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Review article

Today's cancer research and treatment – highly sophisticated and molecularly targeted, yet firmly bolstered in the classical theories

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Abstract
Cancer research is linked to modern life-sciences, encompassing achievements in virology, yeast-biology, molecular-biology, genetics, systems-biology, bioinformatics, and so on. With these fascinating developments, it's easy to overlook that the fundamental theories and treatment strategies were established in the early 20th century and have remained valid ever since. Therefore, tribute must be paid to the founders of the field. The main hypotheses on carcinogenesis, the genetic model and the metabolic model, and the concept of cancer-treatment with cytotoxic, targeted or metabolic drugs were proposed more than 100 years ago by great minds such as T. Boveri, O. Warburg, and P. Ehrlich. Hence nothing about these cancer concepts is really new. Through development of powerful new technologies, we have been able to decipher the mechanisms of malignant transformation, thus significantly advancing the field. Our own studies have been focused on the cross-talk between cell-growth-signaling and lipid-metabolism in ovarian cancer to find crossover-points for co-targeting in order to achieve synergistic treatment effects. Notably, a side-effect of the application of current methods of molecular-cell-biology is a deeper knowledge of the laws of normal cell-biology and cell-life. Thus we anticipate the field will advance rapidly in the near future.

Keywords: Chemotherapy; Genetics; Metabolism; Molecular targeting; Oncogene; Tumor suppressor gene

Highlights:
- The original cancer theories from the early 20th century are still paradigmatic.
- The cancer gene/metabolic network reconciles genetic and metabolic cancer theories.
- The cancer gene/metabolic network provides numerous targets for cancer drugs.
- Old cytostatics vs. modern targeted drugs – are they really that different?
- Molecular biology yielded a unified cancer theory and highly effective therapies.

Abbreviations:
ACC, acetyl-CoA carboxylase; ACLY, ATP citrate lyase; AMPK, AMP-activated protein kinase; DAG, diacylglycerol; EGFR, epidermal growth factor receptor; FASN, fatty acid synthase; FAT, CD36, fatty acid translocase; G6PD, glucose-6-phosphate dehydrogenase; GLS, glutaminase; GLUT, glucose transporters; GSK3, glycogen synthase kinase-3; HIF-1, hypoxia-inducible factor-1; HK2, hexokinase-2; LDH, lactate dehydrogenase; PFK, phosphofructokinase; PFKFB, 6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase; PI, phosphatidylinositol; PI3K, phosphatidylinositol 3-kinase; PIP, PI phosphate; SIRT4, sirtuin-4; SREBP, sterol regulatory element-binding protein; TAZ, tafazzin; TIGAR, TP53-induced glycolysis and apoptosis regulator; YAP, yes-associated protein

Introduction

Overall, research on neoplastic diseases is now around 250 years old, and today's cancer research is based on fundamental ideas and concepts that emerged in the early years of the 20th century. When it comes to the major milestones in cancer research, we are now in an era of important anniversaries. It's been around 100 years since two geniuses proposed two independent theories of cancer. In 1914, Theodor Boveri was the first to link the genome to malignant transformation by framing a chromosomal theory of cancer (Boveri, 1914). Ten years later, Otto Warburg reported that cancer cells use much more glucose than normal cells (Warburg et al., 1924). Even in the presence of oxygen they exhibit hyperactive glycolysis, a trait now known as aerobic glycolysis or the 'Warburg

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effect'. Warburg was the first to recognize that cancers have a characteristic cancer-metabolism phenotype. Another great oncologist was Sidney Farber, the founder of modern cancer chemotherapy. About 75 years ago, he was the first to successfully use the folate antagonist, aminopterin, against leukemia (Farber and Diamond, 1948). Further progress was made quickly, and approximately 50 years ago former U.S. president Richard Nixon officially declared the 'War on Cancer', making ample funds available to spur cancer research (National Cancer Institute (1971), National Cancer Act of 1971). Around that time, the first molecular targeted cancer therapy was developed (Cole et al., 1971), and just 10 years later, the first oncogene, *SRC*, was fully sequenced (Czernilofsky et al., 1980). In addition, about 20 years ago, evidence emerged that many prominent oncogenes control metabolic pathways (Osthus et al., 2000). Therefore, the two views of cancer as a genetic disease or as a metabolic disease can now be easily reconciled. Below we briefly describe both concepts, highlighting advances in these areas and how these have impacted the development of cancer therapeutics.

Cancer research is applied molecular cell biology and genetics

Modern cancer research would not have been possible without the numerous recent advances in cell biology and molecular genetics. By comparing normal and malignant cells, how they manage to balance their chemical and energetic needs, how they grow, multiply, cope with stress, age and die, researchers were able to uncover many of the intricate mechanisms of malignant transformation and cancer development. Remarkably, however, the basic hypotheses of carcinogenesis and malignant progression were put forward long before the disciplines of cell biology and molecular genetics emerged. In the meantime, these hypotheses have been turned into theories and confirmed on countless occasions.

Genetic theory of cancer

The now prominent oncogene/tumor suppressor gene model belongs to this important group of theories, whose origins date back to 1914. At that time, Theodor Boveri had already formulated his gene theory of cancer (Boveri, 1914). However, no further significant progress was made until the year 1953, when Watson and Crick presented the molecular structure of the DNA double helix. For the first time, this made it possible to assign a functional gene to an unambiguous molecular structure. The real heyday of genetic cancer theories began around the year 1970 when the first oncogenes and tumor suppressor genes were identified. This was also roughly the time that the concept of molecular targeted therapy was born, for oncogenes were soon considered powerful molecular cancer targets and it was hoped that this class of genes would include key growth regulators that represent the Achilles heel of cancer that has long been sought in cancer treatment and which needs to be targeted. In the subsequent years, many signaling pathways were discovered. With more and more details uncovered, the ensembles of pathways – once considered linear – turned out to be intricately woven networks of signaling cascades. Pharmacological targeting of specific molecular hubs in those chemical networks which have been considered crucial for cancer cell survival yielded novel drugs with high therapeutic efficacy. Unfortunately, however, complete cures for many cancers remain far out of reach. The main obstacle is drug resistance, thus it is now common practice to combine molecular targeted drugs with classical cytotoxic chemotherapeutics to improve treatment outcomes (Wang et al., 2021).

Metabolic theory of cancer

Scientific interest in cancer cell metabolism also dates back to the early years of the 20th century. In 1924 Otto Warburg observed for the first time that cancer cells consume high amounts of glucose – not only when oxygen is scarce but also when it is abundant. Cancer cells typically conduct glycolysis in both the absence and presence of oxygen (aerobic glycolysis or 'Warburg effect') (Warburg et al., 1924). The molecular reasons for this uncommon behavior have long been discussed and are still not fully elucidated, although several explanations have been offered over the decades. Due to the predominance of the oncogene/tumor suppressor gene model, relatively little attention has been paid to metabolic theories of cancer for many years. However, around the year 2000, significant molecular crosstalk between oncogenic pathways and cancer cell metabolism was identified. Major roles in this game have been assigned to prominent oncogenes and tumor suppressors such as MYC, RAS, HIF-1 and others (Osthus et al., 2000; Park et al., 2020). This has led to a reactivation of Warburg's old insights and a revival of studies in the field of cancer cell metabolism (Seyfried et al., 2014). The combination of current knowledge from both areas (molecular cancer genetics and cancer cell metabolism) has led to a much deeper understanding of cancer cell biology (Park et al., 2020).

Combining both theories – the oncogene-metabolism connection

The realization that oncogenes and tumor suppressor genes regulate metabolic enzymes and pathways made it possible to relate and ultimately combine both theories into a unified theory of cancer. Some of the most prominent oncoproteins have been identified as crucial regulators of pathways of the central carbon metabolism. RAS, for instance, has been described as regulating glucose uptake and glutamine metabolism. Phosphatidylinositol 3-kinase (PI3K) and AKT signaling have been found to modulate crucial steps of glycolysis, pentose phosphate pathway, glutamine metabolism, and fatty acid synthesis. Moreover, MYC and the context-dependent oncogenes Yes-associated protein (YAP) and tafazzin (TAZ) are regulators of glycolysis, glutamine metabolism, glycosylation, serine/glycine synthesis, one-carbon metabolism, and folate cycle. The hypoxia-inducible factor-1 (HIF-1) protein controls glycolysis and fatty acid uptake, and the oncogenic transcription factor sterol regulatory element-binding protein (SREBP) regulates fatty acid synthesis. Tumor suppressor proteins also bear several metabolic regulators. TP53, by far the most prevalent tumor suppressor protein, interferes with cellular import of glucose and with the downstream pentose phosphate pathway, whereas sirtuin-4 (SIRT4) controls glutamine metabolism, and AMP-activated protein kinase (AMPK) and glycogen synthase kinase-3 (GSK3) interact with fatty acid synthesis. Here are a few specific examples in more detail. The RAS/PI3K/AKT cascade inhibits glycogen synthesis by blocking GSK3 and supports glycolysis by activation of hexokinase-2 (HK2), 6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase (PFKFB), and HIF-1alpha. RAS downstream signaling stimulates lipid metabolism and histone acetylation by the activation of ATP citrate lyase (ACLY) and SREBP, respectively (Grunt, 2018; Wagner et al., 2017). RAS signaling stimulates glutamine metabolism by upregulating MYC. The latter is an activator of glycolysis, pentose phosphate pathway and glutamine metabolism in its own right as it upregulates glucose transporters (GLUT), HK2, phosphofructokinase (PFK), glucose-6-phosphate dehydrogenase (G6PD), and glutaminase (GLS), respectively. On the other hand, the tumor suppressor

TP53 inhibits glucose catabolism by downregulating GLUT and lactate dehydrogenase (LDH) and inducing TP53-induced glycolysis and apoptosis regulator (TIGAR). Meanwhile, AMPK inhibits synthesis and activates the uptake of fatty acids by blocking acetyl-CoA carboxylase (ACC) and upregulating fatty acid translocase (FAT, CD36), respectively (Park et al., 2020). Thus, it became evident that cancer genes directly control metabolic genes, their products, and functions. These data provide at least a partial explanation for the widely observed occurrence of specific metabolic features characteristic of the cancer cell phenotype.

Cancer research and cancer drug treatment, from the early days to the present

Advances in cancer research over the past century have had a major impact on strategies to combat the disease, and the development of various cancer treatment approaches accurately reflects the progress. Next, we will present three groups of anticancer drugs that appear to work through fundamentally different mechanisms, but on closer inspection it becomes clear that this is not the case at all; some of the differences lie more in the way drugs are developed than in the molecular mechanisms of action of the drugs. The three groups include classic cytotoxic chemotherapy drugs, targeted molecular drugs, and metabolic drugs.

First cancer drugs

Alkylating agents represent the oldest group of anticancer drugs and are still the most used agents in chemotherapy. These drugs act directly on DNA; they covalently connect adjacent bases lying on the same (intrastrand cross-link) or on opposite DNA strands (interstrand cross-link), cause abnormal base pairing, or induce DNA strand breaks. These alterations interfere with DNA replication and thus block the cell cycle and subsequent cell division. Nitrogen mustard (mechlorethamine, nitrogen lost) was the first of these types of drugs. Its anticancer activity was identified by chance in 1942, during World War II. It was the first anticancer chemotherapeutic drug ever. Since then, a plethora of derivatives with improved features such as chlorambucil, melphalan, cyclophosphamide, and steroidal nitrogen mustards have been developed (Singh et al., 2018). A few years later, Sidney Farber identified and attempted to manipulate another biochemical process on which cancer cells depend. This was the birth of the antimetabolites. Specifically, he searched for folic acid analogs that would antagonize the growth promoting effects of folic acid (vitamin B_9). This led to the development of aminopterin in 1948 and later to its derivative methotrexate (Weber, 2015). Both compounds disrupt a very complex process called the folate cycle, which along with two other subcycles (the methionine cycle and the choline cycle) make up the one-carbon pathway. This metabolic process is required for biosynthesis of purines and thymidine, of the amino acids glycine, serine, and methionine, and for epigenetic maintenance of protein and DNA methylation patterns (Friso et al., 2017). Nucleoside analogs are another group of antimetabolites. The first drug in this group, cytarabine, was introduced in cancer chemotherapy in the late 1950s. Its mechanism of action is direct interference with DNA synthesis. In cytarabine, a cytosine is linked to arabinose instead of glucose. It is incorporated into replicating human DNA, but subsequent elongation of the nascent DNA strand cannot be maintained, leading to S-phase arrest (Sun et al., 2019).

Old chemotherapy versus modern molecular drug targeting and metabolic targeting – what is the difference between these approaches?

The concepts of attacking cancer cells with toxic chemicals (chemotherapy) or targeting specific characteristics (molecular drug targeting) such as metabolic activities (metabolic targeting) of these cells with so-called 'magic bullets', were originally developed by Paul Ehrlich at the turn of the 19th and 20th century. Therefore, neither concept deserves to be called 'modern' and opposed to 'older' strategies. According to the definition by the U.S. National Cancer Institute, 'Chemotherapeutic drugs/therapies are treatments with drugs to stop cancer growth either by killing cells or blocking cell division' (National Cancer Institute; Chemotherapy). Whereas 'Molecular targeted drugs/therapies are treatments that target molecules involved in the growth/spread of cancer cells, with few side effects' (National Cancer Institute; Molecularly targeted therapy). These definitions sound pretty plain. Of course, both approaches interfere with molecules that are associated with processes crucial to cancer cells: they stop growth or kill the cancer cells. Overall, chemotherapeutic cytotoxic drugs ('chemo' for short) are not as untargeted as the common terminology would suggest. So, how do they differ to molecular targeted drugs ('targeted' for short)? There are a few key features distinguishing both classes. Chemo drugs interfere with the normal cell cycle. They eradicate already existing cancer cells, show general cytotoxicity, and are usually only identified in large screenings by chance. In contrast, targeted drugs may be considered as a subtype of the chemo drugs. They preferentially inhibit cancer cells, meaning they primarily prevent the proliferation of cancer cells, while non-malignant cells are less affected. Most importantly, however, the development of molecular targeted drugs requires detailed prior knowledge and in-depth understanding of cancer cell biology (Schulenburg et al., 2010). The advent of molecular targeted treatment has thus been causally linked to the rise and progress of molecular cancer cell biology. The first targeted drug for use in cancer treatment, known as tamoxifen, was introduced as early as 1971. It is a partial anti-estrogen for the treatment of estrogen receptor-positive breast cancer (Cole et al., 1971). It therefore seems that the major difference lies in the nature of the approach to drug development. The old chemo approach did not require detailed knowledge of the molecular biology of cancer and was focused on basic life-saving mechanisms of both malignant and non-malignant cells. These cytotoxic drugs have typically been identified by non-targeted functional screening assays of large chemical libraries. In contrast, the targeted approach only became possible after gaining detailed understanding of the molecular mechanisms of malignant transformation and cancer progression, enabling a focus on specific molecular aberrations and carcinogenic pathways not present in normal cells. The molecular targeted approach of anticancer drug development is typically hypothesis-driven. With the recent revival of studies in the field of cancer cell metabolism, another type of targeted cancer drug has come to the fore – the metabolic drug. As discussed above, a compound that interferes with metabolic pathways in cancer cells is by no means a new treatment approach; some of the very first chemotherapy drugs were antimetabolites. The only major distinguishing feature of the new metabolic drugs seems to lie in the strategy of their development, which is again based on the principles and techniques of molecular targeting.

Harnessing cancer metabolic pathways for treatment

In general, unlike normal cell metabolism, cancer cell metabolism has the typical attributes of a stress-response metabolism. Unlike normal cells, metabolically blocked cancer cells cannot permanently retreat into the G_0 phase of the cell cycle. These specifics can be exploited for the development of metabolic cancer therapeutics. A significant number of such drugs are already approved for clinical use, including compounds that disrupt nucleotide metabolism and DNA replication. Examples comprise pemetrexed, 5-fluorouracil, hydroxyurea, gemcitabine, fludarabine, 6-mercaptopurine, and methotrexate. They target thymidylate synthase, ribonucleotide reductase, DNA synthesis, phosphoribosyl pyrophosphate amidotransferase, and dihydrofolate reductase, respectively (Stine et al., 2022). In addition, several other compounds that disrupt critical nodes in central carbon metabolism are currently in clinical use or in the development pipeline. Another group of effective drugs are the biguanides, which include metformin, phenformin, and IM156. These drugs block oxidative phosphorylation by interfering with respiratory chain complexes I and IV. The same mechanism applies to the small molecule IACS-010759. Other compounds, like the lipoic acid derivative CPI-613, interfere with enzymes of the tricarboxylic acid cycle. Moreover, sulfasalazine, CB-839, IPN60090, and DRP-104 are agents that disrupt hyperactive glutamine metabolism. In contrast, AZD-3965 blocks the export of lactate by binding to monocarboxylate transporter 1. This enzyme pumps lactate out of the cells. Lactate, the end product of aerobic glycolysis, is toxic to the cells. The cells thus need to dispose of lactate for survival. Two novel drugs, ivosidenib and enasidenib, selectively block the mutant but not the wild-type forms of isocitrate dehydrogenase 1 or 2 (IDH1 or 2). While wild-type IDH1 and 2 generate the metabolite alpha-ketoglutarate, mutant IDH1 and 2 give rise to 2-hydroxyglutarate. This intermediate of the tricarboxylic acid cycle is an oncometabolite and causes cell transformation. Lipid metabolism is also a target of several small-molecule inhibitors, including the ACLY specific compound bempedoic acid, and the FASN inhibitors Fasnall and TVB-2640. Another group of compounds known as statins interfere with the mevalonate pathway by inhibiting its key enzyme hydroxymethylglutaryl-CoA reductase. Many of these compounds are efficient against a variety of hematologic and solid malignancies (Stine et al., 2022).

Combination of drugs targeting oncogenic signaling with drugs that disrupt cancer cell metabolism

The crosstalk concept

Cells receive a variety of extracellular signals (e.g., hormones, nutrients, stress-related factors). Upon entering the cells, these stimuli interact with receptor molecules and are processed into chemical forms that can be interpreted by the intracellular signaling system, which in turn regulates the metabolic network. This molecular crosstalk between cell signaling and cell metabolism ultimately determines the cell phenotype. In cancer, cell signaling becomes increasingly autonomous and hyperactive, independent of external stimuli. Ultimately, this process leads to a transformation of the metabolic system to produce the characteristic malignant cell phenotype, which includes high growth rate and rapid cell division, increased cell survival, and loss of cell differentiation. Two strategies are available to reverse this phenotype. Reduction of hyperactive signaling or normalization of cell metabolism – or both at the same time. In other words, combining molecular targeted drugs that inhibit oncogenic signaling with therapeutics that specifically interfere with metabolic functions to achieve a synergistically enhanced treatment effect would be a promising approach (Fig. 1).

Co-targeting epidermal growth factor receptor (EGFR) signaling and lipid metabolism – a novel strategy against ovarian cancer

Experimental and clinical evidence indicates that overexpression of oncogenic receptors of the epidermal growth factor receptor-family (EGFR/HER1, HER2, HER3 and HER4) correlates with high levels of fatty acid synthase (FASN). This suggested that EGFR downstream signaling interacts with the fatty acid synthesis pathway. FASN is the key enzyme for the *de novo* production of long-chain saturated fatty acids (Cai et al., 2015; Menendez et al., 2021; Tomek et al., 2011). In ovar-

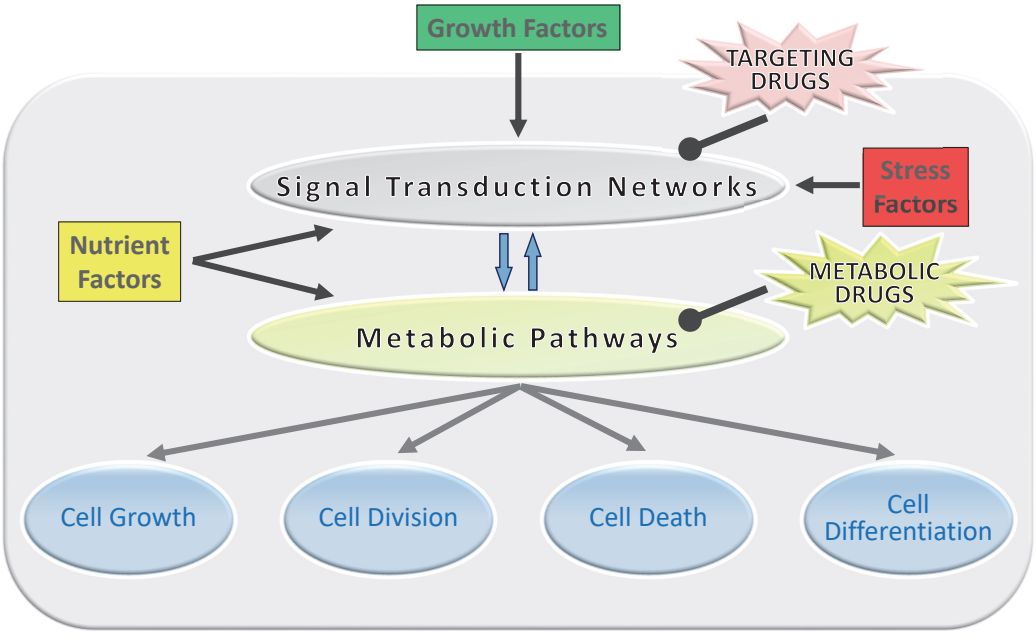

Fig. 1. Metabolism interacts with signaling and determines the cell phenotype

ian cancer, increased growth inhibition was observed when FASN and EGFR or HER2 were blocked simultaneously (Grunt et al., 2009; Wagner et al., 2017). Furthermore, expression of FASN was downregulated when EGFR or HER2 protein function was blocked by small-molecule inhibitors or when EGFR or HER2 mRNA expression was knocked-down by specific siRNAs. Conversely, EGFR and HER2 were downregulated when FASN enzyme function was impaired using FASN specific inhibitors. This clearly indicated that a close crosstalk regulates both systems in ovarian cancer (Grunt et al., 2009; Wagner et al., 2017). Further in-depth analyses revealed that downregulation of FASN by inhibitors of the EGFR family is due to reduced expression of SREBP-1c. This transcription factor is a downstream target of the EGFR-PI3K-mTORC1 signaling cascade and controls the expression of several lipogenic enzymes, including FASN (Swinnen et al., 2000). On the other hand, pharmacological or genetic abrogation of fatty acid synthesis leads to depletion of membrane lipid rafts, these membrane domains harbor many receptor tyrosine kinases. Blockade of FASN also reduced recruitment of the adaptor protein GRB2 to EGFR, caused depletion of the signaling lipids diacylgly-cerol (DAG), phosphatidylinositol (PI), and PI phosphate (PIP), decreased posttranslational activation of RAS by blocking RAS palmitoylation, and stimulated HIF-1alpha and AMPK. Altogether, FASN targeting drugs and siRNAs silence EGFR-PI3K-mTORC1 signaling using a whole panel of different molecular mechanisms (Grunt et al., 2009; Tomek et al., 2011; Wagner et al., 2017). In contrast to the PI3K cascade, the second major EGFR downstream route, the MAPK/ERK1/2 cascade, was found not to be diminished by FASN inhibitors in ovarian cancer. Accordingly, combined treatment with MAPK inhibitory drugs together with FASN targeting compounds yielded synergistic inhibition of cell growth in ovarian cancer, whereas combination with PI3K specific drugs did not improve the growth inhibition induced by FASN specific drugs. Altogether, these findings provide rationales for combined treatment of ovarian cancer using FASN specific therapeutics together with MAPK/ERK1/2 signaling inhibitors (Wagner et al., 2017).

Conclusion

Contemporary cancer research is one of the most fascinating and dynamic areas of life-science research. Over the last fifty years, we have witnessed a wealth of groundbreaking new discoveries – and progress continues at breathtaking speed. After the end of World War II, cytotoxic chemotherapy drugs that disrupt cell replication became available. Then, the elucidation of the chemical nature and structure of the DNA double helix, the carrier of the entire genome, paved the way for the advancement of molecular cell biology. This new discipline enabled a wealth of important discoveries, ushering in the era of oncogene- and tumor suppressor-research, followed by signal transduction-research and the advent of pharmacological research and development of targeting drugs, which today encompass an incredible variety of compounds specific for a multitude of regulatory proteins, including oncogenes, signaling proteins, hormones, angiogenic effectors, and epigenetic modifiers (Grunt et al., 2009; Harant et al., 1993; Rogers-Broadway et al., 2019; Tomek et al., 2011; Wagner et al., 2017). This group of novel therapeutics revolutionized clinical oncology and is now available for combination with traditional cytotoxic chemotherapeutics. Despite these successes, which have greatly expanded the therapeutic options, some types of cancer are still incurable and there remains much to be done.

Authors' contribution

Thomas W. Grunt conceived the topic, designed the study, conducted the literature research and data analysis, and wrote the manuscript.

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Ethical aspects and conflict of interest

The author declares that he has no known competing financial interests or personal relationships that could have influenced the work reported in this paper.

References

Boveri T (1914). Zur Frage der Entstehung maligner Tumoren. Jena: Gustav Fischer, pp. 29–32.

Cai Y, Wang J, Zhang L, Wu D, Yu D, Tian X, et al. (2015). Expressions of fatty acid synthase and HER2 are correlated with poor prognosis of ovarian cancer. Med Oncol 32: 391. DOI: 10.1007/s12032-014-0391-z.

Cole MP, Jones CT, Todd ID (1971). A new anti-oestrogenic agent in late breast cancer. An early clinical appraisal of ICI46474. Br J Cancer 25: 270–275. DOI: 10.1038/bjc.1971.33.

Czernilofsky AP, Levinson AD, Varmus HE, Bishop JM, Tischer E, Goodman HM (1980). Nucleotide sequence of an avian sarcoma virus oncogene (src) and proposed amino acid sequence for gene product. Nature 287: 198–203. DOI: 10.1038/287198a0.

Farber S, Diamond LK (1948). Temporary remissions in acute leukemia in children produced by folic acid antagonist, 4-aminopteroyl-glutamic acid. N Engl J Med 238: 787–793. DOI: 10.1056/NEJM194806032382301.

Friso S, Udali S, De Santis D, Choi SW (2017). One-carbon metabolism and epigenetics. Mol Aspects Med 54: 28–36. DOI: 10.1016/j.mam.2016.11.007.

Grunt TW (2018). Interacting Cancer Machineries: Cell Signaling, Lipid Metabolism, and Epigenetics. Trends Endocrinol Metab 29: 86–98. DOI: 10.1016/j.tem.2017.11.003.

Grunt TW, Wagner R, Grusch M, Berger W, Singer CF, Marian B, et al. (2009). Interaction between fatty acid synthase- and ErbB-systems in ovarian cancer cells. Biochem Biophys Res Commun 385: 454–459. DOI: 10.1016/j.bbrc.2009.05.085.

Harant H, Korschineck I, Krupitza G, Fazeny B, Dittrich C, Grunt TW (1993). Retinoic acid receptors in retinoid responsive ovarian cancer cell lines detected by polymerase chain reaction following reverse transcription. Br J Cancer 68: 530–536. DOI: 10.1038/bjc.1993.381.

Menendez JA, Papadimitropoulou A, Vander Steen T, Cuyàs E, Oza-Gajera BP, Verdura S, et al. (2021). Fatty Acid Synthase Confers Tamoxifen Resistance to ER+/HER2+ Breast Cancer. Cancers 13: 1132. DOI: 10.3390/cancers13051132.

National Cancer Institute (1971). National Cancer Act of 1971. [online] [cit. 2024-03-30]. Available from: https://www.cancer.gov/about-nci/overview/history/national-cancer-act-1971

National Cancer Institute. Chemotherapy. [online] [cit. 2024-03-30]. Available from: https://www.cancer.gov/publications/dictionaries/cancer-terms/def/chemotherapy

National Cancer Institute. Molecularly targeted therapy. [online] [cit. 2024-03-30]. Available from: https://www.cancer.gov/publications/dictionaries/cancer-terms/def/molecularly-targeted-therapy

Osthus RC, Shim H, Kim S, Li Q, Reddy R, Mukherjee M, et al. (2000). Deregulation of glucose transporter 1 and glycolytic gene expression by c-Myc. J Biol Chem 275: 21797–21800. DOI: 10.1074/jbc.C000023200.

Park JH, Pyun WY, Park HW (2020). Cancer Metabolism: Phenotype, Signaling and Therapeutic Targets. Cells 9: 2308. DOI: 10.3390/cells9102308.

Rogers-Broadway KR, Kumar J, Sisu C, Wander G, Mazey E, Jeyaneethi J, et al. (2019). Differential expression of mTOR components in endometriosis and ovarian cancer: Effects of rapalogues and dual kinase inhibitors on mTORC1 and mTORC2 stoichiometry. Int J Mol Med 43: 47–56. DOI: 10.3892/ijmm.2018.3967.

Schulenburg A, Brämswig K, Herrmann H, Karlic H, Mirkina I, Hubmann R, et al. (2010). Neoplastic stem cells: current concepts and clinical perspectives. Crit Rev Oncol Hematol 76: 79–98. DOI: 10.1016/j.critrevonc.2010.01.001.

Seyfried TN, Flores RE, Poff AM, D'Agostino DP (2014). Cancer as a metabolic disease: implications for novel therapeutics. Carcinogenesis 35: 515–527. DOI: 10.1093/carcin/bgt480.

Singh RK, Kumar S, Prasad DN, Bhardwaj TR (2018). Therapeutic journery of nitrogen mustard as alkylating anticancer agents: Historic to future perspectives. Eur J Med Chem 151: 401–433. DOI: 10.1016/j.ejmech.2018.04.001.

Stine ZE, Schug ZT, Salvino JM, Dang CV (2022). Targeting cancer metabolism in the era of precision oncology. Nat Rev Drug Discov 21: 141–162. DOI: 10.1038/s41573-021-00339-6.

Sun F, Li N, Tong X, Zeng J, He S, Gai T, et al. (2019). Ara-c induces cell cycle G1/S arrest by inducing upregulation of the INK4 family gene or directly inhibiting the formation of the cell cycle-dependent complex CDK4/cyclin D1. Cell Cycle 18: 2293–2306. DOI: 10.1080/15384101.2019.1644913.

Swinnen JV, Heemers H, Deboel L, Foufelle F, Heyns W, Verhoeven G (2000). Stimulation of tumor-associated fatty acid synthase expression by growth factor activation of the sterol regulatory element-binding protein pathway. Oncogene 19: 5173–5181. DOI: 10.1038/sj.onc.1203889.

Tomek K, Wagner R, Varga F, Singer CF, Karlic H, Grunt TW (2011). Blockade of fatty acid synthase induces ubiquitination and degradation of phosphoinositide-3-kinase signaling proteins in ovarian cancer. Mol Cancer Res 9: 1767–1779. DOI: 10.1158/1541-7786.MCR-10-0467.

Wagner R, Stübiger G, Veigel D, Wuczkowski M, Lanzerstorfer P, Weghuber J, et al. (2017). Multi-level suppression of receptor-PI3K-mTORC1 by fatty acid synthase inhibitors is crucial for their efficacy against ovarian cancer cells. Oncotarget 8: 11600–11613. DOI: 10.18632/oncotarget.14591.

Wang Z, Meng F, Zhong Z (2021). Emerging targeted drug delivery strategies toward ovarian cancer. Adv Drug Deliv Rev 178: 113969. DOI: 10.1016/j.addr.2021.113969.

Warburg O, Posener K, Negelein E (1924). Über den Stoffwechsel der Carcinomzelle. Biochemische Zeitschrift 152: 309–344.

Weber GF (2015). DNA Damaging Drugs. In: Cham (Ed.). Molecular Therapies of Cancer. Springer, pp. 9–112. DOI: 10.1007/978-3-319-13278-5_2.