

Researchers from The Institute of Cancer Research (London, UK) investigated the *PALB2* gene in women with a family history of breast cancer that was not linked to *BRCA1* or *BRCA2*. Out of 923 women with breast cancer, ten were found to have faulty *PALB2* genes, compared with no faults found in 1048 healthy controls ( $p = 0.0004$ ); the mutations were found to confer a 2.3-fold increased risk of developing breast cancer (95% CI: 1.4–3.9,  $p = 0.0025$ ). Nazneen Rahman, lead author of the study, commented, “We estimate that faults in the *PALB2* gene contribute to around 100 cases of breast cancer in the UK each year. Interestingly, one of the ten breast cancer cases we identified as being linked to *PALB2* was a male breast cancer.”

It has long been known that a family history of breast cancer carries a slightly increased risk for the disease, particularly if two or more close relatives have been affected. Women with mutations of the well-known cancer-susceptibility genes *BRCA1* and *BRCA2* have a much higher chance of developing breast cancer (approximately 80%). However, faults in these genes only account for approximately 5–10% of all cases of breast cancer. Genetic testing is available for *BRCA1* and *BRCA2* mutations; the National Institute for Clinical Excellence (UK) recommends that only high-risk women (e.g., those with relatives who were diagnosed with breast cancer at a young age, with male relatives who have had breast cancer or with a family history of ovarian cancer) be referred to a specialist genetics service. Other genetic mutations that are associated with breast cancer are *CHEK2*, *ATM* and *BRIP1*, which confer a similar increased risk to *PALB2*. However, *PALB2* is the first low-risk gene found that interacts with *BRCA2*.

In addition to increasing the likelihood of developing breast cancer, a second study, also led by Rahman, found that children who inherit two faulty copies of *PALB2* have a recently identified aggressive subtype of Fanconi anemia, characterized by a high risk of childhood solid tumors, such as medulloblastoma and Wilms' tumor.

As we learn more about the genes responsible for breast and other cancers, it is hoped that this will lead to advances in cancer treatment and prevention.

Source: Rahman N, Seal S, Thompson D *et al.* *PALB2*, which encodes a *BRCA2*-interacting protein, is a breast cancer susceptibility gene. *Nat. Genet.* (2006) (Epub ahead of print).

### New target halts breast cancer cell proliferation

By inhibiting tumor necrosis factor- $\alpha$ -converting enzyme (TACE) in a breast cancer cell culture, researchers from the Lawrence Berkeley National Laboratory (CA, USA) have demonstrated a novel method of targeting epidermal growth factor receptor (EGFR) signaling.

Many anticancer agents have been developed with the aim of reducing high EGFR levels, as the EGFR is known to be important in cell division. Most research to date has focused on kinase antibodies or blockers. Approaching the problem from the idea that the tumor microenvironment, as well as genetic mutations in tumor cells, contributes to tumor cell growth, Pariaic Kenny and Mina Bissell discovered a protease (TACE; also known as a disintegrin and metalloproteinase [ADAM]17) that provides an oncogenic stimulus in the absence of proto-oncogene mutation. By blocking the actions of TACE, two critical growth factor proteins were immobilized. Previous studies of TACE have demonstrated that it acts like ‘molecular scissors’, releasing amphiregulin and transforming growth factor (TGF)- $\alpha$ , which activate EGFR. The inhibitory actions of TACE were demonstrated in a series of breast cancer cell lines. In addition, the researchers looked at existing patient-outcome data from 295 breast cancer patients and found that TACE expression correlates strongly with TGF- $\alpha$  expression and poor prognosis.

A new generation of TACE inhibitors is currently being developed for the treatment of rheumatoid arthritis. It is hoped that some of these drugs may also be tested against breast cancer. As EGFR is a significant factor in many other

forms of cancer (e.g., bladder, head and neck, colorectal, kidney and lung cancer), this latest research could potentially lead to a treatment against all EGFR-overexpressing tumors.

Source: Kenny PA, Bissell MJ. Targeting TACE-dependent EGFR ligand shedding in breast cancer. *J. Clin. Invest.* (2007) (Epub ahead of print).

### Targeting the niche in brain cancers with antiangiogenics

In the January issue of the journal *Cancer Cell*, two articles highlight the potential of antiangiogenic compounds in the treatment of brain tumors. Researchers at St Jude Children's Research Hospital (TN, USA) have identified niches of capillaries that surround tumors and protect and stimulate cancer stem cells (CSCs). Antiangiogenic drugs were shown to block the formation of new blood vessels in these niches, thereby inhibiting tumor growth. In the second article, the initial results from the Phase II trial of Recentin™ (AZD2171), an angiogenesis inhibitor, are reported as highly promising.

Richard Gilbertson and colleagues at St Jude's found that the number of CSCs surrounding a tumor was associated with the density of the system of capillaries; the denser the capillary network, the greater the number of CSCs.

“The finding that brain CSCs exist in protective vascular (blood vessel) niches helps explain the origin of brain tumors and suggests a new strategy for eliminating them,” said Gilbertson, codirector of the Neurobiology and Brain Tumor Program at St Jude and senior author of one of the papers.

When brain CSCs and human blood vessels cells were transplanted into mouse brains, the rapid formulation and growth of tumors occurred. However, when the CSCs were transplanted into mouse brains alone, tumor growth was much slower.

“Our data indicate that brain CSCs are nurtured by these vascular niches and that disrupting them blocks tumor growth by removing CSCs from