF system components. This Review addresses interactions between the IGF and BRCA1 signalling pathways, and emphasises the convergence of IGF-1-mediated cell survival, proliferative pathways, and BRCA1-mediated tumour protective pathways. Understanding the complex interactions between these signalling pathways might improve our understanding of basic molecular oncology processes and help to identify new molecular targets, predictive biomarkers, and approaches for optimising cancer therapies.

Lancet Oncol 2012; 13: e537–44

Department of Human Molecular Genetics and Biochemistry, Sackler School of Medicine, Tel Aviv University, Tel Aviv, Israel
(Prof H Werner PhD); **and Gynecologic Oncology Unit, Department of Obstetrics and Gynecology, Meir Medical Center, Kfar Sava, Israel**
(I Bruchim MD)

Correspondence to:
Prof Haim Werner, Department of Human Molecular Genetics and Biochemistry, Sackler School of Medicine, Tel Aviv University, Tel Aviv 69978, Israel
hwerner@post.tau.ac.il

Introduction

Breast cancer is the most frequently diagnosed oncological disease and the leading cause of death related to malignancy among women. With almost 1·4 million new cases annually, breast cancer accounts for 23% of the total cancer cases and 14% of cancer deaths worldwide.[1] Historically, population-based risk factors, including older age at first birth, nulliparity, socioeconomic status, and first-degree family history of breast cancer, were associated with less than half of breast cancer cases.[2] Cellular and molecular mechanisms were sought to explain breast cancer development and progression, particularly the association with oestrogen receptor (ER) signalling pathways.[3] Proliferation of breast epithelial cells is also responsive to various peptide growth factors.[4] The insulin-like growth factor (IGF) system has a major role in development of breast cancer—evidence shows that IGFs are mediators in the chain of events by which phenotypically normal cells adopt neoplastic traits.[5–8]

The IGF axis constitutes a network of secreted ligands (insulin, IGF-1, IGF-2), cell-surface receptors (insulin receptor, IGF-1 receptor [IGF1R]), and IGF-binding proteins (IGFBPs) that regulate metabolic, nutritional, endocrine, growth, and ageing events, among others. IGF1R, which mediates the biological actions of IGF-1 and IGF-2, shows potent antiapoptotic and, potentially, transforming activities, and is considered a key factor in cancer development.[9,10] IGF1R has emerged as a promising therapeutic target, and efforts are underway to translate experimental and preclinical data into standard medical protocols.[11–14] In addition to its direct effect on cellular proliferation and survival, the IGF network interacts with several genetic and environmental factors that have been implicated in development of breast cancer. This Review examines interactions of the IGF axis with *BRCA1* and *BRCA2*, a family of high-penetrance genes with key roles in familial cancer. Analysis of the interplay between IGF and BRCA signalling pathways might shed light on important questions in modern oncology.

Endocrine IGF-1 and cancer risk: analysis of epidemiological data

The potential association between circulating IGF-1 concentrations and breast-cancer risk is a controversial issue.[7,15] Large-scale epidemiological studies suggested that high circulating IGF-1 concentrations were associated with increased risk for several types of cancer, including breast and prostate.[16,17] In a prospective, nested control study (the Nurse's Health Study),[17] premenopausal women with high IGF-1 concentrations (upper tertile) had a relative risk of breast cancer of 4·6, compared with premenopausal women who had low IGF-1 concentrations (lower tertile). Furthermore, the relative risk increased to 7·3 when concentrations of IGFBP-3 were included in the analysis.[17] In this study, IGF-1 concentrations were measured an average of 7 years before disease diagnosis. Several subsequent epidemiological studies reported diverse (and sometimes opposing) outcomes.[18–20] A comprehensive meta-analysis by Clayton and colleagues[21] concluded that circulating IGF-1 values are positively associated with risk of prostate, premenopausal breast, and colorectal tumours, although the relative risks were substantially lower than those reported in earlier studies. Similarly, the Endogenous Hormones and Breast Cancer Collaborative Group, in an analysis of 17 prospective studies from 12 countries, reported that IGF-1 is positively associated with breast cancer risk.[15] By contrast with Clayton and colleagues' analysis, the association of IGF-1 with breast cancer was not substantially modified by IGFBP-3 and was not affected by menopausal status; however, the association was confined to ER-positive tumours. Taken together, these epidemiological observations could have major implications for risk assessment and cancer prevention.

Studies have shown that the *IGF1R* gene is expressed in 39–93% of primary breast carcinomas; however, data are conflicting regarding the diagnostic and prognostic significance of these values.[22] Most data are consistent with the notion that IGF1R expression is lower in benign lesions and normal breast tissue than in malignant tissue.[23] However, several studies have suggested that as

breast cancer progresses it becomes IGF independent (probably associated with oestrogen independence).[24,25] As a result, IGF1R expression levels are reduced and become inversely associated with tumour progression. A recent study of 2871 patients with breast cancer showed that IGF1R expression was associated with age older than 50 years, lower histopathology grade, ER positivity, and HER2 negativity.[26] This study clearly established that IGF1R correlates with good prognostic variables (ie, markers predicting breast cancer-specific survival) among patients with early disease. Furthermore, IGF1R is differentially expressed with varying prognostic impact among breast cancer subtypes.[26]

Role of IGF1R in malignant transformation

Several mechanisms have been proposed to explain the role of the IGF axis in initiation and progression of neoplasia. Typical features of the IGF1R include potent antiapoptotic and mitogenic capacities, important roles in invasion, metastasis, and angiogenesis, and involvement in oncogenic transformation.[5,8,27,28] The IGF system, including IGF1R, is not oncogenic per se; the ligand-activated receptor is not genotoxic and is unable to induce mutations or other types of DNA damage. Rather, IGF-1 functions as a progression factor capable of pushing cells, including already transformed cells, through the cell cycle.

The idea that IGF1R expression is a prerequisite for acquisition of a malignant phenotype is widely accepted,[10] and is based on realisation that raised IGF1R levels and enhanced IGF signalling are indispensable for the cell to adopt proliferative and oncogenic pathways. However, this paradigm is not necessarily valid for every type of cancer. IGF1R overexpression is common in most paediatric tumours, which are often associated with recurrent chromosomal translocations, and in other solid tumours, such as brain and renal cancers, but the situation in adult epithelial tumours (eg, prostate and breast) is more complex. *IGF1R* is a target for oncogene and tumour suppressor action, and the mechanisms of action of several cancer genes (eg, *TP53*, *VHL*, *WT1*) involve transcriptional modulation of the *IGF1R* promoter or activation of the receptor tyrosine-kinase domain.[29]

BRCA1 and BRCA2 in hereditary breast–ovary cancer syndrome

Inactivating germline mutations within *BRCA1* and *BRCA2* are detected in a large proportion of families with inherited breast or ovarian cancer.[30] Mutation carriers have an increased lifetime risk of developing breast (40–85%) and ovarian (16–64%) cancer.[31,32] In most ethnically diverse, high-risk families, *BRCA1* germline mutations are private, family specific, and are scattered throughout the gene, with no particular hot spots. In Jewish Ashkenazi women, recurring mutations 185_186delAG and 5382_5383insC are the only molecular defects described in *BRCA1*.[33]

Complex regulation of BRCA1 and IGF1R

IGF1R has been identified as a molecular target for BRCA1 action.[29] Consistent with its tumour suppressor role, wild-type BRCA1 expression led to a marked decrease in *IGF1R* promoter activity and endogenous IGF1R levels in breast-cancer cell lines.[34] However, a mutant *BRCA1* encoding a truncated version of the molecule (185_186delAG) had no effect on IGF1R expression.[35] The paradigm that emerges is that activation of BRCA1 after DNA damage, oxidative stress, or other cellular insult could lead to transcriptional suppression of *IGF1R* expression, with an ensuing reduction in IGF1R activation by endocrine IGF-1 or locally produced IGF-1 or IGF-2. Abrogation of IGF1R signalling might favour apoptotic and cell-protecting pathways—ie, the prototypical mission of a tumour suppressor. In familial cancer, loss-of-function mutation of *BRCA1* might abolish its tumour protective function, leading to constitutive activation of the IGF1R signalling pathway, a typical hallmark of cancer cells. In addition to breast cancer, transcriptional suppression of the *IGF1R* gene by BRCA1 has been reported in prostate and endometrial cancer.[36,37]

Gel shift assays have not shown binding of BRCA1 to the *IGF1R* promoter, in accordance with studies showing that, in general, BRCA1 is not a DNA-binding protein. However, BRCA1 was able to bind with high affinity to zinc-finger protein SP1, a member of the transcription machinery, and prevent it from binding and transactivating the *IGF1R* promoter.[35] Additionally, the transcriptional activity of BRCA1 depends on the cellular status of P53. BRCA1 and P53 were shown to associate in coimmunoprecipitation assays, and BRCA1 was able to suppress *IGF1R* transcription in both P53-expressing and P53-null cellular backgrounds, but not in mutant P53-containing cells.[38] Therefore, loss-of-function mutation of the *TP53* gene, a common event in human cancer, might result in inability of BRCA1 to suppress *IGF1R* expression, with major clinical implications.

Although inactivating *BRCA1* germline mutations substantially increase breast and ovarian cancer risk, little is known about the cellular and circulating factors involved in regulation of *BRCA1* expression. Developmental analyses have shown that BRCA1 is highly expressed in rapidly proliferating cells,[39] and expression is stimulated by positive signals at the cell cycle point where cells become committed to replicating their DNA and undergoing cell division.[40] BRCA1 expression is high during the prereplicative (G_1) phase, and BRCA1 is involved in control of the G_1–S and G_2–M transition checkpoints.[41] Evidence of a close interplay between the IGF-1 and BRCA1 pathways was provided by studies showing that IGF-1 and IGF-2 enhance *BRCA1* expression in a dose-dependent manner.[42] Abrogation of BRCA1 action leads to roughly a doubling in the IGF-1-induced proportion of cells arrested at G_0, and a decrease of about a third in the proportion of cells at M phase.[42] Since IGFs regulate cell division by controlling events

that occur mainly during G_1, it is reasonable to assume that at least some IGF actions are mediated by BRCA1. Additionally, transfection experiments using *BRCA1* promoter fragments fused to a luciferase reporter showed that the effect of IGF-1 on *BRCA1* expression was mediated at the transcriptional level.[42] Similar to repression of the *IGF1R* promoter by BRCA1, activation of the *BRCA1* promoter by IGF-1 involves enhanced SP1 binding to *cis*-elements in the promoter. AKT, a downstream mediator of IGF-1 action, was shown to regulate BRCA1 stability independent of new protein synthesis, suggesting that IGF-1 signalling modulates BRCA1 abundance at various control levels.[43] These studies suggest that a feedback loop controls expression and action of the IGF-1 and BRCA1 signalling pathways in a synchronised manner. Deregulated expression of *BRCA1* as a result of aberrant IGF signalling might have consequences in breast cancer development.

BRCA1-mutant breast tumours show increased IGF1R expression

An association between somatic IGF1R expression and *BRCA1* status in breast cancer has been described.[44] Immunohistochemical analyses of 36 primary breast tumour specimens (11 tumours from patients with 185_186delAG *BRCA1* mutation and 25 specimens from patients who tested negative for four common *BRCA1* and *BRCA2* mutations) showed that IGF1R expression was twice as high in tumours from *BRCA1* mutation carriers as it was in tumours from non-*BRCA1* mutation carriers (ie, sporadic tumours). Additionally, surrounding healthy breast tissue from the *BRCA1* mutation carriers showed higher IGF1R levels than similar tissue from non-carriers.[44] The capacity of wild-type, but not mutant, BRCA1 to inhibit IGF1R biosynthesis might provide an explanation for the lower IGF1R levels seen in tumours from non-*BRCA1* mutation carriers, and for the reduced mitogenic activity in wild-type BRCA1-expressing cells (figure 1). Voskuil and colleagues[45] showed that concentrations of some IGF system components, including IGF1R mRNA, in healthy and malignant breast tissues were higher in individuals with a strong family history of breast cancer (usually associated with *BRCA1* or *BRCA2* mutations) than in individuals with no such history. Finally, support for the notion that BRCA1 can also control expression of the IGF-1 ligand was provided by studies showing that intratumoral IGF-1 concentrations were upregulated in tumours from *BRCA1* or *BRCA2* mutation carriers, compared with concentrations in matched sporadic tumours.[46]

Analysis of ER status in *BRCA1*-associated tumours showed that only 27% (three of 11) *BRCA1* mutation carriers were ER-positive, compared with 96% (24 of 25) non-carriers.[47] These results are concordant with extensive data showing that breast cancers in patients with *BRCA1* mutations are more often ER-negative than tumours from non-carriers.[48] Additionally, mutant *BRCA1* tumours are often progesterone receptor (PR) and HER2 negative (ie, triple negative), usually associated with P53 mutations, and present with a higher malignancy grade.[49] The absence of ER in mutant *BRCA1*-associated cancers might be evidence of hormone independence of *BRCA*-associated familial breast cancer.[48] Eerola and colleagues[50] reported that tumours from *BRCA1* or *BRCA2* mutation carriers aged 50 years or older differed from tumours in younger carriers in terms of histology, grade, ER, PR, P53, and HER2 status. These differences might reflect different biological behaviours and pathways of tumour development in older compared with younger *BRCA*-mutant patients, with a potential effect on prognosis and survival.

Role of steroid hormones in BRCA1 and IGF-1 action

The IGF-1 and BRCA1 signalling pathways are closely interconnected with cellular paths that mediate steroid hormone action. For example, BRCA1 inhibited the estradiol-inducible transcriptional activity of ERα in breast and prostate cancer cells, whereas cancer-associated *BRCA1*-mutant cells did not show inhibited ERα activity.[51,52] The reciprocal activity, enhancement of BRCA1 expression by oestrogens, seems to be a result of the mitogenic activity of oestrogens, although studies have suggested that estradiol directly stimulates the

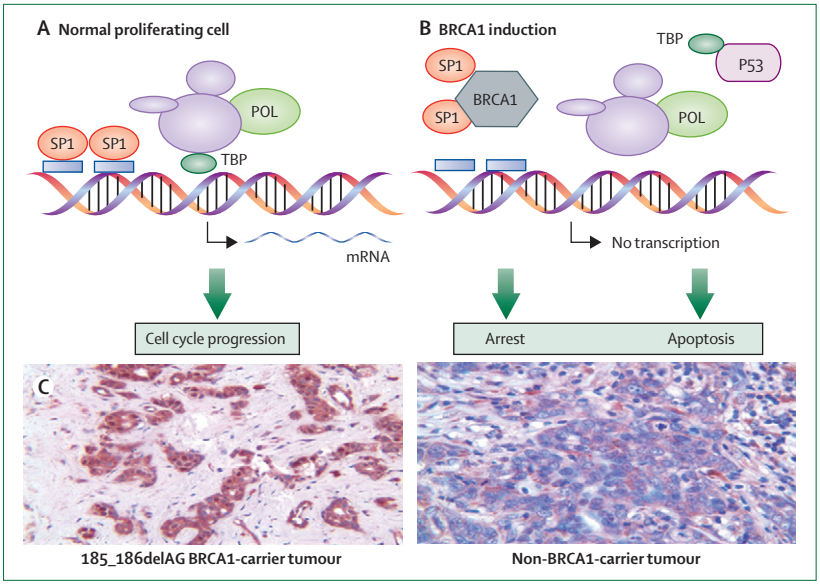

Figure 1: **Model for negative regulation of *IGF1R* gene expression by BRCA1**
(A) *IGF1R* expression is heavily dependent on a family of zinc-finger transcription factors, including SP1, which bind GC boxes in the proximal promoter region and stimulate gene transcription. TBP nucleates the basal transcription machinery at the initiator element, a promoter motif from which transcription starts in vivo. *IGF1R* expression is usually linked to cell cycle progression. (B) After DNA damage or other cellular insults, BRCA1 interacts with and prevents SP1 from binding to the *IGF1R* promoter, and P53 binds to TBP, disrupting formation of the transcription initiation complex. (C, D) Quantitative evaluation of IGF1R immunostaining revealed a higher score in 185_186delAG mutant BRCA1-associated tumours (C) than in tumours from non-carriers (D): mean 4·6 (SE 0·5) versus 2·6 (0·2); p<0·002. Panels C and D were reproduced with permission from reference 44. TBP=TATA-box binding protein. POL=RNA polymerase II.

BRCA1 promoter.[48,53] Likewise, oestrogens were shown to strongly transactivate the *IGF1R* promoter in ER-positive, but not ER-negative, breast cancer cells.[24] Chromatin immunoprecipitation assays revealed that part of oestrogen's effect on *IGF1R* expression was mediated through activation of the SP1 transcription factor. Combined clinical and experimental data emphasise the complexity of the functional interactions between BRCA1, IGF-1, and ER signalling pathways (figure 2), and the multifaceted biological regulation required to modulate these processes.

Is IGF-1 a breast-cancer risk modifier among *BRCA1* mutation carriers?

Risk estimates for breast cancer in women who carry mutations for *BRCA1* or *BRCA2* range from 20–80%, suggesting that penetrance of the *BRCA* genotype is dependent on genetic or environmental risk modifiers, or both.[54] The IGF-1 signalling pathway has been identified as an important modifier of BRCA1 action. Neuhausen and colleagues[55] did a single nucleotide polymorphism (SNP) analysis of *IGF-1, IGF1R, IGFBP-1, IGFBP-2, IGFBP-5,* and *IRS1* in a cohort consisting of 1122 *BRCA1* mutation carriers (433 breast cancer cases) and 543 *BRCA2* carriers (238 cases), and performed Cox proportional-hazards regression analyses for time from birth to diagnosis of breast cancer for mutation carriers. The study identified a significant association among *BRCA1* carriers between risk of breast cancer and linkage disequilibrium blocks in *IGF1R*. Among *BRCA2* carriers, a linkage disequilibrium block in *IGFBP-2* was associated with time to breast cancer diagnosis. No significant associations between breast cancer risk and linkage disequilibrium block were found for the other genes. In a second study, Neuhausen and colleagues[56] identified a significant association between breast cancer risk and linkage disequilibrium blocks in the *IGF-2* gene. A recent study based on 209 cases and 99 controls suggested that serum concentrations of IGF-1 might be a risk factor for breast cancer among *BRCA* mutation carriers.[57] However, no association between IGF-1 concentrations and early diagnosis in *BRCA* mutation carriers was reported in a Swedish cohort.[58] The pathophysiological mechanisms underlying these associations are unclear (panel).

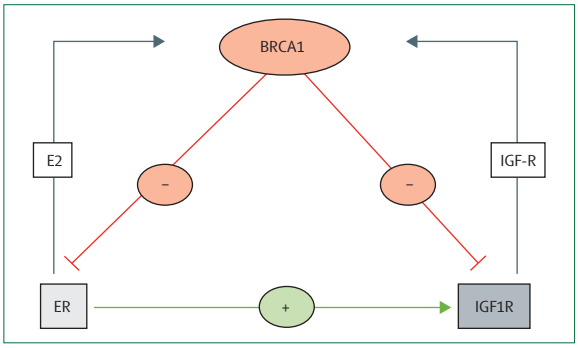

Figure 2: **Functional interactions between BRCA1, IGF-1, and ER signalling pathways**

Breast cancers in patients with *BRCA1* mutations are more often ER negative than tumours from non-carriers. Lack of ER in mutant *BRCA1*-associated tumours might reflect the fact that *BRCA*-associated breast cancers are usually hormone indepenent. The BRCA1, IGF-1, and ER signalling pathways are tightly interconnected, and feedback loops controlling the expression and action of these hormonal networks in a coordinated fashion have been identified.[24,35,42,51-53] Dysregulated expression of single components of this complex regulatory system might lead to amplified pathological outcomes. E2=oestradiol. IGF-1=insulin-like growth factor 1. ER=oestrogen receptor. IGF1R=IGF-1 receptor.

Klotho is a transmembrane protein that acts as a circulating hormone after shedding from the cell membrane. It has been identified as a candidate tumour suppressor in breast and pancreatic cancers. Wolf and colleagues[59] examined the role of klotho as a cancer-risk modifier, by investigating an association between KL-VS, a functional variant of klotho containing two aminoacid substitutions (Phe352Val and Cys370Ser), and breast cancer among Jewish Ashkenazi women with BRCA1 or BRCA2 mutations. Among *BRCA1* carriers, heterozygosity for the KL-VS allele was associated with increased risk of breast and ovarian cancer (hazard ratio [HR] 1·4 for each) and younger age at breast cancer diagnosis (median age 43 *vs* 48 years). Additionally, *klotho* and *BRCA2* are located at 13q12, and a linkage disequilibrium between KL-VS and *BRCA2* 6174delT mutation was noted.[59] Studies in breast cancer cells showed reduced inhibitory growth activity and reduced secretion of klotho Phe352Val compared with wild-type klotho.[59] Hence, klotho KL-VS can be considered a risk modifier for breast and ovarian cancer among *BRCA1* mutation carriers. Klotho has also been shown to modulate IGF-1 action; forced expression of klotho or addition of soluble klotho to cultured breast cancer cells inhibited activation of the IGF-1 pathway, and coimmunoprecipitation assays showed a physical interaction between klotho and IGF1R.[60] Therefore, the ability of klotho to modify cancer risk among *BRCA1* mutation carriers might reflect its biological interaction with the IGF-1 signalling pathway.

Metabolic consequences of the BRCA1–IGF-1 link

Hyperinsulinaemia and obesity are well known risk factors for breast cancer. The epidemiological correlations are very complex; obesity is associated with increased cancer risk in postmenopausal women, but not in premenopausal women.[21] However, it is unclear whether obesity and diabetes are associated with breast cancer risk in *BRCA1* or *BRCA2* mutation carriers. A recent comprehensive study analysed the medical histories of 6052 women with *BRCA1* or *BRCA2* mutations, half of whom developed breast cancer.[61] There was no excess of diabetes among patients with breast cancer in the period before diagnosis, compared with control individuals without cancer. However, there was a doubling in the risk of diabetes among *BRCA1* or *BRCA2* mutation carriers in

the 15-year period after diagnosis of breast cancer (compared with mutation carriers without breast cancer). The risk was even higher for women with a body-mass index higher than 25. Although the reason for this increased diabetes risk is unknown, the researchers postulated that the risk of diabetes might be associated with weight gain after cancer therapy.

In terms of insulin effects, mutant BRCA1 has been associated with increased lipogenesis due to relaxation of the inhibitory action of wild-type BRCA1 on acetyl-CoA carboxylase, a key enzyme in fatty acid synthesis.[62] Additionally, *BRCA* mutation carriers seem to have decreased blood IGFBP concentrations and sometimes lack an allele containing cytosine–adenine repeats in the *IGF-1* promoter, which has been linked to decreased insulin sensitivity.[48] The association between metabolic disorders, including diabetes and the metabolic syndrome, and *BRCA1* and *BRCA2* mutations warrants further investigation.

Panel: BRCA1–IGF-1 interactions

- IGF1R variants are associated with breast-cancer risk among *BRCA1* or *BRCA2* mutation carriers
- Risk of diabetes might be increased among patients with *BRCA1* or *BRCA2* breast cancer
- IGF1R expression is higher in breast tumours from *BRCA1* mutation carriers than in non-*BRCA1* (sporadic) tumours
- Intratumoral IGF-1 concentrations are upregulated in tumours from *BRCA1* or *BRCA2* mutation carriers
- Klotho, a candidate breast tumour suppressor, inhibits activation of the IGF-1 pathway
- Hypermethylation is an inactivating mechanism for BRCA1 expression
- *BRCA1* mutation status might affect IGF1R-directed therapies

Epigenetic control of *BRCA1* and *IGF1R*

Although the studies discussed here provide evidence of functional and physical interactions between the BRCA1 and IGF1R pathways at transcriptional and post-transcriptional levels, no studies so far have investigated the effect of epigenetic events on joint regulation of *BRCA1* and *IGF1R* expression and action. DNA methylation is a key epigenetic alteration affecting gene expression. Methylation of CpG islands leads to inactivation of transcription and has an important role in development. Promoter CpG island methylation of tumour suppressor genes is a classic hallmark of cancer and affects most cellular pathways, including genes involved in DNA repair and microRNAs. The relevance of DNA methylation in cancer diagnosis and management has been described. Developments in the area of DNA methylation include the potential identification of molecular markers for early detection, the discovery of epigenetic targets for therapy, and others.[63]

Several studies have examined possible methylation of the *BRCA1* promoter and the association between *BRCA1* methylation, gene expression, and cancer phenotype. For example, evaluation of the methylation status of a 600-bp region of the human *BRCA1* promoter, which contains 30 CpG sites, established that these sites were largely unmethylated in mammary epithelial cells, peripheral blood lymphocytes, and several sporadic breast-cancer cell lines.[64] However, one sporadic cancer cell line was roughly 60% methylated at all 30 CpG sites, in association with a substantial decrease in BRCA1 mRNA compared with normal breast cells.[64] An additional study detected hypermethylation of the *BRCA1* promoter in 51% of breast tumour biopsies, of which 67% did not express the protein.[65] These results suggest that hypermethylation could be considered an inactivating mechanism for BRCA1 expression, either as a first or second hit. A recent clinical study examined the potential methylation of *BRCA1* in peripheral blood cells of patients with sporadic breast cancer; *BRCA1* promoter hypermethylation was more common in circulating cells of patients with breast cancer than in healthy controls.[66] Additionally, an association between *BRCA1* methylation and a specific SNP (ACA/ACA genotype at Thr594) in *ESR1* (oestrogen receptor gene), usually associated with increased breast-cancer risk, was noted. Therefore, analysis of *BRCA1* methylation might provide relevant prognostic information.

Finally, bioinformatic analysis revealed the presence of multiple CpG islands in the human *IGF1R* promoter.[67] However, comprehensive analyses done in our laboratory did not detect *IGF1R* methylation in a series of prostate and endometrial cancer cell lines.[67,68] Nevertheless, methylation has an important role in control of *IGF2*. Specifically, loss-of-imprinting of *IGF2* leads to biallelic expression of the gene, providing a proliferative advantage to transformed cells by increasing the concentration of available IGF2 ligand.

MicroRNAs in regulation of BRCA1 and IGF1 pathways

MicroRNAs are short, non-coding RNAs that control gene expression by targeting mRNAs and triggering translation inhibition or degradation. Studies have identified several microRNAs that negatively control expression of various components of the IGF1 signalling pathway, as well as BRCA1, BRCA2, and associated genes.[69]

Chang and colleagues[70] showed that Arg1699Gln, a moderate-risk variant of BRCA1, does not impair DNA damage repair, but abrogates the repression of microRNA-155, a putative oncomir (ie, a microRNA associated with cancer). The investigators showed that BRCA1 epigenetically represses microRNA-155 expression via its association with histone deacetylase 2, which deacetylates histones H2A and H3 on the *microRNA-155* promoter. Furthermore, overexpression

Search strategy and selection criteria

We identified data for this Review by a systematic search of Medline with the terms "insulin-like growth factors", "IGF-1", "IGF-2", "IGF-1 receptor", "BRCA1", "BRCA2", and "breast cancer genes" for peer-reviewed basic and clinical studies. The search was limited to reports written in English. Since the *BRCA1* gene was first identified in 1994, our search was restricted to reports published between Jan 1, 1994, and April 30, 2012. The final reference list was selected on the basis of originality and scientific and clinical relevance.

of microRNA-155 accelerates the in-vivo growth of tumour cell lines, whereas knockdown of microRNA-155 attenuates growth. This study emphasises the complex (transcriptional, post-transcriptional, and epigenetic) interplay between microRNAs and BRCA1, and suggests that microRNA-155 is a potential therapeutic target for BRCA1-deficient tumours.

Can *BRCA1* status predict response to IGF1R-directed therapies?

The IGF1 axis, and particularly IGF1R, have emerged as promising therapeutic targets in oncology.[13] Initial phase 3 studies in unselected patients using monoclonal antibodies against IGF1R have been disappointing, highlighting the need to identify predictive biomarkers that can identify potential responders.[71] The effect of selective IGF1R-targeted therapies according to *BRCA1* or *BRCA2* mutational status has not been rigorously examined. Since BRCA1 exhibits a key role in DNA-damage repair mechanisms elicited by exposure to antitumour agents, the contribution of BRCA1 to cisplatin sensitivity was examined in HCC1937 cells (a BRCA1-null breast-cancer cell line) or BRCA1-reconstituted HCC1937/BRCA1 breast cancer xenografts in SCID mice.[72] Cisplatin treatment induced almost complete growth inhibition of BRCA1-defective xenografts, whereas BRCA1-reconstituted xenografts were only partially inhibited. Cell-cycle analysis showed an S and G_2–M blockade in BRCA1-defective cells. Furthermore, gene arrays identified perturbations of major proliferation and survival pathways, including IGF1 and ER. These results lend support to a recent study showing that endometrial cancer cells with high IGF1R levels are more likely to benefit from an anti-IGF1R-directed therapy than cells with reduced IGF1R levels.[73]

Conclusion

IGF1R has been identified as a potent antiapoptotic, prosurvival and, potentially, transforming receptor. These attributes positioned IGF1R at a crucial location on oncogenic maps. IGF1R has emerged as a promising therapeutic target; however, we need to identify biomarkers that can predict responsiveness to IGF1R-directed therapies.

Wild-type, but not mutant, BRCA1 can lead to transcriptional suppression of *IGF1R* expression (with ensuing reduction in IGF1R activation by circulating or local IGF-1 or IGF-2). Loss-of-function mutation of *BRCA1* in breast, ovarian, and other types of cancer might abolish its tumour protective action, leading to constitutive activation of the IGF1R signalling pathway. *BRCA1* expression is also regulated by several cellular events, including cell-cycle phase and ambient concentrations of IGF-1. Data presented in this Review emphasise the convergence of IGF1R-mediated cell survival, proliferative pathways, and BRCA1-mediated tumour protective pathways. Although these interactions have been mainly characterised in familial cancers (because of the high incidence of *BRCA1* or *BRCA2* mutations), it is clear that IGF1R and BRCA1 might also be involved in sporadic cancers. Elucidation of the complex interplay between these signalling pathways at the transcriptional, post-transcriptional, and epigenetic levels will enhance our understanding of basic molecular oncology processes and our ability to design and optimise cancer therapies.

Contributors

Both authors designed the report, searched the literature, and wrote the manuscript.

Conflicts of interest

We declare that we have no conflicts of interest.

Acknowledgments

HW's laboratory is supported by grants from the US-Israel Binational Science Foundation, Israel Science Foundation, Israel Cancer Association, Insulin-Dependent Diabetes Trust (IDDT; UK), and Israel Cancer Research Fund (ICRF; Montreal, Canada).

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