BIEŚ, Rafał, MIKOSIŃSKA, Agnieszka, PARYS, Jakub, LITWIN, Mateusz, KAŁUZIAK, Patrycja, JAJCZAK, Marta, MOSSAKOWSKI, Maciej, WITEK, Aleksandra, KAŹMIERCZAK, Martyna and JESIONEK, Stanisław. The influence of hepatocyte growth factor on the proliferation and differentiation of stem cells. Journal of Education, Health and Sport. 2025;77:57418. eISSN 2391-8306.
https://doi.org/10.12775/JEHS.2025.77.57418
https://apcz.umk.pl/JEHS/article/view/57418

The journal has had 40 points in Minister of Science and Higher Education of Poland parametric evaluation. Annex to the announcement of the Minister of Education and Science of 05.01.2024 No. 32318. Has a Journal's Unique Identifier: 201159. Scientific disciplines assigned: Physical culture sciences (Field of medical and health sciences); Health Sciences (Field of medical and health sciences).
Punkty Ministerialne 40 punktów. Załącznik do komunikatu Ministra Nauki i Szkolnictwa Wyższego z dnia 05.01.2024 Lp. 32318. Posiada Unikatowy Identyfikator Czasopisma: 201159. Przypisane dyscypliny naukowe: Nauki o kulturze fizycznej (Dziedzina nauk medycznych i nauk o zdrowiu); Nauki o zdrowiu (Dziedzina nauk medycznych i nauk o zdrowiu).
The authors declare that there is no conflict of interests regarding the publication of this paper.
Received: 20.12.2024. Revised: 07.01.2025. Accepted: 07.01.2025. Published: 08.01.2025.

Review article

The influence of hepatocyte growth factor on the proliferation and differentiation of stem cells

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Abstract

Background: The HGF/c-Met signaling pathway is central to various biological processes, including tissue regeneration, cell proliferation, and differentiation. Dysregulation of this pathway has been implicated in cancer progression and poor prognosis. Despite its potential as a therapeutic target, the complexity of HGF/c-Met signaling and the associated challenges,

such as off-target effects and limited understanding of its role in different disease contexts, pose significant obstacles to clinical translation.

Objectives: This review aims to examine the role of the HGF/c-Met pathway in tissue regeneration and cancer, with a focus on its therapeutic potential. We explore how HGF/c-Met signaling contributes to stem cell function, tissue repair, and cancer biology, as well as the development of targeted therapies aimed at modulating this pathway.

Limitations: Although preclinical studies have shown promising results, clinical applications of HGF/c-Met-targeted therapies remain limited due to issues such as a lack of standardized methodologies for pathway assessment, potential off-target effects of small-molecule inhibitors, and incomplete understanding of HGF and c-Met roles in various diseases. Additionally, the short half-life of HGF in circulation complicates long-term therapeutic strategies.

Methods: A thorough review of the literature was conducted, focusing on studies examining HGF/c-Met signaling in cancer and tissue regeneration. Relevant research databases were explored to identify key findings related to HGF/c-Met interactions, the effects of HGF on stem cell function, and the development of therapeutic agents targeting this pathway.

Conclusions: The HGF/c-Met pathway holds significant promise in both cancer treatment and tissue regeneration, particularly through its role in stem cell biology. Further research is needed to better understand its mechanisms and optimize targeted therapies. Combining pharmacological agents that modulate HGF/c-Met signaling with personalized treatment approaches could enhance therapeutic outcomes for cancer patients. Addressing current limitations, including the refinement of diagnostic and therapeutic strategies, will be essential in fully harnessing the potential of HGF/c-Met in clinical practice.

Key words: hepatocyte growth factor; HGF/c-MET pathway; proto-oncogene proteins c-MET; stem cells; stem cell differentiation; stem cell proliferation;

1. Introduction

Hepatocyte growth factor (HGF) was first described in 1984 as a potent mitogenic factor acting on mature rat hepatocytes in vitro [1,2]. Initially, it was isolated from rat platelets and later from human plasma as well [3]. Numerous subsequent studies demonstrated that HGF is a pleiotropic cytokine, which not only affects hepatocytes but also possesses

various other functions. It plays a role in embryogenesis and osteogenesis, among others [4,5]. In 1985, it was shown that fibroblasts secrete a factor that, when acting on tightly packed epithelial cells, causes their dispersion [6]. The protein responsible for this process was termed "Scatter Factor" (SF), which corresponded to the then-unknown HGF molecule. Only decades after the discovery of HGF and SF was it proven that both act on the same receptor and exhibit similar biochemical actions, suggesting that they are the same protein. Moreover, cDNA of SF and HGF obtained from human fibroblasts, placenta, and liver displayed virtually identical sequences [7].

Hepatocyte growth factor belongs to the plasminogen protein family, indicating structural homology with enzymes in the blood coagulation cascade [8]. HGF is secreted primarily by cells of mesenchymal origin but also by stem cells, cancer cells, and other cell lines [9,10,11]. Regardless of the cell line producing it, secreted HGF is initially inactive, existing in a precursor form known as pro-HGF [12]. Its activation involves proteolytic cleavage of the precursor chain between Arg494 and Val495 [13], mediated by HGF activator (HGFA), type II transmembrane serine proteases such as matriptase (ST14), and hepsin [14]. In vivo studies have shown that blood coagulation factor XIIa, urokinase, and plasminogen activator can also activate HGF [15]. Inhibiting pro-HGF activation through specific inhibitors is a novel approach to blocking oncogenic HGF/c-Met signaling [16]. HGF acts primarily in a paracrine manner; however, there is increasing evidence of autocrine loops in various cellular systems, notably in ocular cells, including corneal endothelial cells, lens epithelium, retinal pigment epithelium (RPE), and others [17].

Unlike other growth factors, hepatocyte growth factor (HGF) has only one receptor, which is the product of proto-oncogene c-Met expression. The c-Met protein consists of an extracellular domain that binds the ligand, a transmembrane domain, and an intracellular domain containing tyrosine kinase activity. Typically, c-Met is activated by HGF binding, which induces its dimerization and autophosphorylation of tyrosine residues within the intracellular domain [18]. The binding of HGF to c-Met leads to the activation of multiple intracellular signaling pathways. Phosphorylation of c-Met enables the binding of various cytoplasmic effector proteins, including GRB2-associated binding protein (GAB1), growth factor receptor-bound protein 2 (Grb2), phosphoinositide 3-kinase (PI3K), signal transducer and activator of transcription 3 (STAT3), and subsequent signal transduction [19]. Phosphorylation of GAB1 bound to c-Met provides additional docking sites for cytoplasmic effector proteins [20]. Further signaling molecules, such as RAS/MAPK and

PI3K/AKT/mTOR pathways, exert effects at the nuclear level, regulating cell proliferation, epithelial-mesenchymal transformation, and anti-apoptosis [21]. Additionally, activated Rac1/β-catenin and FAK/integrin signaling pathways influence the cell membrane, inducing migration, invasion, and epithelial-mesenchymal transition (EMT) [22].

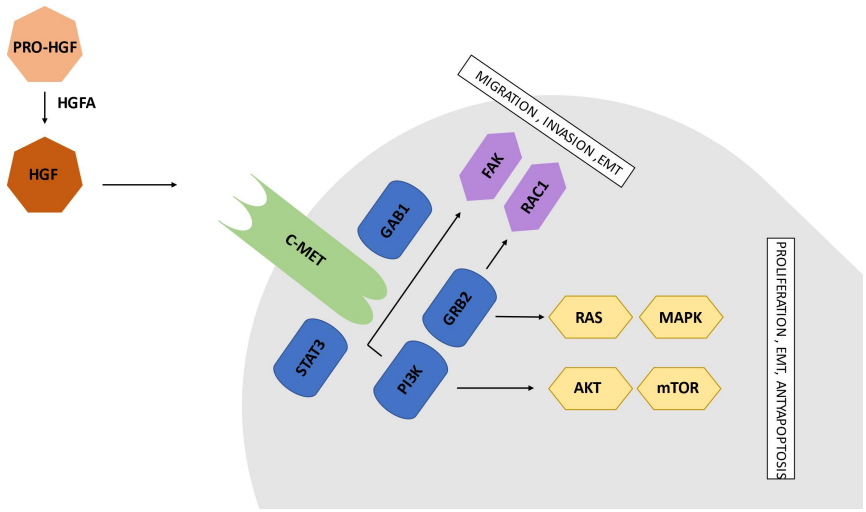

Figure 1. Signaling pathways activated by HGF/c-MET interaction
Abbreviations: Pro-HGF – inactive precursor of hepatocyte growth factor; HGF – hepatocyte growth factor (active); HGFA – hepatocyte growth factor activator; c-MET –catalytic receptor with tyrosine kinase activity; MAPK - mitogen-activated protein kinases; STAT - signal transducer and activator of transcription; GRB2 -growth factor receptor-bound protein 2; PI3K - phosphoinositide 3-kinase; AKT - protein kinase B (PKB); mTOR - mammalian target of rapamycin kinase; FAK – focal adhesion kinase; EMT - epithelial-mesenchymal transition

The amount of c-Met protein on a single cell can be regulated. Cross-interactions, often amplified in tumors and cancerous conditions, play a crucial role in increasing c-Met expression and the development of chemotherapy resistance [23]. Following its activation, c-Met expression may decrease through internalization. It undergoes clathrin-mediated endocytosis, is subsequently ubiquitinated, and then degraded. Disruption of c-Met ubiquitination can lead to increased activity [24].

Studying the HGF/Met axis appears to be significant since serum HGF levels are correlated with the development of tumors [25] and other pathological conditions. Elevated HGF plasma levels have been observed in patients with ischemic myocardial injury, acute kidney failure, and acute lung injury [26-28]. Moreover, it has been demonstrated that HGF,

acting in a paracrine manner, can influence tumor cell proliferation, tumor vascularization, and metastasis [29]. The straightforward nature of the HGF/c-Met axis makes it a potential target for cancer therapies. Currently, several methods are used to regulate this pathway, including anti-HGF antibodies, anti-MET antibodies, and tyrosine kinase inhibitors to inhibit intracellular signal transduction [30].

2. The effect of HGF on stem cell proliferation

Cell proliferation refers to the rate at which the number of cells increases in a population of progeny cells [31]. This process is controlled by the coordinated entry into the cell cycle, which can be activated by both extracellular and intracellular signals. It is critically important during tissue remodeling and regeneration [32]. Abnormalities resulting from defective proliferation control are of significant importance in medicine, impacting processes ranging from embryogenesis to tissue repair and oncogenesis [33]. Cells are typically in a resting state but begin to divide when tissue repair is needed [34].

The study of stem cell proliferation is crucial as their ability to divide and differentiate into various cell types may provide future solutions for replacing tissues damaged or destroyed by disease. Therefore, identifying growth factors that promote stem cell proliferation, migration, and differentiation opens vast possibilities for future stem cell-based tissue engineering [35]. The literature indicates that HGF has a stimulatory effect on the proliferation of various stem cell populations, including satellite muscle cells [36], cardiac stem cells [37], bone marrow stem cells [38], neural stem cells [39], liver stem cells [40], and endothelial progenitor cells [41]. Furthermore, HGF has been shown to induce proliferation in somatic cells [42] and cancer cells [43].

The exact mechanism by which HGF triggers cell proliferation has not yet been directly determined. However, various mechanisms have been proposed based on research findings. Current evidence shows that the HGF/c-MET axis influences the cell nucleus, triggering the early transcription and activation of JUN and FOS genes in a time- and dose-dependent manner [44]. The transcription factors Jun and Fos play a role in cell proliferation by regulating the expression and function of cell cycle regulators, such as cyclin D1, cyclin A, cyclin E, p53, p21, p16, and p19 [45]. The increased transcription and translation of FOS mRNA are mediated by adaptor proteins activated following HGF binding to c-Met, such as the PI3K/mTOR pathway [46]. Studies have repeatedly confirmed that HGF stimulation

increases the expression of cell cycle progression proteins, including cyclins A, B, D, and E [47]. A critical mediator necessary for HGF-induced cell proliferation is NF-κB. It has been demonstrated that blocking its activation inhibits cell proliferation [48].

The ability of the HGF/c-Met axis to promote proliferation, survival, and mitogenic activity appears to play a critical role in embryonic development and tissue repair. However, coupling these actions into an "invasive growth program" poses the risk of tumor metastasis [49]. The genetic structure of the HGF/c-Met axis and its epigenetic actions contribute to tumor progression through various mechanisms [50]. Abnormalities in this axis are observed in multiple types of cancer, including liver cancer [51], gastric cancer [52], breast cancer [53], and cervical cancer [54]. The established relationship between the overexpression and excessive activation of the HGF/c-Met axis serves as a significant indicator of tumor progression and can be considered a prognostic, predictive, or therapeutic biomarker in oncology patients [55]. Inhibiting HGF/c-Met pathways presents a potential therapeutic target. In vitro studies have shown that verticillin can act as an HGF/c-Met inhibitor by suppressing c-Met activity and downstream FAK/Src signaling pathways. Verticillin impairs HGF-induced c-Met phosphorylation, thereby inhibiting the migration of human cancer cells and reducing the metastatic potential of tumors [56].

Despite HGF's strong mitogenic capabilities, its antagonistic, anti-mitogenic effects have also been documented in several cancer cell lines. The proliferation of HepG2 liver cancer cell lines in vitro is inhibited through cell cycle arrest in the G1 phase, driven by strong ERK signaling induced by HGF. This response is accompanied by the induction of the proteins p16-INK4a [57] and p21 [58], which inhibit cell cycle progression by binding to CDK-cyclin complexes [59].

3. The effect of HGF on the differentiation of embryonic stem cell lines

The HGF/c-Met signaling pathway is crucial for embryonic and placental development. Studies reveal that homozygous mice with HGF mutations exhibit abnormalities in the labyrinth region of the placenta—a structure analogous to human chorionic villi responsible for substance exchange between the fetus and the mother. Consequences of the HGF mutation in mice include a reduced number of trophoblast cells and fetal demise before birth [60]. Furthermore, the absence of HGF/c-Met signaling disrupts terminal differentiation and polarization of syncytiotrophoblasts, leads to fetal liver hypocellularity, and causes

placental underdevelopment in mice [61]. This occurs because HGF directly regulates trophoblast development, and c-Met signaling is essential for maintaining multipotent trophoblast precursors. Placental hypoplasia results from decreased expression of cell cycle-related genes in trophoblast cells. Genetically engineered mice with embryonic deletion of c-Met or HGF genes demonstrate reduced expression of key genes, including *Ccna2*, *Ccne1*, *Ccne2*, *Chek1*, and *Cdc45*. Trophoblasts in mice with c-Met deficiency exhibit impaired expression of transcription factors essential for their differentiation into syncytiotrophoblasts, which mediate maternal-fetal substance transport. These trophoblasts also show defective localization of the transferrin receptor (CD71), critical for placental iron transport [61]. Similar patterns of HGF and c-Met expression have been observed during human embryonic development. In the first and second trimesters, HGF is present in the stromal core of villi, while c-Met is expressed in cytotrophoblastic cells (CTBs) and mammary glands [62]. Enzyme immunoassays indicate that isolated trophoblasts do not produce HGF, whereas isolated villous stromal tissues and mesenchymal cells do. The localization of c-Met primarily in cytotrophoblasts suggests that HGF produced in the villous core acts paracrinally to regulate trophoblast development [63]. In the third trimester, HGF is found in extravillous trophoblast cells, mesenchymal cells, syncytiotrophoblasts (STBs), and vascular endothelial cells, while c-Met is highly expressed in vascular endothelial cells and STBs [64].

During the pre-implantation stage, mammalian embryos exist as blastocysts with two distinct layers of cells: the outer trophoblast layer, known as the trophectoderm, and an inner cell mass (ICM) composed of undifferentiated cells. The ICM contains pluripotent cells capable of differentiating into any tissue type within the organism. These cells are influenced by bioactive molecules, such as embryokines, primarily secreted by the reproductive tract to regulate embryonic growth and development. Among these, hepatocyte growth factor (HGF) plays a significant role, as low concentrations of HGF can inhibit the progression of the zygote into the blastocyst stage [65]. The epiblast of the blastocyst is the origin of embryonic stem cells (ESCs), which represent the inner mass of cells at this developmental stage. The fate of ESCs is determined by interactions with their microenvironment. In vitro studies demonstrate that culture media supplemented with HGF significantly increases the expression of differentiation-associated genes while substantially decreasing the expression of pluripotency markers such as *Oct4* and *Nanog*. This indicates that HGF promotes the differentiation of ESCs [66]. HGF strongly supports ESC differentiation, facilitating their development into cells of all three embryonic germ layers—endoderm,

mesoderm, and ectoderm—though the final differentiation pathway depends on the influence of other growth factors [67]. Of particular interest is the potential to derive hepatocytes from ESCs. In in vitro cultures of rat ESCs, the addition of HGF and β-NGF over 15 days resulted in the detection of markers such as α1-antitrypsin (α1-AT), alpha-fetoprotein (AFP), albumin, transthyretin, glucose-6-phosphate, hepatic nuclear factor 4, and the expression of mRNA for SEK1. These findings suggest successful differentiation of ESCs into functional hepatocytes [68].

Using human embryonic stem cells (hESCs) in experimental research carries ethical limitations, and in the case of cell transplantation, it is associated with immune rejection [69]. These limitations may be overcome by using human parthenogenetic embryonic stem cells – hPESCs. These are embryonic stem cells derived exclusively from a single gamete, expressing maternal genes. They are capable of indefinite self-renewal and totipotency. hPESCs are cell lines derived through the activation of oocytes at the second meiotic phase (M II) without sperm fertilization. Ethical concerns related to ESC research do not apply to these cells since they originate from parthenogenetic embryos with no developmental potential. Moreover, hPESCs come from a single gamete, making their MHC allele homozygous, theoretically minimizing immune rejection during cell transplantation [70]. A literature review revealed that only one study has been conducted on the directed differentiation of these cells into hepatocytes using HGF. At the mRNA level, genes characteristic of hepatocyte lines such as AFP, ALB, and HNF4a, as well as cytochrome P450 genes like CYP3A4 and CYP3A7, along with transporter genes SLC10A1, SLCO1B3, ABCC2, and ABCB4, were strongly expressed after culture with HGF [71].

Another alternative to human embryonic stem cells are amniotic epithelial cells (AEC), which exhibit stem cell characteristics. The collection of these cells from the amniotic membrane of the human placenta does not raise ethical concerns. A study showed that HGF effectively increased the expression of genes characteristic of hepatoblast and hepatocyte lines, such as AFP, GSTA1, and ALB. This activity, after 18 days of differentiation, allows for their successful differentiation into hepatocytes [72].

4. The effect of HGF on the differentiation of adult stem cell lines

It is believed that a subpopulation of cells capable of self-renewal, with proliferative potential, and capable of generating large progeny with specific differentiation potentials exists in every tissue and organ of the adult organism [73]. These are referred to as adult stem

cells. They have the potential to differentiate into specific cell lineages or into cells of the tissue from which they originate [74].

One source of stem cells is the bone marrow, where hematopoietic stem cells (HSC) and mesenchymal stem cells (MSC) can be found. These cells may originate from a common precursor capable of differentiating along the MSC or HSC pathways [75]. HGF is present in the hematopoietic microenvironment, and its interactions with synergistic factors in the bone marrow microenvironment represent a natural regulatory mechanism of HSC physiology [76]. The c-Met receptor is expressed in several murine hematopoietic cell lines [77], and HGF/c-Met signaling influences hematopoiesis mechanisms [78]. Literature reports that HGF promotes the differentiation of hematopoietic progenitor cells (HPC) towards the CD41+ cell lineage, in cooperation with other hematopoietic growth factors such as IL-3, granulocyte-macrophage colony-stimulating factor, or IL-11 [79]. Furthermore, transgenic mice producing human HGF exhibited increased numbers of megakaryocytes and platelets [79]. This phenomenon was confirmed in another study [80], which demonstrated that HGF increases thrombopoietin expression. Based on these findings, it can be concluded that HGF may also stimulate HSC differentiation into megakaryocytes.

Adult hematopoietic stem cells (HSC) removed from their niche are capable of differentiating in vitro into various tissue types, including bone, heart, muscle, epithelial cells, neuronal cells, pneumocytes, and hepatocytes [81]. The role of key hepatic growth factors such as HGF in regulating the process of transdifferentiation has been studied, and results indicate that HSC are capable of inducing hepatic transdifferentiation in response to sequential addition of growth factors such as HGF and FGF-4 [81]. These cells, cultured in vitro in media supplemented with HGF, exhibit morphological and physiological features characteristic of hepatocytes [82].

Approximately 30% of human cells from bone marrow aspirates are mesenchymal stem cells (MSC), which can be explored in vitro and stimulated to form bone, cartilage, tendons, muscle, or adipose tissue [83]. MSC can also be isolated from adipose tissue [84], umbilical cord blood [85], dental pulp [86], or through the induction of pluripotent stem cells (iPS cells) [87]. MSC can effectively contribute to tissue regeneration within inflammatory microenvironments by modulating immune responses. In response to pro-inflammatory stimuli such as TNF-α, MSC secrete immunoregulatory factors, including HGF [88]. The HGF/c-Met axis regulates the immune response [89], and HGF can counteract the inflammatory effects of transforming growth factor (TGF-β), contributing to the reduction of inflammatory foci in damaged tissues [90].

One of the key signals received by stem cells following tissue injury is the local activation of HGF. This induces the migration of stem cells to the injured area of the tissue and contributes to repair and cell survival at that site [91]. In damaged muscle tissue, HGF stimulates the activation and early division of satellite cells [92], particularly influencing their myogenic differentiation [93]. It regulates the PI3K/Akt pathway by mediating paracrine activation of the Akt signaling pathway, thereby inducing myogenic differentiation of satellite cells [94]. There is also strong evidence that HGF promotes osteogenesis in human MSCs [95]. After culturing human MSCs isolated from bone marrow in vitro, supplemented with HGF at 40 ng/ml, primary osteogenic markers such as osteocalcin, osterix, osteoprotegerin, bone sialoprotein 2, and collagen 1α1 show increased expression by day 2, supporting HGF's role in promoting osteogenesis.

Recently, clonogenic and multipotent stem cells residing in the adult heart (cardiac stem cells, CSC) capable of replacing damaged cardiomyocytes have been identified [96]. Both in vivo and in vitro studies have demonstrated HGF's ability to promote the migration of CSC to the injured areas of the heart muscle and activate their growth and differentiation into cardiomyocytes [97]. The ability to induce CSC migration via HGF is attributed to increased expression of matrix metalloproteinases (MMPs) [98], which degrade collagen and other extracellular matrix components, facilitating cell migration and implantation in the heart [97].

5. Discussion

The HGF/c-Met signaling pathway is involved in numerous cellular processes such as osteogenesis, tissue regeneration, and cell proliferation. It is essential for embryonic development in humans and animals. HGF protein mediates these processes by interacting with the c-Met receptor. However, along with its beneficial roles, there are several risks associated with mutations and overexpression of c-Met. Increased HGF signaling can contribute to tumorigenesis, as tumors can be maintained and stimulated to grow due to the widespread presence of c-Met in the extracellular matrix.

The broad spectrum of HGF/c-Met signaling holds significant therapeutic potential. The available literature continues to expand, providing insights into new treatment strategies for various diseases. Pharmacokinetic modulation of HGF levels in plasma could potentially offer effective treatment options for chronic kidney disease, cardiomyopathy, and liver cirrhosis in the future [99]. However, despite promising results in animal studies, HGF has not

proven effective in treating fibrotic diseases in humans [99]. Researchers must exercise caution in therapies involving intravenous HGF, as excessive dosing could lead to adverse effects. To develop future therapeutic methods, a thorough understanding of the mechanisms regulating HGF levels in the body is essential. Currently, it is known that HGF has a relatively short half-life in plasma—ranging from 3 to 4 minutes, with complete degradation taking approximately 15 minutes [100].

Several clinical studies have shown that c-Met amplifications can serve as prognostic biomarkers in various cancer types, such as breast cancer [101] and head and neck cancer [102]. c-Met signaling activation by HGF plays a critical role in tumor angiogenesis. HGF, by activating c-Met, exerts angiogenic effects in cancer by stimulating VEGF production [103]. In mouse models of pancreatic tumors resistant to bevacizumab—an antibody that targets and neutralizes VEGF—there was an observed increase in c-MET expression [104]. This suggests that VEGF-induced angiogenesis inhibition leads to upregulation of c-Met, contributing to resistance to anti-angiogenic therapies due to increased tumor invasion potential [103]. Additionally, abnormal HGF expression has also been reported as a diagnostic, prognostic, and predictive biomarker in various cancer types [105]. Elevated HGF concentrations in cancer tissue lysates are significantly higher in tumors resistant to the anti-angiogenic treatment sunitinib compared to sensitive tumors. Moreover, systemic administration of HGF has been shown to induce sunitinib resistance in animal models that were initially responsive to sunitinib [106]. However, the lack of standardized methodologies for evaluating and screening these biomarkers remains a significant limitation in their clinical application.

6. Conclusion

The simplicity of the HGF/c-Met pathway sheds new light on cancer therapies as a potential molecular target for pharmacotherapeutic agents. Various small-molecule c-Met inhibitors, anti-c-Met antibodies, and anti-HGF antibodies are being developed in preclinical and clinical research for different cancers. Currently available inhibitors include: bosutinib, cabozantinib, crizotinib, MSC2156119J, MK-2461, AMG-337, capmatinib, tepotinib, amuvatinib, elzovantinib, savolitinib, glumetinib, and golvatinib [107]. Additionally, monoclonal antibodies targeting c-Met and HGF, as well as competitive HGF analogs, have been constructed to block the HGF/c-Met signaling pathway involved in tumorigenesis and tumor progression [108]. Monoclonal antibodies against c-Met and HGF show greater

specificity in binding to c-Met compared to small-molecule tyrosine kinase inhibitors, which may also interact with other cellular kinases [109].

Further research into the HGF/c-Met signaling pathway is necessary, as a deeper understanding of the molecular mechanisms underlying its function could revolutionize regenerative medicine and overcome current limitations in medicine. Further studies combining pharmacological agents with therapies targeting the HGF/c-Met pathway are essential to develop the best personalized treatment strategies for cancer patients.

Disclosure: Authors do not report any disclosures.

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Project administration: Patrycja Kałuziak, Jakub Parys
All authors have read and agreed with the published version of the manuscript.

Funding Statement: Study did not receive special funding.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: Not applicable.

Acknowledgments: Not applicable.

Conflict of Interest: The authors of the paper declare no conflict of interest.

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