nature REVIEWS CANCER

Oncogene

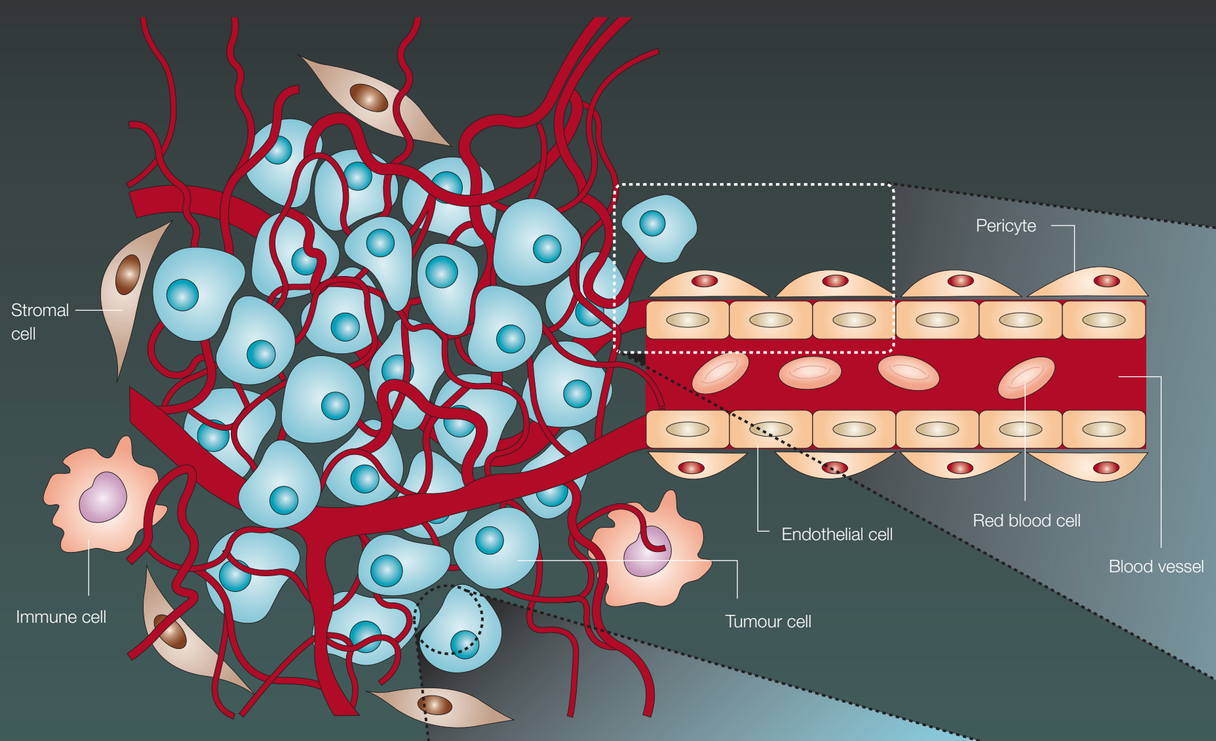
Targeting cancer pathways

NOVARTIS ONCOLOGY

Tumour formation and progression occur through a range of defects that develop both within and outside the cancer cell. Defects in cell-signalling pathways allow cancer cells to alter their normal programmes of proliferation, transcription, growth, migration, differentiation and death. Changes in the surrounding stroma and immune response allow the tumour to expand, form new blood vessels and spread to other organs. Many different anticancer agents have therefore been developed to target proteins that act in all of these pathways. Several agents — both small-molecule inhibitors and monoclonal antibodies (mAbs) — are on the market, and many more are in clinical trials or at earlier stages of development. The combined use of these inhibitors with standard anticancer treatments could allow researchers to attack tumours on many fronts.

The tumour

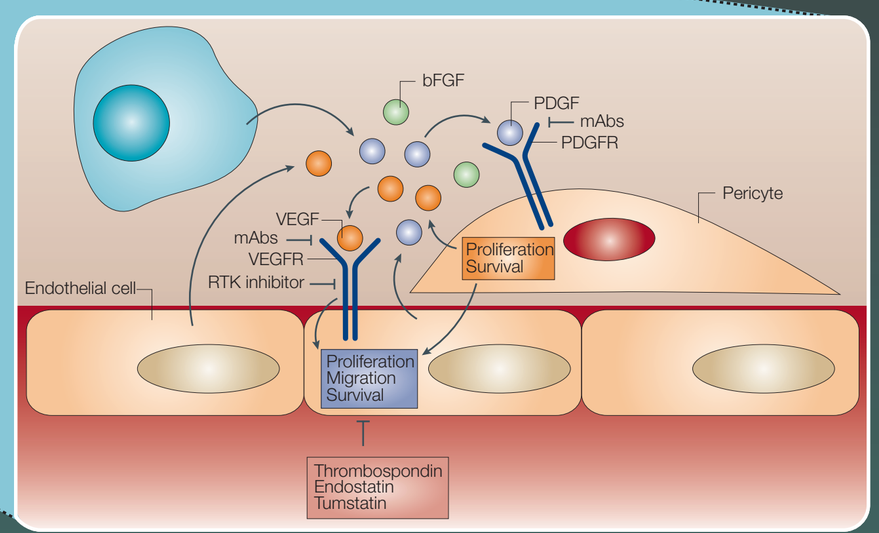
A tumour is composed of more than just cancer cells — it consists of an intricate network of cell types, including endothelial cells that comprise blood vessels and the stromal pericytes that stabilize the developing tumour vasculature. Many other cell types, including stromal cells and immune cells, also surround the cancer cells and influence their development. Anticancer agents are being developed against many of these cell types. Combination therapies that target more than one cell type might be particularly effective.



Angiogenesis

The development of tumour vasculature — angiogenesis — is important for progression of many tumour types, although tumours frequently form abnormal leaky vessels. Angiogenesis is induced by factors such as vascular endothelial growth factor (VEGF), basic fibroblast growth factor (bFGF) and platelet-derived growth factor (PDGF). VEGF receptors (VEGFRs) are expressed on the endothelial cells of the tumour vessels, whereas PDGF receptors (PDGFRs) are expressed by the pericytes that support blood-vessel growth. VEGF is produced by both pericytes and endothelial cells, and PDGF is produced by endothelial cells, so each cell type produces the growth factor that promotes proliferation and survival of the other cell type.

A number of mAbs and receptor tyrosine kinase (RTK) inhibitors have been developed to block these signalling pathways, and have been shown to slow tumour growth in preclinical and clinical studies. Endothelial cells also produce endogenous inhibitors of angiogenesis, such as thrombospondin, endostatin and tumstatin. These are also being developed as anticancer agents.

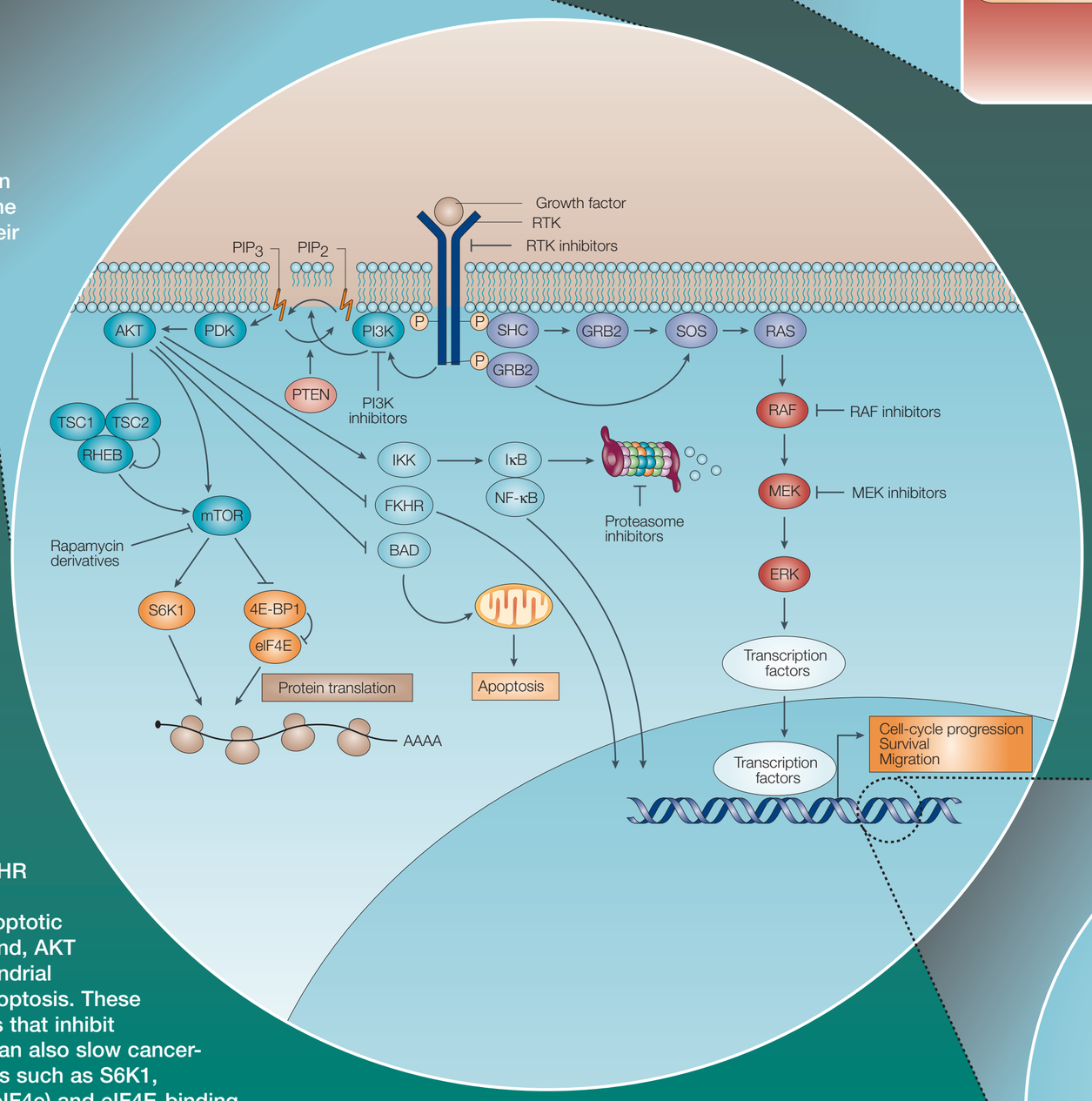


Tumour-cell pathways

Many of the signalling pathways involved in tumour-cell development are initiated by the interaction between growth factors and their receptors. These combinations include receptor tyrosine kinases (RTKs) such as human epidermal growth factor receptors (HER and EGFR family members) and their ligands, as well as insulin-like growth factor (IGF) and IGF1R. mAbs have been developed to disrupt the interaction between receptor and ligand, and small-molecule inhibitors inhibit their signalling pathways.

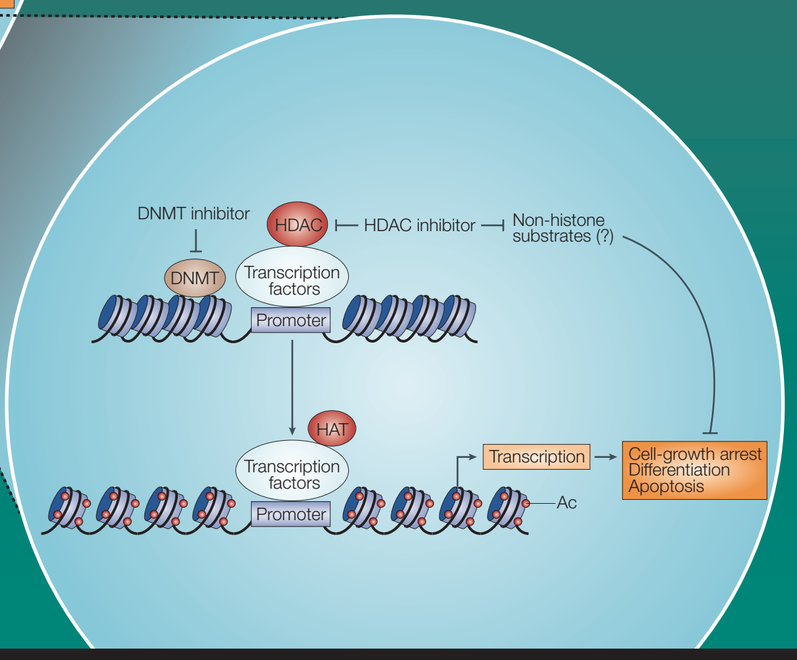
When an RTK binds its ligand, its tyrosine-kinase domain becomes activated, leading to its autophosphorylation (P) and signalling. Two of the most important pathways in tumour development involve RAS and phosphatidylinositol-3-kinase (PI3K)-mediated signalling. Many agents have been developed to disrupt these pathways, including RAF and MEK inhibitors, which block cancer cell proliferation. PI3K inhibitors promote apoptosis in at least two ways. First, they lead to the nuclear translocation of the FKHR transcription factor, which activates transcription of genes that encode pro-apoptotic factors such as BIM and FAS ligand. Second, AKT signalling regulates the activity of mitochondrial proteins such as BAD, which promotes apoptosis. These inhibitors, as well as rapamycin derivatives that inhibit mammalian target of rapamycin (mTOR), can also slow cancer-cell protein translation, mediated by factors such as S6K1, eukaryotic translation initiation factor 4E (eIF4e) and eIF4E-binding protein 1 (4E-BP1). PI3K inhibitors also disrupt transcriptional regulation by DNA-binding factors such as nuclear factor of κB (NF-κB), and this can also be affected by proteasome inhibitors, which have been found to selectively kill cancer cells. Crosstalk exists between these different pathways (not shown), and the inhibitors might also work by affecting non-linear pathways.

By altering these pathways, cancer cells can evade apoptosis, increase protein production, and activate transcription of genes that promote cell-cycle progression, survival and migration.



Chromatin modification

In addition to the transcription factors, a number of DNA and chromatin-modifying enzymes also regulate transcription of cancer-associated genes. Histone deacetylases (HDACs) and DNA methyltransferases (DNMTs) alter chromatin structure to prevent transcription, whereas histone acetylases (HATs) allow transcription initiation. HDAC inhibitors and DNMT inhibitors are being tested in preclinical and clinical trials for their ability to reactivate normal gene transcription in tumour cells. HDAC inhibitors might also have effects on non-histone substrates. These agents might be used together in the clinic, as they are suspected to work synergistically. Upregulated genes include tumour suppressors such as cyclin-dependent kinase (CDK) inhibitors.



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Combining the productivity of research scientists at facilities in the United States and Switzerland and the contributions of our commercial partners, Novartis Oncology is conducting a programme directed toward understanding the basic mechanism of malignancy from uncontrolled cell growth to angiogenesis and metastasis. The goal is to produce innovative new medicines that will extend and enhance the life of patients and improve the management of all types of cancer, particularly haematological cancers and cancers affecting the lung, breast, gastrointestinal and urogenital tracts.

Compounds in the Novartis pipeline encompass innovative platforms that target multiple pathways. For example, ongoing research efforts target growth-factor signal transduction to impact tumour-cell growth and apoptosis. This includes investigation into two tyrosine-kinase inhibitors: one, which is in Phase I development, targets EGFR, HER2 and VEGFR, whereas the other agent, which targets FLT3, is in Phase II trials.

Phase III research is being conducted with an anti-angiogenesis agent that blocks tumour vascularization to prevent tumour growth and metastasis and targets all VEGFR tyrosine kinases. Therapies are also being investigated in the cytotoxic and cell-cycle/apoptosis platforms to inhibit aberrant genetic processes that are responsible for malignant transformation. Research in cytotoxics includes Phase II trials that are being conducted into a microtubule-stabilizing agent and in an inhibitor of the enzyme topoisomerase I, while one other microtubule stabilizer is in Phase I development. Meanwhile, inhibitors of the mTOR kinase pathway and an inhibitor of histone deacetylase are in Phase II and Phase I trials, respectively.

By approaching oncology research from these multiple fronts, Novartis Oncology hopes to optimize the future treatment of patients with cancer.

For further information, please consult http://www.novartis.com
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