ALFRED GRECH
ALEXANDRA BALDACCHINO

ONCOGENE ADDICTION MIGHT BE THE ACHILLES HEEL IN CANCER - PART I

ABSTRACT

Multiple and complex genetic and epigenetic abnormalities underlie the multistage transformation of normal cells into cancerous ones. Among these abnormalities are the activation of oncogenes and loss of function of tumour suppressor genes. Besides these abnormalities, it is becoming evident that specific cancers are dependent on one or a few genes for their malignant phenotype, and this could be their 'Achilles heel'. This survival dependency of cancer cells on an activated oncogene or inactivation of tumour suppressor gene is called 'oncogene addiction' and may well be a potential way to provide more rational molecular targeted therapy. This strategy needs to integrate new approaches into the clinical setting in order to characterise the state of oncogene addiction and accordingly, apply more effective and selective anti-cancer therapies.

ONCOGENE ADDICTION: DEFINITION AND SUPPORTING EVIDENCE

Human cancer develops through a multistage process which can take decades to evolve. Such a process involves progressive accumulation of mutations and epigenetic aberrations in multiple genes.[1-4] For this reason, many cancer cells feature extensive disruptions in their genome. However, some human cancers seem to depend on one or a few genes to maintain their malignant phenotype. It is as if the cancer cells become 'addicted' to these genes and their products. Indeed, deactivating the implicated oncogene or re-activating the tumour suppressor gene can inhibit proliferation and growth of the cancer cells. Such behaviour has led to the introduction of the concept of 'oncogene addiction', first described by Weinstein et al. in 1997.[1]

Since then, several research papers have supported the role of oncogene addiction in the proliferation and survival of different types of cancer cells. Supporting evidence emerged mostly from studies carried out using (i) human cancer cell lines, (ii) genetically engineered mouse models of human cancer, and from (iii) clinical trials involving specific molecular targeted agents.

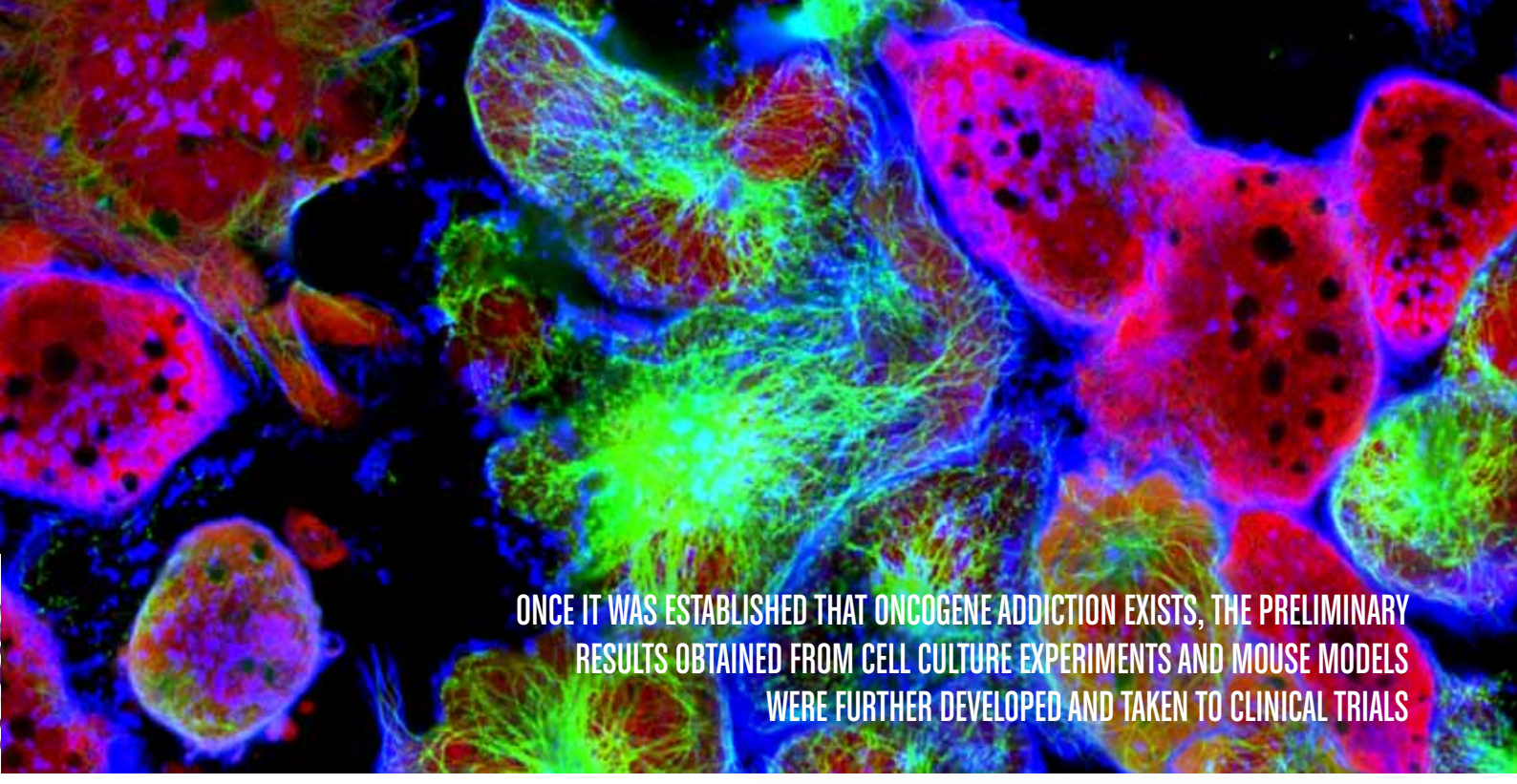
(I) STUDIES IN HUMAN CANCER CELL LINES

Throughout the years, established human cancer cell lines have been used as experimental models of human cancers. To address the role of oncogene addiction, some of these cell lines were treated with an antisense oligonucleotide, or an RNA interference (RNAi), directed to (and thus inhibiting) the respective oncogene. For instance, some investigations[5-7] targeted the cyclins, which play a key role in regulating the progression of cells through the phases of the cell cycle. One such investigation was carried out by Arber et al., who showed that the stable transfection of a cyclin D1 antisense construct in human colon cancer cells is associated with growth inhibition and decreased tumourigencity. Kornmann et al., who applied a similar approach, but used human pancreatic cancer cells instead, observed comparable results. Besides cyclin D1, other cyclins have also been targeted. Indeed, Li et al., through the use of a siRNA (small interfering RNA), showed that the depletion of cyclin E promotes apoptosis, and thus blocks cell proliferation, in hepatocellular carcinoma cells.

Oncogene addiction studies have targeted other oncogenes as well. For instance, Colomer et al.[8] showed that erbB-2 antisense oligonucleotides inhibit the proliferation of breast cancer cells. Similarly, inhibition of β-Catenin,[9] K-*ras*^{mut},[10] K-*ras*^{v12},[11] MITF,[12] and Mutant B-Raf,[13] all of which are involved in complex cell signalling pathways, has been shown to cause growth inhibition in other types of cancer cells.

(II) STUDIES IN GENETICALLY ENGINEERED MOUSE MODELS OF HUMAN CANCER

Further investigations into oncogene addiction have used genetically engineered mouse models of human cancer. Such models have been particularly useful when studying the *in vivo* mechanisms of oncogene addiction. Oncogenes or their products, such as *Bcr-Abl*,[14] c-*myc*,[15-18] erbB-2,[19] H-*ras*,[20] K-*ras*,[21] and Wnt-1,[22] have been targeted.



ONCE IT WAS ESTABLISHED THAT ONCOGENE ADDICTION EXISTS, THE PRELIMINARY RESULTS OBTAINED FROM CELL CULTURE EXPERIMENTS AND MOUSE MODELS WERE FURTHER DEVELOPED AND TAKEN TO CLINICAL TRIALS

For instance, Huettner et al. generated a conditional transgenic model of BCR-ABL-induced leukaemia, and discovered that this oncogene is required for both the induction and the maintenance of leukaemia. Similarly, D'Cruz et al. expressed the human c-MYC oncogene in the mammary epithelium of transgenic mice, and found that c-MYC expression results in the formation of mammary adenocarcinomas. Subsequently, when this gene was switched off, the cancer cells stopped dividing and underwent apoptosis. Other studies by Chin et al. and Jackson et al. showed that H-*ras* and K-*ras* are associated with tumour maintenance in skin and lung cancer, respectively. Together, these, and other studies, have shed more light into the concept of oncogene addiction.

(III) CLINICAL TRIALS INVOLVING SPECIFIC MOLECULAR TARGETED AGENTS

Once it was established that oncogene addiction exists, the preliminary results obtained from cell culture experiments and mouse models were further developed and taken to clinical trials. Targeted oncogenes included BCR-ABL,[23] EGFR,[24-26] HER-2,[27,28] and VEGF.[29,30]

One such clinical trial investigated the tyrosine kinase activity of BCR-ABL. Back in 1990, it was established that this kinase blocks apoptosis and triggers unregulated proliferation in chronic myeloid leukaemia (CML).[31] Thirteen years later, imatinib (Gleevec®, Novartis), a drug which blocks the tyrosine kinase activity of BCR-ABL, was successfully used in a clinical trial to treat CML.[23] Another tyrosine kinase inhibitor used in clinical trials is erlotinib,[25,26] which acts on the epidermal growth factor receptor (EGFR). EGFR is highly expressed in cancers such as non-small cell lung cancer and pancreatic cancer. Erlotinib is currently marketed in the EU as Tarceva® (Roche Registration Ltd).

In addition to small-molecule tyrosine kinase inhibitors, clinical trials have also made use of monoclonal antibodies. For instance, trastuzumab (Herceptin®) is a humanised monoclonal antibody that interferes with the human epidermal growth factor receptor (HER2) which is amplified in 25-30% of breast cancers.[27,28] Similarly, bevacizumab (Avastin®) inhibits vascular endothelial growth factor A (VEGF-A) which is a chemical signal that stimulates angiogenesis, especially in cancers such as breast and colorectal cancers. Together, these and other similar clinical trials have emphasised the 'addiction' of some cancers to one or a few genes for the maintenance of the malignant phenotype.

To be continued...