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ABOUT COVER

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REVIEW

Targeting metabolism: A potential strategy for hematological cancer therapy

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Abstract

Most hematological cancer-related relapses and deaths are caused by metastasis; thus, the importance of this process as a target of therapy should be considered. Hematological cancer is a type of cancer in which metabolism plays an essential role in progression. Therefore, we are required to block fundamental metastatic processes and develop specific preclinical and clinical strategies against those biomarkers involved in the metabolic regulation of hematological cancer cells, which do not rely on primary tumor responses. To understand progress in this field, we provide a summary of recent developments in the understanding of metabolism in hematological cancer and a general understanding of biomarkers currently used and under investigation for clinical and preclinical applications involving drug development. The signaling pathways involved in cancer cell metabolism are highlighted and shed light on how we could identify novel biomarkers involved in cancer development and treatment. This review provides new insights into biomolecular carriers that could be targeted as anticancer biomarkers.

Key Words: Metabolism; Metastasis; Hematological cancer; Biomarker; Cancer; Anticancer

Core Tip: Hematological cancer is a type of cancer in which metabolism plays an essential role in progression. We provide a summary of recent developments in the understanding of metabolism in hematological cancer and provide a general understanding of biomarkers currently used and under investigation for clinical and preclinical applications involving drug development. This review provides new insights into biomolecular carriers that could be targeted as anticancer biomarkers.

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INTRODUCTION

Resistance to cancer therapy is diverse and multifactorial, and is the most difficult challenge in oncology. Although the early phase of treatment is often successful, resistance 75% characterized by relapse, anti-tumoral drug desensitization, or even aggressive spread 75% can develop. Many studies have investigated the basis of tumorigenesis, progression, and drug resistance, and over the last decade, the diverse roles of host cells in promoting cancer development and progression have been comprehensively studied. Different biomarkers serve as cancer drug targets and as diagnostic markers, and distinct cancer-related signaling pathways involved in tumor progression have been characterized. An increasing number of data indicate that cancer therapy can induce host-mediated local and systemic responses, many of which modify the equilibrium of the tumor microenvironment, facilitating or supporting tumor progression, as well as resistance to antitumor treatment. Most hematological cancer-related relapses and deaths are caused by metastasis; thus, the importance of this process as a therapeutic target should be considered. Metastatic tumor cells that arrive in distant tissues, surrounded by unfamiliar cells and a foreign microenvironment, are likely to die; however, those that survive can generate metastatic tumors with markedly different biology from that of the primary tumor.

This review describes recent advances in understanding how tumor progression is precisely tuned by signaling pathways, how these regulators control therapeutic outcome, the mechanisms that regulate the metabolism in hematological cancer, and the biomarkers currently used and under investigation for clinical and preclinical applications involving drug development. Evaluating the host response and the biological targets for cancer therapy is key to the development of precision medicine in oncology.

CANCER SIGNALING PATHWAYS

Hypoxia signaling in cancer and approaches to enforce tumor regression

Cancer cells progress as a consequence of genetic alterations of signaling pathways that promote cell growth and survival, whereas their expansion relies on nutrient storage. Oxygen limitation is central in control of neovascularization, glucose metabolism, survival, and tumor spread. This pleiotropic action is orchestrated by hypoxia-inducible factor (HIF), which is a master transcriptional factor in nutrient stress signaling[1]. HIF-1α is recognized as an important cancer drug target, despite its location and expression pattern. Many recent studies have shown promising evidence to correlate HIF-1α and tumor metastasis, angiogenesis, poor prognosis, and drug resistance. Low oxygen supply (or hypoxia) is a common characteristic in solid tumors. Since an adaptive response to hypoxic stress is triggered, tumor cells undergo several survival activation pathways to initiate their essential biological processes in ways that are different compared with normal cells. Recent findings at both cellular and molecular levels rule out a role for the HIF-1α pathway and its downstream signalosome as a crucial cancer cell survival pathway. Targeting the HIF-1α pathway has been challenging due to its expression level, location, and drug accessibility, but promising progress has been made in the past 20 years. This section attempts to summarize the role and regulatory mechanism of HIF-1α during cancer development, and recent therapeutic approaches specifically targeting this important pathway[1].

HIF-1α is the most studied of the HIF proteins, and the roles of other HIF-1 subunits remain elusive in cancer cells related to intracellular pH regulation, metabolism, activation, invasion, autophagy, apoptosis, and necrosis. Targeting HIF is a focus of efforts to develop novel anticancer therapies. There are many new therapeutic approaches to accelerate necrotic cell death (not apoptosis, which is considered to inhibit cancer cell growth) and tumor regression by targeting metabolism within the microenvironment and downstream signaling[2] (see Figure 1A).

Recent research suggests that induction of HIF proteins in normoxic conditions (oxygen tensions between 10%-21%) is likely to have serious consequences, such as chronic inflammation or pathological symptoms[3]. Chronic inflammation is self-perpetuating, distorting the microenvironment as a result of aberrantly active transcription factors[4]. As a consequence, alterations in growth factors, chemokines, cytokines, and reactive oxygen species balance occur within the cellular milieu that enable the growth and survival needed for *de novo* development of cancer and metastasis[5]. It is thought that understanding the crosstalk between two key transcription factors, nuclear factor-kappaB (NF-κB) and HIF, will greatly enhance the process of drug development[6].

HIF activity is also involved in angiogenesis that is required for tumor growth, so HIF inhibitors, such as phenethyl isothiocyanate and acriflavine, have been under investigation for anticancer effects[7,8].

HIF signaling pathways in metabolic regulation

Different metabolic regulatory mechanisms affect the functions of HIF, highlighting the possibility that HIF activation alters the metabolic signatures in cancer, and disordered metabolism triggers HIF-1α activation of HIF. HIF hydroxylation was assumed to be regulated by the Krebs cycle product 2-oxoglutarate (2-OG), which is a substrate in reductive amidation/oxidative deamidation. The latter is further catalyzed by glutamate dehydrogenase[9]. It is likely that substrates like 2-OG become metabolic signal receivers by modulating HIF hydroxylase function. In parallel, 2-OG decreases in the cytosol in the absence of amino acid complementation related to the activation of prolyl hydroxylase domain protein 2. This signaling pathway is dependent upon mammalian target of rapamycin complex 1 (mTORC1), although the mechanism by which the low concentration of 2-OG could alter the HIF hydroxylase function in the context of cancer remains elusive[10].

Besides activation by multifactorial stimuli, including stress and danger signals, the HIF signalosome complex is activated by different antitumor molecules and signaling pathway oncogenes. The most striking observation concerns mutation of the tumor suppressor von Hippel-Lindau protein[11]. This ubiquitin E3 Ligase subunit targets HIF-α and is responsible for regulating ubiquitin-mediated protein degradation *via* the proteasome pathway[12].

The Ras/Raf/MAPK signaling pathway is affected by the activity of HIF-1α, and regulated by transactivation by several coactivators, such as cyclic AMP response-element-binding protein (see Figures 1B and 1C). In addition, different kinases, such as p42/p44 MAPK or p38, all contribute to the activation of HIF when transcription factor p300 is also transactivated in the nuclei for p300-induced gene expressions[13]. Diverse interactions between HIF-1α and p53 tumor suppressor pathways have been recently reported, but the results are controversial; p53 induction and activation have also been shown to suppress HIF activity in some aspects of cancer. In particular, different modes of interactions between p53 and HIF-1α show differential outcomes by adopting different molecular complexes and different signaling pathways[14].

Despite HIF-1α activation in cancer cells targeting a group of metabolic enzymes, signaling energy regulators and transporters suggest that HIF contributes to the Warburg effect (described in detail below). Several studies (mostly using murine models) have shown that upregulated glycolysis continues independently of HIF-1α expression[15]. Experiments on the mechanisms of oncogenes and tumor suppressors have revealed a large spectrum of crosstalk comprising glycolysis regulation and oncogenic glycolytic activation, and these could result in HIF-1 activity *in vitro* and *in vivo*[16]. Therefore, the enzymes that target HIF-1α in the glycolytic pathway suggest that HIF is involved in different canonical and noncanonical pathways leading to glycolysis upregulation in cancer, mimicking the Warburg effect, without being restricted by mitochondrial involvement (see Figure 1A).

Triple pathways involving PI3K–Akt/Ras–ERK/mTORC1 as examples of oncogenic signaling pathways for tumor progression

Many of the genes commonly mutated in cancer, especially during proliferative growth under aerobic glycolysis (or under the Warburg effect), generate subproducts by regulating the PI3K-Akt and Ras-ERK pathways in the early stages of tumor development from benign tissue. These pathways are differentially activated in response to hormone or cytokine signaling exclusively elicited from cell surface receptors, cytosolic receptors, and integrin molecules, which can bind to adhesion receptors (see Figures 1C and 1D). However, genetic alterations from chromosomal defects, genomic errors, transcriptomic dysfunction, and even epigenetic disorders can lead to constitutive signaling, like an oncogene signaling pathway without on-off control, in the absence of stimuli[17].

The PI3K-Akt pathway is activated through amplification or activating mutations acting on PI3K-Akt-pathway molecules, such as type I PI3K isoform PIK3CA (p110a), Akt, and the Akt signaling pathway regulator and adaptor protein PIK3R1, among others, or through splicing deletion or signaling-induced inactivation of the phosphatases hydrolyzing PI3K products acting on the phosphatase and tensin homolog and INPP4B tumor suppressors. Therefore, diverse mutations in the tumor suppressors tuberous sclerosis complex (TSC)1 and TSC2 are activated *via* signaling controlled by mTORC1[18] (see Figure 1D). The latter is indeed one important target molecule in PI3K-Akt signaling.

The Ras-ERK signaling pathway is induced through Ras mutations, or the homologous molecule Raf, which constitutively activate these proteins. Alternatively, inactivation of GTPase-activating proteins, including RASAL2 and NF1, could also lead to Ras activation (see Figure 1B)[19]. An important downstream target of Ras-ERK signaling is the transcription factor Myc. Notably, Myc (*i.e.*, c-Myc) as a transcription factor promotes transcriptionally important enzymes for survival and proliferation, and therefore, mutations that alter the Ras-ERK pathway can, when activated, amplify gene expression to promote cancer cell proliferation[20].

In addition to the specific mutations described above, other mutations can act *via* the Ras-ERK and PI3K-Akt pathways, including those that mutate the structure of oncogenes, trigger gene over-amplification, and cause fusion protein products in these cancers or proliferation-related signaling

pathways. For example, mutations of kinases, such as epidermal growth factor receptor (EGFR) and ErbB2 [examples of receptor tyrosine kinases (RTKs)], fibroblast growth factor receptor, and platelet-derived growth factor receptor (PDGFR), can be frequently detected in cancer patients. Mutations of oncogenes for G protein-coupled receptors provide another pathway to activate them[21].

Deregulated synthesis of growth factors also plays an important role in almost all cancers. Incorrect mRNA splicing-based growth factors in cancer cells expressing the appropriate receptor leads to an autocrine loop, driving persistent signaling that lacks a stop signal. Alternatively, these signaling molecules involved in carcinogenesis can be produced by proximal cells (*via* paracrine stimulation). Both possibilities involve the Ras-ERK or PI3K-Akt signaling pathways. AKT signaling is also multipotent, as it can interact with glycogen synthase kinase 3 to be recruited to mitochondria-related cell death *via* the FAS/FASL axis. AKT signaling also negatively controls the cancer suppressor gene for p53[22].

NF-κB in cancer development and progression

The earliest evidence implicating pathogen-induced NF-κB activation in the development of cancer was the existence of the reticuloendotheliosis virus T viral oncogene that causes avian reticuloendothelial lymphomatosis[23], and v-Rel, which shares a Rel transactivation domain with the mammalian homologs NF-κB1, NF-κB2, RelA (p65), cRel, and RelB to compose the NF-κB complex[24] (see Figure 1E).

Different oncogenes from the oncocytic viruses are key activators that are responsible for NF-κB activation in cancer T lymphocytes[25]. The cells, under such restricted response, promote cell proliferation, survival, and inflammation, contributing to the pathogenesis of lymphomas and adult T-cell lymphoblastic leukemias.

Human papillomavirus viral proteins E6 and E7 that inactivate p53 and Rb tumor suppressor genes have also been involved in NF-κB activation, and are associated with carcinogenesis of the larynx, oropharynx, and cervix. Hepatitis B and C viruses lead to hepatocellular carcinoma, and *Helicobacter pylori* generates ulcerative colitis and gastrointestinal carcinoma, where NF-κB activation is triggered [26].

Major chemical and physical carcinogens implicated in the initiation and/or promotion of human cancer can also activate NF-κB. Specifically, nicotine and carcinogens in tobacco and betel nut (Areca catechu), have been demonstrated in the pathogenesis of head and neck and lung cancer, inducing AKT and NF-κB and promoting cell proliferation and survival and inflammation[27]. Nicotine has been reported to directly activate these pathways *via* nicotinic receptors and AKT, whereas chemotherapy and radiation-induced DNA damage have been reported to induce NF-κB activation *via* nuclear to cytoplasmic signaling mechanisms involving SUMOylation of the IκB kinase complex. tumor necrosis factor-α/interferon-γ (IFN-γ), radiation, and certain chemotherapeutic drugs also induce NF-κB activation and several target antiapoptotic genes (*TRAF*, *IAP*, *BCL*-2 and *Bcl-XL*) that protect cells from therapeutic injury by these efficient chemical antitumor agents.

Warburg effect, a metabolically regulated mechanism of cancer cell proliferation

Cancer cells can grow with a high rate of glycolysis followed by lactic acid fermentation, even in the presence of abundant oxygen. They can even proliferate in a hypoxic microenvironment. This condition requires cancer cell mitochondria and related apparatus to shut down all the processes of cellular respiration[28]. The energy that supports this growth is provided by aerobic glycolysis. This phenomenon is opposite to the Pasteur effect in that the energy of aerobic glycolysis is dependent on mitochondrial oxidation. The Warburg effect shows that cancer cell energy under such circumstances is supported *via* aerobic glycolysis after mitochondrial dysfunction[29]. Cellular respiration occurs by metabolism of glucose to pyruvate and is independent of the tricarboxylic acid cycle, which is replaced by lactate dehydrogenase, which converts glucose into lactic acid that is excreted into the extracellular environment. This leads to the increased generation of additional metabolites that may particularly benefit proliferating cells.

Although the Warburg effect has been studied extensively since its discovery in 1924, its precise nature remains unclear, which hampers research of its therapeutic potential. The Warburg effect forms the basis of positron emission tomography, in which a radioactive glucose analog is injected and can be detected at higher concentrations in malignant tumors compared with healthy tissues[30].

The Warburg effect may simply be considered a consequence of mitochondrial damage in cancer, *via* an adaptation mode for low-oxygen environments within tumors. Cancer genes working as a network, help to shut down the mitochondrial functions that could be actively involved in cancer cell apoptosis [31]. In some cancers, this effect could be due to the presence of mutations in the tumor suppressor genes involved in regulation of glycolytic enzymes within mitochondria, including the M2 splice isoform of pyruvate kinase. For example, mutations in TP53 affect energy metabolism and increase glycolysis in breast cancer and colorectal carcinoma (CRC)[32]. The Warburg effect is associated with tightly regulated glucose uptake and utilization, which indicates how mitochondrial activity is regulated. Tumor cells present with increased rates of glycolysis, which can be manifested as mitochondrial damage[33].

MAJOR HEMATOLOGY CANCER TYPES

Leukemia

Leukemia is characterized by a large increase in the numbers of leukocytes in the circulation or bone marrow. Leukemia is defined as acute or chronic, and as myelogenous, lymphocytic, or mixed phenotype. Acute leukemia affects immature cells; the disease develops rapidly, with symptoms including anemia, fever, bleeding, and swelling of the lymph nodes. In chronic leukemia, the cells develop and are transported to the tissues, but the cells do not function normally.

Acute myeloid leukemia (AML) is a disorder characterized by a clonal proliferation derived from primitive hematopoietic stem cells or progenitor cells. Acute lymphoblastic leukemia (ALL) is the most common cancer found in children. When ALL develops from T cells, it is called T-ALL. T-ALL represents 15% of pediatric ALL and 25% of adult ALL[34].

Chronic myeloid leukemia is a clonal myeloproliferative neoplasm characterized by a genetic change called the Philadelphia chromosome. More than 95% of cases with chronic lymphocytic leukemia involve B lymphocytes, with the expression of CD19, CD23, CD21, CD24, and CD40, as well as CD5[35].

Growing evidence shows that deregulation of PI3K/AKT/mTORC1 signaling contributes to the pathogenesis of leukemia. Upregulated mTORC1 and mTORC2 activity has been reported to play a critical role in leukemia initiation, propagation and relapse[36-41]. mTOR constitutive activation is usually found in leukemia patients, which contributes to chemoresistance, disease progression, and unfavorable prognosis. Constitutive NF-κB activation protects tumor cells from apoptosis and plays a crucial role in the acquisition of resistance to chemotherapy[42,43]. Constitutive NF-κB activation frequently occurs in patients with leukemia[44].

Lymphoma

Lymphoma is a type of blood cancer that affects the lymphatic system. Abnormal lymphocytes become lymphoma cells, which are found in the lymph nodes, spleen, thymus, bone marrow, and other parts of the body[45]. The two main types of lymphoma are Hodgkin's lymphoma (HL) and non-HL (NHL). The differences in these two types are certain unique characteristics of the different lymphoma cells. In NHL, PI3K/AKT/mTOR upregulation is found frequently[46]. HL cells also have unchecked PI3K pathway activation[47]. HL cells in classical HL patients show the constitutive activity of both the canonical and noncanonical NF-Kb signaling pathways[48].

Multiple myeloma

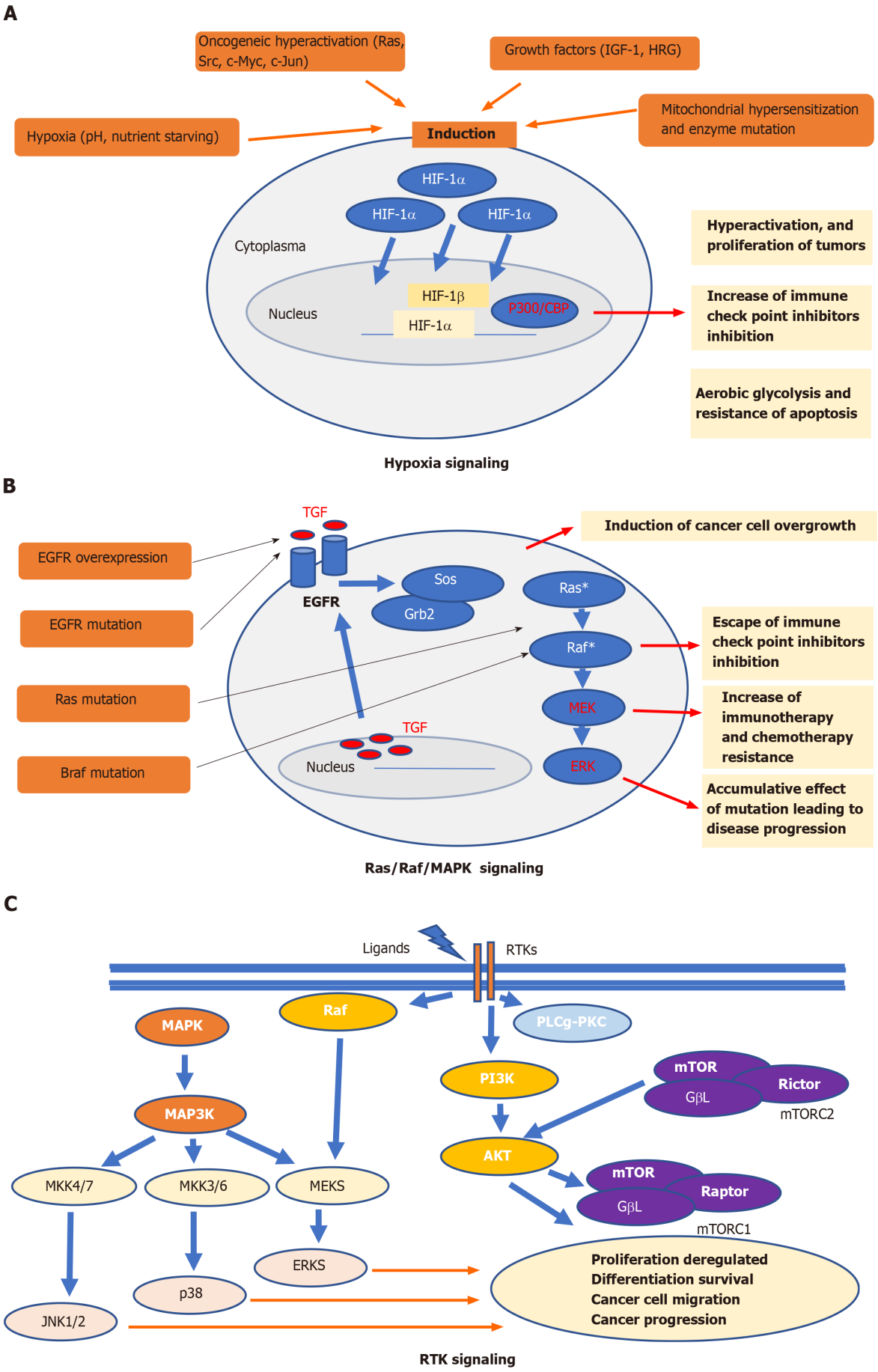
Multiple myeloma is a cancer of the plasma cells. Plasma cells are white blood cells that normally produce antibodies. The activated mTOR signaling pathway is regarded as an essential pathway associated with disease progression[49]. The deregulated activity of the NF-κB family of transcription factors has also been implicated in the pathogenesis of multiple myeloma, with multiple signals through the canonical and noncanonical arms to activate the NF-κB system in myeloma cells. In fact, NF-κB signaling promotes proliferation, survival and drug resistance of myeloma cells[50].

TARGETS FOR THE METABOLIC SIGNALING PATHWAY FOR HEMATOLOGICAL CANCERS

Target for the PI3K/AKT/mTOR pathway

Since mTOR functions as a point of convergence between a nutrient-sensing pathway (*via* mTORC1) and as a regulator of AKT itself (*via* mTORC2), mTOR plays an important role in controlling cellular metabolism and energy homeostasis in normal and cancer cells, which is fundamental in developing effective therapies for leukemia. Several molecules that target the PI3K/AKT/mTOR signaling pathway have been investigated, showing potential therapeutic efficacy in hematological cancers, alone or in combination with chemotherapeutic drugs.

Rapamycin, an immunosuppressant and antiproliferative agent, strongly inhibits mTORC1 activity. Rapamycin forms a complex with a FK506 binding protein 12 (FKBP12), and this complex directly interacts and inhibits mTORC1, leading to cell cycle arrest and apoptosis. Rapamycin demonstrates antileukemic activity in AML blast cells, and in combination with etoposide (a topoisomerase inhibitor) shows a synergistic effect in an AML mouse model[51]. An mTORC1/2-specific inhibitor blocks AKT phosphorylation in AML cell lines and blast cells, suppresses activation of two regulator proteins S6K (S6 Kinase 1) and eukaryotic translation initiation factor 4E-binding protein 1 (4EBP1) and elicits potent antileukemic effects[52]. NVPBEZ235, a strong inhibitor of PI3K and mTORC1/2 complexes, shows strong inhibitory effects on leukemia cell proliferation and survival[53]. The emergence of compensatory mechanisms induced by long-term treatment of primary AML blast cells with PI3K/AKT/mTOR inhibitors has been discovered[54]. These mechanisms involve the upregulation of RTKs (insulin-like growth factor receptor 1, PDGFR, and EGFR). Therefore, the combined treatment with RTK inhibitors, such as sunitinib, linsitinib, or quizartinib, together with PI3K/AKT/mTOR inhibitors, is


A
Oncogeneic hyperactivation (Ras, Src, c-Myc, c-Jun)
Growth factors (IGF-1, HRG)
Hypoxia (pH, nutrient starving)
Induction
Mitochondrial hypersensitization and enzyme mutation
HIF-1α
HIF-1α
HIF-1α
Cytoplasma
HIF-1β
Nucleus
P300/CBP
HIF-1α
Hyperactivation, and proliferation of tumors
Increase of immune check point inhibitors inhibition
Aerobic glycolysis and resistance of apoptosis
Hypoxia signaling
B
TGF
EGFR overexpression
EGFR mutation
Ras mutation
Braf mutation
EGFR
Sos
Grb2
Ras*
Raf*
MEK
ERK
TGF
Nucleus
Induction of cancer cell overgrowth
Escape of immune check point inhibitors inhibition
Increase of immunotherapy and chemotherapy resistance
Accumulative effect of mutation leading to disease progression
Ras/Raf/MAPK signaling
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Proliferation deregulated
Differentiation survival
Cancer cell migration
Cancer progression
RTK signaling

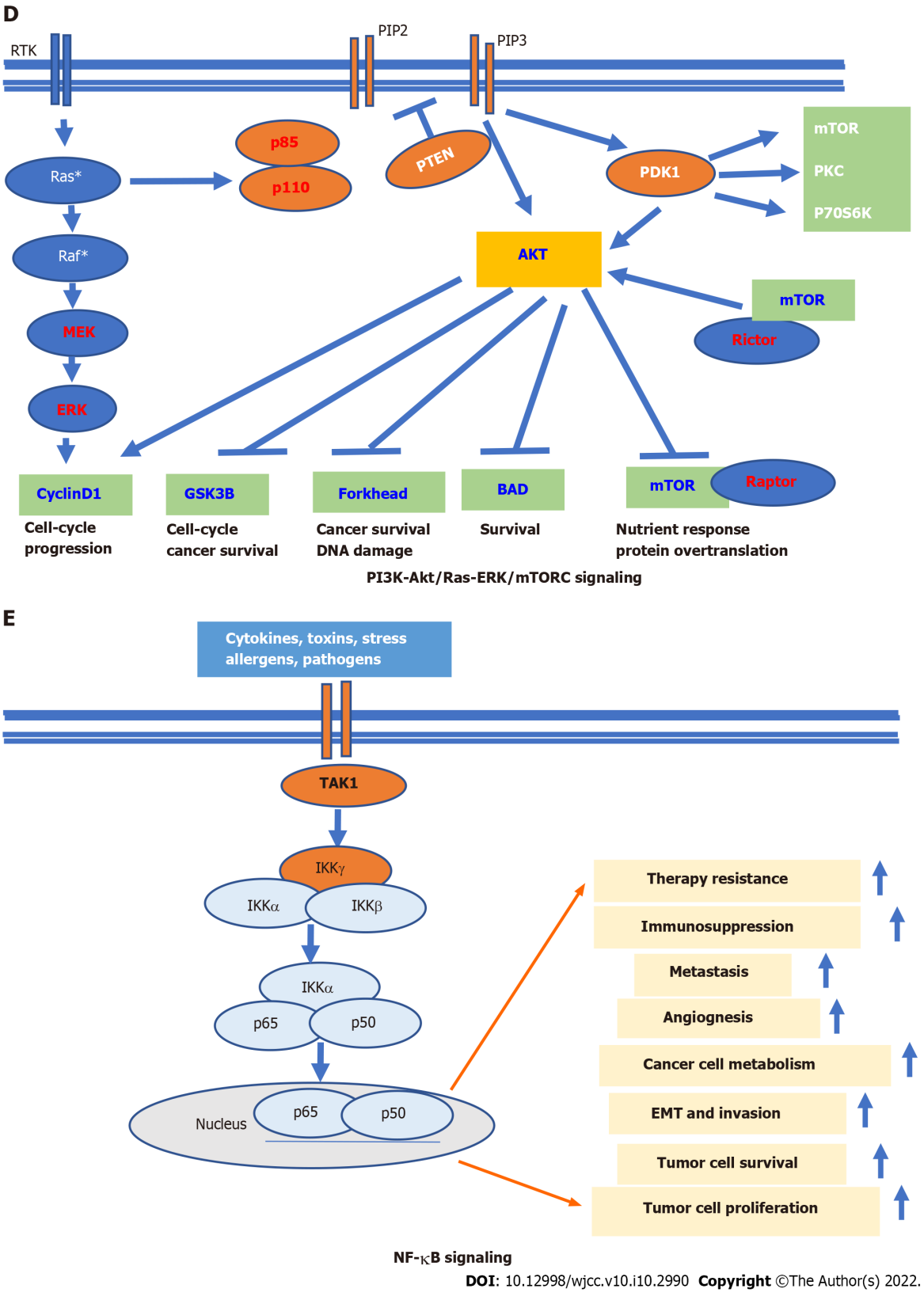

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Figure 1 Summary of various signaling pathways of hematological cancers that induce cancer development and therapy resistance. A: Hypoxia signaling; B: Ras/Raf/MAPK signaling; C: RTK signaling; D: PI3K-AKT/Ras-ERK/mTOR signaling; E: NF-κB signaling. HIF: Hypoxia-inducible factor; IGF: Insulin-like growth factor; HRG: Heregulin; CBP: Cyclic AMP response-element-binding protein; TGF: Transforming growth factor; EGFR: Epidermal growth factor receptor; GSK: Glycogen synthase kinase; PDK: Phosphoinositide-dependent kinases; PKC: Protein kinase C; mTORC: Mammalian target of rapamycin complex; mTOR: Mammalian target of rapamycin; RTK: Receptor tyrosine kinase; NF-κB: Nuclear factor-kappaB.

recommended to induce a potent cytotoxic effect on AML blast cells in a clinical setting. Despite these promising findings, the combination of rapamycin analogs and chemotherapy failed to display the expected synergistic effect in clinical studies. One of the main reasons could be the presence of drug

resistance in several cell lines, caused by mutations in mTOR, FKBP12, or one of mTOR's substrates, such as 4EBP1, S6K, and cyclin-dependent kinase inhibitor[55]. Moreover, mTORC1 inhibition can produce feedback mechanisms mediated by S6K/IRS-1 that in turn increases PI3K/AKT activity, reducing the anticancer activity of mTROC1 inhibitors[54]. Some other inhibitors of mTORC, AKT, and PI3K have also been investigated for other hematological cancers; some of which also showed beneficial effects, see Table 1.

Taken together, these results suggest the potential importance of PI3K/AKT/mTOR pathway inhibitors alone or in combination with other chemotherapeutics for the treatment of leukemia.

Target for NF-κB

Constitutive NF-κB activation protects tumor cells from apoptotic stimuli and plays a crucial role in the acquisition of resistance to chemotherapy[81]. Several antitumor agents enhance NF-κB activation, promoting development of these mechanisms of resistance. In this context, inhibition of the NF-κB signaling pathway has emerged as an attractive therapeutic strategy for cancer. Bortezomib, a proteasome inhibitor, has been approved by the United States' Food and Drug Administration to treat multiple myeloma and now are in clinical trials for AML treatment[44]. Although the mechanism of proteasome inhibition is not fully understood, one of the important activities associated with the anti-myeloma functions of bortezomib is its ability to suppress the NF-κB signaling pathway[82]. In general, IκB, a cellular inhibitory protein of NF-κB, is targeted by the ubiquitin-proteasome pathway for degradation after its phosphorylation at serine residues 32 and 36. Inhibition of the proteasome pathway by bortezomib has been shown to impede the degradation of IκBα, thus blocking NF-κB in the cytoplasm and preventing NF-κB nuclear translocation and activation of NF-κB target genes[83]. Some of the different kinases or proteases that participate in NF-κB activation, such as mucosa-associated lymphoid tissue lymphoma translocation protein 1, are also being evaluated as potential targets[59,60].

Application of biomarkers involved in cancer metabolism

Cancer biomarkers are often identified from the observed phenotype alteration, genetic modification, and epigenetic switching. These molecules could be useful to determine the type of cancer, stage of cancer progression, or the spatiotemporal switch from benign status to disease progression of cancer [84]. A great number of genes including EGFR, c-myc, and Ras, have been used for cancer screening; for example, mutations in BRCA molecules are used to screen for breast cancer in the female[62-64]. Therefore, it has become more necessary to determine the origins of primary or metastatic tumors in different sites. Interestingly, chromosome modifications in tumor cells was shown to be potential indicators (markers) of tumor progression and metastasis. If these epigenetic signatures could be quantified and classified, we could use this information to determine subtypes of different cancers, as well as stage of their disease progression[85].

Prognosis and treatment predictions

Prognosis is one important step linking risk assessment and treatment. As mentioned above, characterized and clinically approved cancer biomarkers can be essential to determine the severity of each cancer by providing a proof of concept of an efficient treatment based on the *in vitro* or pharmacological analyses. Such prognostic biomarkers include: Tissue inhibitor of metallopeptidase, a marker characterizing progressive stage of myeloma; estrogen receptor/progesterone receptor, and overexpressed receptor tyrosine-protein kinase erbB-2 (HER2), which could be associated with breast cancer; and c-KIT, a proto-oncogene which could help to identify stromal tumors in the intestine. These molecules are shown not only to identify cancer types but also to specify resistance level to anticancer drugs, which could help to determine efficient treatment to reduce the burden of patients and increase their chance of survival[86].

Follow-up of anticancer treatment

Cancer biomarkers can be used to continuously monitor the efficacy of cancer treatment. As discussed above, these biomarkers can significantly decrease treatment cost and disease burden. The S100 calcium-binding protein B (S100-B) has the potential to follow up treatment response in melanoma. Melanocytes produce pigment in the epidermis, which is associated with high expression of S100-B protein in cancer cells but not in benign cells. Therefore, the anticancer response can be monitored by the decrease in S100-B in the circulation.

In addition, tumor cells undergo apoptosis *via* the release of several intracellular complexes, such as cytochrome c, cytokeratin-18 (cleaved form), nucleosomes, and other molecules. A number of analyses have shown the roles of these molecules in monitoring the cancer progression, metastasis, and eradication, which assist in providing the essential information of treatment[67,68].

Cancer biomarkers used in cancer research

There is an increased focus on biomarkers for their applications in developing cancer drugs. For example, 60 years ago, it was discovered that a major population of chronic myelogenous leukemia patients had specific defects not only in gene expression but also at the level of chromosomes, which

Table 1 Summary of signaling pathways of hematological cancers

Signaling pathway	Biomarkers	Clinical roles as biomarkers	Ref.
Hypoxia signaling	HIF-1α	Hypoxia strongly correlated clinically to B cell lymphoma and AML proliferation, progression and drug resistance by avoiding oxidative glycolysis but not aerobic glycolysis	[56,57]
Ras/Raf/MAPK	P42/P44 MAPK, P38, P300	Gain-of-function mutation of Kras or Braf (like other kinases) in the tumor cells raise significant resistance to cancer therapy	[58,59]
PI3K-AKT/Ras-ERK/mTOR	Ras-ERK	Mutations affecting kinase activity residues of BRAF (Ras family) and MAPK (ERK family) are correlated to cancer severity, associated to upregulation of these genes in cancer patients as well as increased resistance to conventional chemotherapy; increase of immune checkpoint inhibitors on cancer cells also decreases efficiency of targeted immunotherapy	[60,61]
	mTOR	mTOR constitutive activation is usually found in leukemia patients, which contributes to chemoresistance, disease progression, and unfavorable prognosis	[36-41]
	PI3K-AKT	PTEN, a negative regulator in the PI3K-AKT signaling, becomes inactivated during tumor progression, which deviates the normal signaling and leads to over-reactivation in cancer cells	[62-66]
RTK	Meks/MKKs/ERKs	Mutations that affect RTK signaling often lead to cellular cancerous transformation, and exhibit very limited access to anti-cancer therapy targets	[67,68]
	VEGFR and EGFR	VEGF/VEGFR expression is upregulated in several types of hematolymphoid tumors. It is likely that patients with AML may benefit from EGFR inhibition therapy	[69-76]
NF-κB	NF-κB	NF-κB activity not only promotes tumor cell proliferation, suppresses apoptosis, and attracts angiogenesis but also induces epithelial mesenchymal transition, which facilitates distant metastasis; additionally, it is hardly druggable for specific targeted therapy	[77-80]

Different cellular signaling pathways triggering hematological tumorigenesis, and clinical implications as biomarkers or druggable targets is presented. AML: Acute myeloid leukemia; EGFR: Epidermal growth factor receptor; HIF: Hypoxia-inducible factor; mTOR: Mammalian target of rapamycin; RTK: Receptor tyrosine kinase; NF-κB: Nuclear factor-kappaB; VEGF: Vascular endothelial growth factor; VEGFR: Vascular endothelial growth factor receptor.

were named Philadelphia chromosomes. If both chromosomes are present in the same patient, a fusion protein called BCR-ABL is expressed, which represents a critical cancer-inducing gene and a key gene that is monitored for the physiological manifestations at the early stage of leukemia. BCR-ABL can still be simply measured to classify the type of leukemia. Owing to these discovered molecules, several targeted inhibitors were developed. For example, imatinib targets and inhibits the function of BCR-ABL protein and drastically diminishes the number of cells with Philadelphia chromosomes[87].

Investigations on surrogate endpoints of the disease are ongoing. Biomarkers may predict the side effects of anti-cancer drugs, and thus, increase survival rate. These markers can prevent patients from undergoing tumor biopsies and shorten the duration of clinical trials' period. The decrease in cancer progression and duration of post-treatment survival could be quantifiable for determining the effect of anticancer drugs. Once biomarker surrogates have been identified, anticancer drug design and validation will become less time-consuming and more cost-effective before entering clinical trials.

New signals from the invasive front

MicroRNA: Studies have been carried out extensively on microRNA (miRNA) and cancer. Profiling of the miRNome (global miRNA expression levels in a certain organism) has become prevalent, and abundant miRNome data are currently available for various cancers[88]. The pattern of miRNA expression can be correlated with a distinct cancer type, stage, and other clinical variables, so miRNA profiling can be used as a biomarker for cancer diagnosis and prognosis. Advanced analyses indicate that miRNAs also play roles in almost all fields of cancer biology, such as angiogenesis, invasion/metastasis, proliferation, and apoptosis. Therefore, an ever-increasing number of studies have identified miRNAs as potential biomarkers for cancer diagnosis, prognosis, and also as therapeutic targets or tools using specific individual miRNAs or clustered groups of miRNAs, which need further investigation and validation in different clinical and research studies[89].

Circulating tumor cells: Surrogate markers, including circulating tumor cells (CTCs) and circulating miRNAs, are getting more attention in recent years[90]. These markers are correlated with the number of tumor cells present in the blood. However, because of the low numbers, CTCs are still very difficult to detect and isolate at a satisfactorily high purity and efficiency. New techniques and research are required for their application into clinical practice[91]. However, the clinical regulation and corresponding medical criteria to define the sensitivity and positivity of interpretation of results remain to be optimized, and this protocol requires equipment dedicated to detecting CTCs and validating the results.

Long noncoding RNA: Long noncoding RNAs (lncRNAs) act as crucial biomarkers in tumors. With the development of molecular biology techniques, lncRNAs have gradually become a research hotspot in the field of tumor research[92]. LncRNAs comprise RNA molecules with sizes greater than 200

nucleotides and do not encode any protein. LncRNAs have been demonstrated to regulate various biological activities and processes, such as epigenetics, cell cycle, and regulation of cell differentiation [93]. Different lncRNAs profiles have been observed in various types of tumors compared with normal tissues, and lncRNAs with dysregulated expression can be tumor-promoting or tumor-suppressing factors. LncRNAs have multidimensional regulatory mechanisms, such as activating/repressing the expression of neighboring genes, encoding the upstream promoter of a protein-coding gene, mediating chromatin modifying, binding to transcription factors and specific proteins, regulating post-transcriptional mRNA decay, and acting as sponges of miRNAs. Different lncRNAs have been detected and shown to be significant for measuring development of non-small cell lung cancer, CRC, gastric cancer, lung squamous cell carcinoma, and breast cancer[94].

Exosomes: Exosomes are extracellular vesicles that have pleiotropic functions in living organisms. These 50-nm to 140-nm nanoparticles transport various materials, including DNA, RNA, proteins, and lipids. Exosomes were first identified as recycled fractions of intravesicular membranes released by reticulocytes following endocytosis of the transferrin receptor. Reticulocytes undergo drastic alterations in cell size, shape, and deformability during maturation. Toward the last stage of this process, transferrin receptors are exocytosed with the help of multivesicular bodies (MVB) that carry 50-nm small vesicles or exosomes[95]. These bilipid-layered vesicles carry a certain number of molecules from the plasma membrane and the interior of the cytoplasm. The release of exosomes occurs when MVBs fuse with the plasma membrane. MVBs are now well known as intracellular endosomal organelles dispersed in the cytoplasm. Exosomes in cancer biology have attracted a lot of attention for their role in the development of the tumor microenvironment. Exosomes play a role in creating a premetastatic niche conductive to metastasis at distant sites. These exosome-delivered tolerogenic signals to cancer-specific immune cells could therefore interrupt immune cell proliferation and induce apoptosis of activated $CD8^+$ T lymphocytes, interfering with monocyte differentiation and negatively favoring the expansion of regulatory T cells, leading to immunosuppression (peripheral tolerance) through a paracrine effect. Chen *et al*[96] recently showed that programmed death ligand 1 (PD-L1) expression is enhanced when melanoma cells are exposed to IFN-γ, resulting in increased PD-L1 expression on circulating human-derived melanoma exosomes[97].

Also, EGFR and other metabolic reprogramming using miRNA regulation (*e.g.*, miR-155 and miR-210)[98] show a reverse Warburg effect that contributes to tumor-specific $CD8^+$ T-cell inhibition. Therefore, the exosome-derived tumor microenvironment not only creates a favorable immediate layer but a macrostructure to facilitate the metastatic process[99].

Tumor exosome secretion is suggested to participate in promoting cancer cell invasiveness. For example, exosomes derived from pancreatic ductal adenocarcinoma (PDAC) can induce niche formation of premetastatic hepatocytes. This pathological niche formation in a murine model increases the burden of hepatocyte metastasis. Uptake of PDAC-derived exosomes by Kupffer cells could induce a high level of transforming growth factor-β secretion and greater production of fibronectin by stromal cells in the liver[100]. Apparently, this fiber-like microenvironment enhances the recruitment of type 1 macrophages derived from bone marrow. The extracellular matrix is clearly greater in exosomes derived from patients with early-stage PDAC compared with later stages. When MIF expression in the PDAC-derived exosomes was blocked, the formation of the pre-metastatic niche in the liver and subsequent tumor metastasis is also prevented. These observations suggest that the molecules expressed in the tumor exosomes help to prime or target the tumor tissue to become metastatic and resistant to chemotherapy. Therefore, these exosomes could act as a prognostic biomarker to monitor PDAC progression and liver metastasis development and progression[101]; however, precision therapy is still far from being designed, due to the unstable expression level and isoforms of materials presented within the exosomes[102].

CONCLUSION

A more profound understanding of the cellular and molecular mechanisms of cancer and malignant disorders has translated into a biologically adapted classification providing evidence for therapeutic development. Imatinib, a BCR-BRL inhibitor, has been shown to dramatically improve B cell lymphoma patients' prognosis, and it has been established that a significant number of patients defined by older classification systems exhibited poor prognosis, probably due to the biomarkers selected at that time. Cancer therapies, including corticosteroids, IFN-α, chemotherapies, targeted monoclonal antibodies, and small molecule drugs, can elicit significant clinical effects by targeting these biomarkers, with variable durability of response, followed by short- and long-term adverse effects lasting for an undetermined period. Therefore, in the future, a new generation of targeted drugs with better resolution and precision is needed.

For example, Pitson *et al*[103] have found that SK1 is activated by site-directed phosphorylation of ERK-1/2 of S225. Future studies can use anti-phosphor S225 SK1 monoclonal antibodies to determine the impact of phosphorylated SK1 on clinical prognosis[104-106].

It is likely that more biomarkers are continuously being discovered and identified, and new technologies are necessary to measure biomarkers at the time of diagnosis. Ideally, these methods should be high-throughput as well as tissue-sensitive, cost-effective, and rapid[107,108]. However, an additional challenge for molecular and cell biologists, geneticists, and clinical investigators lies in bridging the gap between their worlds and that of biotechnology. Notably, some overlapping technologies have already created unexpected successes in the last decade and are continuously being developed. Essentially, anti-cancer drug discovery frameworks targeted at developing anti-cancer drugs, specifically for metastasis, should be taken into consideration globally. Extensive advanced development of a more sensitive detection method is required.

Limitations of these detection assays include the logistical challenges associated with high-quality results from fresh biopsy specimens in the hospital setting. The ongoing development of these promising techniques of high resolution and detection sensitivity, with the translation to a widespread clinical application from basic science, will also be vitally reviewed and appreciated by all aspects. There are still some examples regarding the technologies under investigation, including high-contrast fluorescence detection, multispectral optoacoustic tomography, shortwave infrared emitting nanoprobes, and novel magnetic resonance imaging that is non-toxic and applied with highly permissive contrast agents. In addition, it is important to detect micro-metastasis in the initial stage of development in cancers of different types using all the possible approaches, which will guarantee adapted and appropriate treatment regimens in both ongoing and to-be-started clinical trials.

FOOTNOTES

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