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HUMAN GENETICS • REVIEW

HOXA9 versus HOXB9; particular focus on their controversial role in tumor pathogenesis

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Abstract

The Homeobox (HOX) gene family is essential to regulating cellular processes because it maintains the exact coordination required for tissue homeostasis, cellular differentiation, and embryonic development. The most distinctive feature of this class of genes is the presence of the highly conserved DNA region known as the homeobox, which is essential for controlling their regulatory activities. Important players in the intricate process of genetic regulation are the HOX genes. Many diseases, especially in the area of cancer, are linked to their aberrant functioning. Due to their distinctive functions in biomedical research—particularly in the complex process of tumor advancement—HOXA9 and HOXB9 have drawn particular attention. HOXA9 and HOXB9 are more significant than what is usually connected with HOX genes since they have roles in the intricate field of cancer and beyond embryonic processes. The framework for a focused study of the different effects of HOXA9 and HOXB9 in the context of tumor biology is established in this study.

Keywords HOX family · HOXA9 · HOXB9 · Cancer

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Introduction

The Homeobox (HOX) gene family plays a fundamental role in the regulatory framework of cellular activities, ensuring the precise coordination necessary for embryonic development, cellular differentiation, and tissue homeostasis. The defining characteristic of this group of genes is the existence of the highly preserved DNA sequence referred to as the homeobox, which plays a crucial role in managing their regulatory functions. HOX genes are essential participants in the complex process of genetic regulation. Their abnormal functioning is associated with a range of disorders, particularly in the field of cancer. HOXA9 and HOXB9 have attracted particular interest due to their unique roles in biomedical research, particularly in the intricate process of tumor advancement. HOXA9 and HOXB9 have greater importance than what is typically associated with HOX genes since they have functions beyond embryonic processes and also play a part in the complex field of cancer. This introduction establishes the framework for a targeted investigation of the distinct impacts of HOXA9 and HOXB9 within the field of tumor biology (Gonçalves et al. 2020; Mortimer et al. 2019).

This study attempts to elucidate the divergent functions of these genes in tumor progression by conducting a comprehensive analysis of their molecular properties, prior research findings, and the corresponding signaling pathways. Hence, clarifying the specific roles of HOXA9 and HOXB9 can provide a crucial understanding of the fundamental processes of cancer development, establishing the basis for focused therapy approaches. This research aims to enhance the overall comprehension of cancer biology, facilitating progress in diagnostics, prognostics, and therapeutic interventions (Chen et al. 2020).

Their diverse functions in cellular processes emphasize the importance of HOXA9 and HOXB9 in biomedical research, notably their participation in crucial molecular pathways and their relevance to various physiological and pathological situations. HOXA9 and HOXB9, members of the HOX gene family, have undergone intense scrutiny due to their unique functions and potential implications for human health (Fenelon 2022; Shenoy et al. 2022b). Their importance in biomedical studies can be clarified through the following aspects:

HOXA9 and HOXB9 have been recognized as vital regulators in embryonic development, with significant functions in determining positional identity along the anterior–posterior axis. Accurate spatial and temporal expression of these genes is crucial for the correct differentiation of cells and the formation of diverse tissues and organs. Gaining insight into their contributions to typical development establishes a basis for understanding their potential deviations in pathological circumstances (Bondos et al. 2020; Gonçalves et al. 2020).

Furthermore, scientific investigation has revealed the participation of HOXA9 and HOXB9 in hematopoiesis, which is the biological process responsible for creating blood cells. These genes control hematopoietic stem cells, affecting their transformation into different types of blood cells. The dysregulation of HOXA9 has been linked to hematologic malignancies, highlighting the clinical significance of these genes in illnesses like leukemia (Aryal et al. 2023; Calvanese et al. 2022; Calvanese and Mikkola 2023). Hox paralogous groups 1–8 have hexapeptide domains, while paralogous groups 9 and 10 proteins have a similar motif that keeps some structural and functional roles; paralogous groups 11–13 proteins do not have the hexapeptide motif. This motif is essential to three amino acid loop extension (TALE) co-factor selectivity to control a subset of Hox targets. Another unexplored issue is how Hox genes have significant functional roles after embryogenesis. Examining subsequent activities in different tissues is crucial, as evidenced by the discovering that Hox-expressing cells are adult stem/progenitor cells in at least several organ systems (Hubert and Wellik 2023). HOXA9 and HOXB9 have become significant factors in the field of cancer, as they play diverse and crucial roles in advancing tumors. HOXB9 is frequently linked to cancer promotion by its influence on cell proliferation and angiogenesis (Contarelli et al. 2020).

In contrast, HOXA9 has inhibitory effects and regulates processes such as metastasis and apoptosis. The interaction between these genes and the complex signaling pathways within cancer cells offers an essential understanding of the molecular mechanisms that drive cancer development. Moreover, the research has focused on investigating the diagnostic and prognostic importance of HOXA9 and HOXB9 in different malignancies (Jin et al. 2019; Osmond et al. 2022; Yao et al. 2022; Zhang et al. 2019).

Ultimately, the importance of HOXA9 and HOXB9 in biomedical research spans various areas, including developmental processes, hematopoiesis, and cancer biology. Their roles in these circumstances emphasize their significance as crucial regulators with consequences for normal and abnormal conditions (Grier et al. 2005; Paço et al. 2020). Studying the complex pathways controlled by HOXA9 and HOXB9 helps us better comprehend basic biological processes and can potentially create new therapeutic approaches in biomedicine. The investigation of the specific functions of HOXA9 and HOXB9 in advancing tumors reveals an intricate interaction between these genes and the molecular mechanisms that control cancer development (Contarelli et al. 2020).

HOXA9 and HOXB9 are members of the HOX gene family, which play distinct roles in the complex field of

cancer biology. These genes contribute to the wide range of outcomes observed in tumor formation, often displaying contrasting effects. HOXB9, known for its capacity to control transcriptional processes, significantly contributes to the advancement of tumors. It exerts its impact by regulating critical biological processes, mainly promoting cell growth and supporting the formation of new blood vessels. The overexpression of HOXB9 has been linked to the proliferation of cancer cells, leading to the uncontrolled proliferation observed in many types of malignancies. Furthermore, its influence on angiogenesis highlights its function in promoting the development of new blood vessels, which are crucial for supplying necessary nutrients and oxygen to facilitate tumor growth and spread (Huang et al. 2014; Seki et al. 2012).

On the other hand, HOXA9 is identified as a tumor suppressor that hinders the advancement of tumors by inhibiting essential processes involved in cancer growth. HOXA9 has been found to hamper metastasis, a characteristic feature of aggressive malignancies. Its regulatory function also includes the modulation of apoptosis, where it facilitates programmed cell death, thereby serving as a safeguard against unregulated cell growth. HOXB9 plays a crucial role in limiting the ability of cancer cells to invade and spread, making it an essential factor in preventing tumor growth (Li et al. 2019a).

The molecular mechanisms underlying the different functions of HOXA9 and HOXB9 are revealed. HOXB9 coordinates a tumor-promoting role that supports unrestricted cell proliferation by participating in several signaling pathways. On the other hand, HOXA9 exerts its anti-tumor actions by modulating pathways that hinder the spread of cancer cells and enhance programmed cell death. The complicated interplay between these genes and other molecular components underscores the intricacy of their interactions in the setting of tumor advancement (Contarelli et al. 2020).

Additionally, epigenetic alterations are significant in the intricate functions of HOXA9 and HOXB9 in cancer biology. Regulating gene expression utilizing DNA methylation and histone modifications introduces an extra level of intricacy to their roles, impacting the equilibrium between pro-tumorigenic and anti-tumorigenic states (Gu et al. 2024).

Ultimately, investigating the specific functions of HOXA9 and HOXB9 in advancing tumors offers a thorough comprehension of their roles in cancer development. HOXB9 facilitates tumor progression by enhancing cell proliferation and angiogenesis, whereas HOXA9 suppresses metastasis and boosts apoptotic responses. The complex molecular mechanisms and communication involved highlight the significance of investigating these genes as possible targets for therapeutic interventions aiming at interrupting specific pathways linked with the advancement of cancer (Paço et al. 2020; Tang et al. 2022).

History of HOX genes

Homeobox (HOX) genes are an intriguing aspect of molecular biology, deeply integrated into the foundation of life due to their evolutionary history. This review explores HOX genes' origins, structural changes, and functional adjustments. We aim to shed light on these genes' crucial role in the growth and diversification of life forms by examining their path from ancient metazoans to present-day creatures (Brotto et al. 2020). Also, the HOX genes are significant participants in the complex process of genetic regulation. Many illnesses are associated with their abnormal functioning, particularly those related to malignancy. In this regard, studying the precise activities of HOXA9 and HOXB9 in tumor progression provides a comprehensive understanding of their roles in cancer development. This work establishes the foundation for a targeted investigation of the distinct roles played by HOXA9 and HOXB9 in the context of tumor biology (Paço et al. 2020). However, in the following section, we will first talk about the origin of the HOX gene family.

The origins of HOX genes can be traced back to ancient metazoans, indicating their presence in the early stages of evolution. This section examines the initial occurrences that established the basis for later diversification across different groups of organisms. The enduring preservation of HOX genes among different species provides evidence for their primary function in determining the physical structures of various animals. By analyzing the level of conservation and variation, we can gain valuable knowledge about the specific forces that sustain the fundamental activities of HOX genes for extensive periods (Halanych and Passamaneck 2001, Nery et al. 2016).

HOX genes are crucial in embryonic development because they determine their location along the front-back axis. This section presents a sequential narrative of their participation in developing body segments and organ systems. Precise regulation of the spatial and temporal expression patterns is essential for accurate development. Investigating how HOX genes coordinate these patterns improves our comprehension of their function in embryogenesis (Afzal and Krumlauf 2022; Deschamps et al. 2004; Durston 2019).

The shift from water-based to land-based habitats was a crucial turning point in the evolution of vertebrates. HOX genes played a significant role in facilitating adaption and promoting species variation. Examining their function in this process reveals their importance in evolutionary advancements, such as the formation of limbs and the variety of physical structures (Di-Poi et al. 2010; Fish 2019).

HOX genes, traditionally known for their involvement in embryonic development, also have a role in maintaining

tissue balance and promoting tissue regeneration after the embryonic stage. This section examines the various functions of HOX genes in adult tissues. HOX genes have a functional variety that extends beyond vertebrates, exerting influence on multiple aspects of invertebrate biology and contributing to our comprehension of evolutionary adaptations (Buffry and McGregor 2022; Parker et al. 2016).

The study investigates the abnormal expression of HOX genes, specifically in cancer, by analyzing the molecular pathways that cause their disruption in the development of tumors. Comprehending the pathogenic consequences of HOX genes provides opportunities for therapeutic interventions by investigating the possibility of directing them to novel treatments, diagnostic markers, and therapeutic targets (Brotto et al. 2020; Kelly et al. 2011; Pai and Sukumar 2020).

Lastly, this article discusses new research areas and practical uses, emphasizing advanced technologies and methods influencing the future of studying HOX genes. Studying the complexities of HOX gene evolution reveals the extraordinary path these genes have followed, impacting the biological world.

Most well-defined members of the HOX family

The Homeobox (HOX) gene family consists of highly conserved transcription factors that have essential functions in embryonic development, cellular differentiation, and tissue patterning. HOX genes' unique spatial and temporal expression patterns along the anterior–posterior axis during development determine their uniqueness. In this analysis, I will offer comprehensive information regarding individual members of the HOX family, elucidating their precise modes of action, their specialized tasks within the body, and the potential repercussions resulting from their aberrant expression. Controversial role of HOXA9 and HOXB9 in cancer have been summarized in Table 1 as well as shown in Fig. 1. The results indicate that the HOX genes are involved in a variety of normal stem cell functions and characteristics, such as multilineage differentiation and self-renewal, and that HOX gene dysregulation promotes the development of cancer by causing aberrant stem cell differentiation and self-renewal (Bhatlekar et al. 2018a).

HOXA9

HOXA9, situated on chromosome 7, is crucial in the HOX family. Its expression is controlled during embryonic development, specifically in constructing the central nervous system, axial skeleton, and limbs. HOXA9 functions as a

Table 1 Roles of different HOX genes in various cancers

HOX Gene	Mechanism of Action	Target Molecules	Main Findings	Target Cancer	Ref
HOXA9	Acts as a transcriptional regulator that promotes cell proliferation and survival	Targets include genes involved in cell cycle regulation and apoptosis	HOXA9 is often dysregulated in leukemia, contributing to leukemogenesis	AML CML	(Aryal et al. 2023)
HOXB9	Enhances tumor growth and metastasis through regulation of EMT and stemness pathways	Modulates EMT markers, such as E-cadherin and N-cadherin, and stem cell-related genes	HOXB9 promotes breast cancer progression and metastasis	Breast Cancer	(Hayashida et al. 2010)
HOXC13	Regulates Wnt/β-catenin signaling, promoting proliferation and invasion	Modulates the expression of Wnt pathway components and downstream effectors	HOXC13 contributes to the activation of Wnt/β-catenin signaling in colorectal cancer	Colorectal Cancer	(Dai et al. 2021)
HOXD10	Acts as a tumor suppressor by inhibiting cell proliferation and invasion	Targets include genes involved in cell cycle progression and metastasis	HOXD10 expression is decreased in prostate cancer and is associated with aggressive phenotypes	Prostate Cancer	(Mo et al. 2017)
HOXA5	Suppresses cell migration and invasion, acting as a tumor suppressor	Inhibits genes involved in EMT	HOXA5 downregulation is associated with increased aggressiveness in ovarian cancer	Ovarian Cancer	(Kelly et al. 2011)
HOXB13	Influences androgen receptor signaling, promoting cell growth and survival	Modulates androgen receptor activity and downstream signaling	HOXB13 is implicated in the development and progression of prostate cancer	Prostate Cancer	(Brechka et al. 2017)
HOXC9	Enhances cell proliferation and migration through activation of specific pathways	Modulates genes involved in cell cycle control and migration	HOXC9 promotes lung cancer cell proliferation and migration	Lung Cancer	(Aguiar et al. 2021)

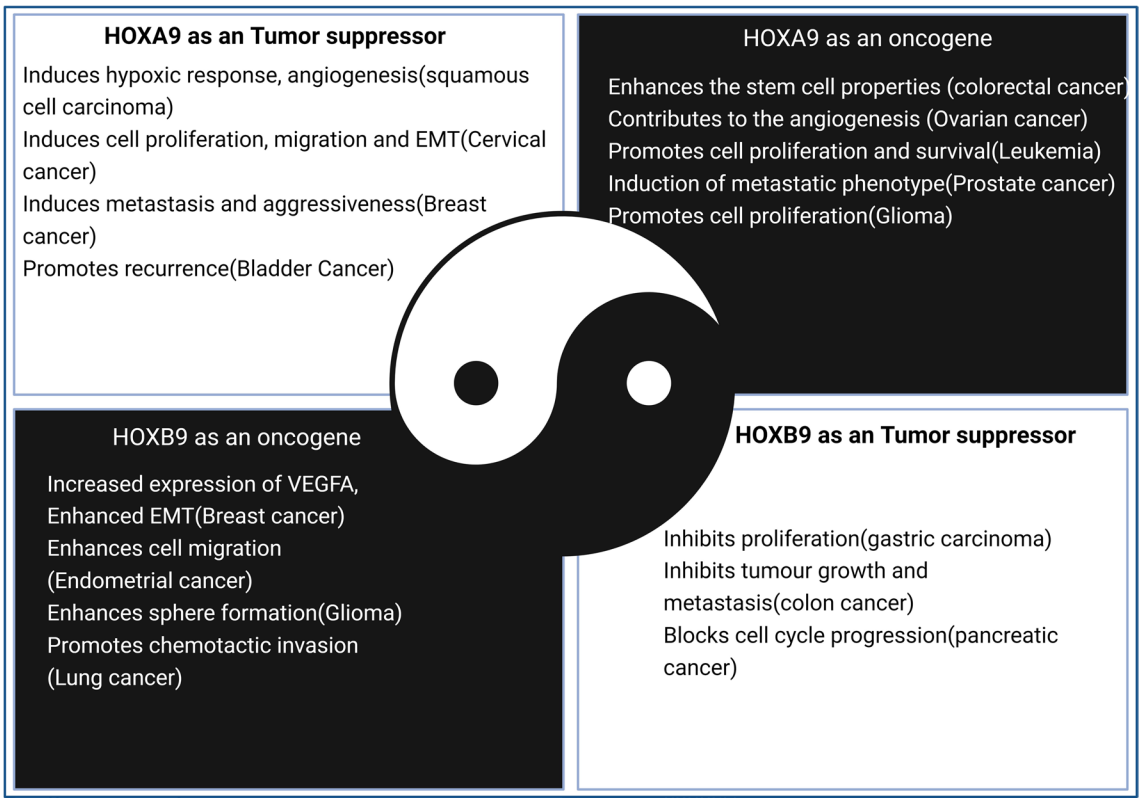

Fig. 1 Controversial role of HOXA9 and HOXB9 family in cancer

transcription factor by selectively binding to particular DNA sequences and controlling the activity of downstream target genes that play a role in cell growth and specialization. HOXA9 is essential in hematopoiesis as it is responsible for the formation of blood cells. It plays a critical role in sustaining the ability of hematopoietic stem cells to reproduce themselves, and it also affects the process of myeloid differentiation (Alsayegh et al. 2019; Huang et al. 2012; Li et al. 2013; Raines et al. 2015).

The abnormal expression of HOXA9 is linked to clinical situations, especially in hematological malignancies. AML is characterized by the excessive expression of HOXA9, associated with heightened cell proliferation, hindered differentiation, and heightened resistance to apoptosis. The excessive overexpression of HOXA9 disrupts the intricate equilibrium of hematopoietic control, hence playing a role in the onset and advancement of leukemia (Dickson et al. 2013; Zhao et al. 2015).

HOXB9

HOXB9, located on chromosome 17, is another notable member of the HOX family. The expression of this gene is crucial in regulating organ formation, especially in the development of the respiratory system. HOXB9 acts as a transcription factor, influencing the expression of genes related to organ development, tissue differentiation, and modulation of the immune response. HOXB9 has been acknowledged for suppressing cancer, specifically in limiting metastasis and increasing apoptosis (Hao et al. 2014; Pai and Sukumar 2020; Sakiyama et al. 2000; Xu et al. 2020).

The dysregulation of HOXB9 has been linked to many types of malignancies, and the effects vary depending on the individual circumstances. Elevated HOXB9 expression in breast cancer is related to heightened metastatic capacity and unfavorable prognosis. In contrast, in the case of pancreatic cancer, the excessive expression of HOXB9 has been associated with increased invasion and migration (Martinou et al. 2021; Seki et al. 2012; Yao et al. 2022).

HOXD13

HOXD13, located on chromosome 2, plays a crucial role in the development of limbs. Its expression is specifically restricted to the developing limbs, which play a role in the precise arrangement of fingers and toes and the overall formation of hands and feet. HOXD13 acts as a transcription factor, playing a role in controlling the genes that are important for the development of the skeleton, the construction of

joints, and the determination of digit identification (Brison et al. 2014; Guéro 2018; Kurban et al. 2011).

Congenital limb deformities, such as synpolydactyly, are linked to mutations in the HOXD13 gene, resulting in fused or webbed fingers and toes in affected individuals. HOXD13 mutations or improper expression can disturb the precisely regulated process of limb development, resulting in structural defects and impaired functionality (Ibrahim et al. 2013, 2016).

HOXC6

HOXC6 on chromosome 12 forms the central nervous system and axial skeleton. It contributes to determining regional identity along the anterior–posterior axis during embryonic development. HOXC6 functions as a transcription factor, exerting influence over the expression of genes that are essential for the development of the neural tube, the patterning of the spinal cord, and the formation of the axial skeleton (Durston 2019; Huang et al. 2016; Kostic and Capecchi 1994; Wilson and Maden 2005).

The abnormal expression of HOXC6 has been linked to several types of malignancies, such as breast cancer. HOXC6 overexpression in breast cancer cells is related to heightened cell proliferation, migration, and invasion. The aberrant activation of HOXC6 contributes to the aggressive activity of cancer cells, emphasizing its significance in the development of tumors (Li et al. 2018; Tang et al. 2019).

HOXA1

HOXA1 on chromosome 7 forms the hindbrain and cranial neural crest cells. It has a role in developing structures like the rhombomeres, which are crucial for correctly segmenting the hindbrain. HOXA1 acts as a transcription factor, controlling the expression of genes involved in the development of the hindbrain and the migration of cranial neural crest cells (Abu-Amero et al. 2013; Makki and Capecchi 2011; Parker et al. 2018).

HOXA1 expression disruptions are linked to developmental abnormalities, specifically in the hindbrain and cranial neural crest derivatives. HOXA1 mutations in humans are associated with the Bosley-Salih-Alorainy syndrome, characterized by facial paralysis, hearing loss, and developmental delay. The inadequate manifestation of HOXA1 highlights its crucial function in the normal development of the hindbrain and cranial neural crest (Makki and Capecchi 2011; Parker et al. 2018).

The examples illustrate the varied roles of HOX genes in the development of embryos and the repercussions of their improper regulation in different disorders. The distinctiveness of each HOX gene highlights the intricacy of their functions in determining the elaborate patterns and structures during embryonic development (Ekanayake et al. 2022; Paço et al. 2020).

The biological role of HOXA9 and HOXB9

The biological functions of HOXA9 and HOXB9 in cancer encompass complex mechanisms, precise molecules, and regulation of signaling pathways:

HOXA9 in cancer

HOXA9 has a complex role in cancer, characterized by its participation in intricate mechanisms, regulation of specific molecules, and initiation of signaling pathways that contribute to tumor development (Agrawal-Singh et al. 2023). The comprehensive investigation of HOXA9's involvement in cancer spans various crucial facets:

Transcriptional regulation

HOXA9, acting as a transcription factor, significantly impacts gene expression patterns essential for the genesis and advancement of cancer, encompassing the direct control of genes linked to critical activities such as cell cycle advancement, proliferation, and viability. HOXA9 targets numerous cancer-associated genes, influencing its oncogenic processes and playing a role in the complex network of molecular events that drive carcinogenesis (Aryal et al. 2023; Shenoy et al. 2023).

In this regard, several prominent genes play a crucial role in cancer and are directly regulated by HOXA9. HOXA9 is a transcription factor that controls genes related to stem cell biology, which is unsurprising. Although there is still much to learn about HOXA9's downstream targets, research has demonstrated that HOXA9 can operate as a transcriptional activator and repressor. Two exons are present in the conventional HOXA9 transcript: exon II, which contains a homeodomain, and exon CD. Many adult and embryonic tissues express this transcript. In addition to encoding the DNA binding domain, exon II is a highly intriguing region since, along with the 3′ UTR, it is the most common region between different HOXA9 isoforms (Popovic et al. 2008).

The expression of Cyclin D1 (CCND1), a controller of the transition from the G1 to S phase of the cell cycle, is directly impacted by HOXA9, hence contributing to the unregulated advancement of the cell cycle that is observed in cancer cells (Gonçalves 2013).

HOXA9 modulates the Cyclin-Dependent Kinase 6 (CDK6), which, in collaboration with cyclins, facilitates the progression of the cell cycle. This modulation affects cell cycle control and promotes cell proliferation (Gong et al. 2020).

The production of the anti-apoptotic protein BCL2, which is essential for cell life, is influenced by HOXA9, causing cancer cells to evade apoptosis and promoting their increased survival (Ye et al. 2023).

The transcription factor MYC, which controls cell proliferation and growth, interacts with HOXA9, potentially affecting its expression and boosting cellular proliferation (Miyamoto et al. 2021).

Vascular Endothelial Growth Factor (VEGF) is crucial for the formation of blood vessels in tumors through angiogenesis. The expression of VEGF is stimulated by HOXA9, which plays a role in triggering the switch to angiogenesis and promoting the growth of tumors (Xue et al. 2020).

HOXA9 modulates Notch1, a signaling pathway regulator crucial in determining cell fate and promoting cell proliferation. This modulation significantly affects cell differentiation and proliferation in cancer (Santaguida et al. 2009).

The expression of the tumor suppressor gene phosphatase and TENsin homolog deleted on chromosome 10 (PTEN), which has a negative role in the PI3K/Akt signaling pathway, can be altered by HOXA9. This, in turn, affects the equilibrium between pro-survival and pro-apoptotic signals in cancer cells (Mouw et al. 2014).

The expression of the cyclin-dependent kinase inhibitor p21 (CIP1)/wildtype p53-activated fragment 1 (WAF1), which plays a critical role in controlling the advancement of the cell cycle, may be influenced by HOXA9, affecting the ability of cancer cells to stop the cell cycle (Sharma and Nag 2014).

The tumor suppressor gene p53, which controls cell cycle, apoptosis, and DNA repair, has been linked to changes in its activity due to the presence of HOXA9, influencing the capacity of cancer cells to undergo programmed cell death and maintain stable DNA structure (Mullany et al. 2015).

Gaining knowledge about the specific control of these genes by HOXA9 offers a valuable understanding of the molecular complexities contributing to the genesis and advancement of cancer. The combined effect of these genes strongly impacts essential cellular processes such as the progression of the cell cycle, cell proliferation, and cell survival, highlighting their importance in the cancer-causing effects of HOXA9 (Paço et al. 2020).

Interaction with co-factors

The interaction between HOXA9 and co-factors such as Myeloid ecotropic viral integration site 1 (MEIS1) and Pre-B cell leukemia transcription factor (PBX) substantially affects its ability to regulate gene expression, enhancing its involvement in encouraging the development of tumors. This collaborative connection also encompasses downstream target genes linked to essential cellular activities such as cell cycle advancement, proliferation, and viability. The upregulation of HOXA9's influence on specific genes contributes to malignant cells' unregulated proliferation and viability (Gİrgİn et al. 2020).

An important gene influenced by this collaborative relationship is CCND1, which plays a crucial role in regulating the cell cycle, namely in the transition from the G1 phase to the S phase. The synergistic interaction between HOXA9, MEIS1, and PBX results in an up-regulation of CCND1 expression, leading to enhanced transcriptional activity. Therefore, the increase in expression of Cyclin D1 is essential in facilitating unregulated advancement of the cell cycle, which is a significant characteristic of the development of tumors (Aksoz et al. 2018).

Essentially, the collaborative interaction between HOXA9 and components such as MEIS1 and PBX intensifies its role in promoting the formation of tumors by enhancing the activation of downstream target genes at the transcriptional level. Cyclin D1 is identified as a crucial factor in promoting the abnormal development of the cell cycle seen in cancer cells. The complex molecular network highlights the importance of HOXA9's cooperative interactions in affecting critical pathways associated with cancer formation and advancement (Collins and Hess 2016a; Tang et al. 2022).

Activation of MAPK/ERK pathway

HOXA9 plays a crucial role in cancer by activating the Mitogen-Activated Protein Kinase/Extracellular Signal-Regulated Kinase (MAPK/ERK) signaling pathway. This activation promotes cellular proliferation and survival, creating a favorable environment for unregulated growth (Wang et al. 2017; Yu et al. 2020).

Modulation of Wnt/β-catenin pathway

HOXA9 is involved in regulating the Wnt/β-catenin signaling pathway, which is an essential controller of cell fate and proliferation. Disruption of this pathway is frequently observed in cancer, and HOXA9's influence on Wnt signaling enhances tumor development (Xu et al. 2021).

Promotion of angiogenesis

HOXA9 is essential in facilitating angiogenesis, a critical mechanism in providing nutrients and oxygen to developing tumors. This process entails the stimulation of pro-angiogenic substances, specifically VEGF, which aids in creating new blood vessels (Contarelli et al. 2020).

Epigenetic regulation

HOXA9 is a critical player in the process of epigenetic regulation. It exerts its influence by altering the DNA methylation

patterns, which impacts gene expression in cell proliferation and angiogenesis. The HOXA9 gene plays a crucial role in controlling epigenetic changes that considerably impact the continuous activation of cancer-causing pathways. The modification of chromatin structure caused by DNA methylation alterations directly affects the ability of transcriptional machinery to access the VEGF gene, therefore altering its transcriptional activity (Fraineau et al. 2015).

HOXA9 enables epigenetic modifications that influence the transcriptional control of the VEGF gene, up-regulating the transcription of VEGF, thus resulting in heightened amounts of VEGF in the cellular environment. VEGF is a crucial element in promoting angiogenesis, serving as a central factor in stimulating the creation of fresh blood vessels. The interaction between HOXA9-induced epigenetic alterations and the consequent increase in VEGF expression highlights the complex function of HOXA9 in coordinating molecular processes that facilitate angiogenesis, a crucial component of tumor development (Feng et al. 2021a).

Clinical implications

HOXA9 is frequently overexpressed in several types of malignancies and is linked to unfavorable prognosis. HOXA9 levels can function as a prognostic marker, indicating the outcome of a disease and offering crucial information about the severity of the illness and the possibility of treatment intervention (Feng et al. 2021a; Li et al. 2022).

An intricate combination of transcriptional regulation, co-factor interaction, activation of crucial signaling pathways, stimulation of angiogenesis, and epigenetic changes characterizes HOXA9's involvement in cancer. Gaining insight into these mechanisms offers a thorough understanding of HOXA9's role in the development of tumors. It reveals prospective approaches for targeted therapies that attempt to disrupt the pathways linked to its cancer-causing actions (Li et al. 2019b).

HOXB9 in cancer

HOXB9, a transcription factor from the HOXB cluster genes, has a diverse involvement in cancer, specifically in enhancing tumor development, advancement, and resistance to anti-angiogenic therapies. The link of this factor with poor prognosis in multiple forms of cancer highlights its participation in various facets of cancer biology (Carbone et al. 2017; Zhan et al. 2015).

HOXB9 is regulated by the wingless-related integration site (WNT)/transcription factor 4 (TCF4) pathway and is activated by N-acetyl-galactosaminyl-transferases 14 (GalNAc-T14). Moreover, estrogen and E2F transcription factors, which play a crucial role in controlling the cell cycle, have been found to regulate the expression of HOXB9 directly. Post-translational changes, including acetylation, also affect the activity of HOXB9. The acetylated form of HOXB9 shows decreased ability to migrate and promote tumor growth (Aros et al. 2021; Kwon et al. 2015; Song et al. 2018; Zhussupova et al. 2014).

HOXB9 plays a crucial role in the development of resistance to anti-angiogenic therapies. The expression of HOXB9 is associated with the increased expression of pro-angiogenic factors, such as VEGF, fibroblast growth factor (bFGF), angiopoietin-like protein 2 (ANGPTL2), TGF-β, IL-1, and IL-8. These findings indicate that HOXB9 has a role in evading anti-angiogenic treatments by promoting an alternate milieu that is both proinflammatory and pro-angiogenic. The complex interplay of variables triggered by the activation of HOXB9 has been linked to resistance against anti-VEGF therapy, highlighting its crucial function in maintaining tumor resistance (Brotto et al. 2020; Carbone et al. 2016, 2017; Gharbaran 2016; Wu et al. 2016; Xu et al. 2020).

Moreover, HOXB9 is involved in enhancing tumor invasiveness and metastasis. The overexpression of this gene in many malignancies is associated with enhanced migration and invasion, as it is connected to the epithelial-mesenchymal transition (EMT) pathway. The TGF-β pathway seems responsible for these effects, emphasizing the role of HOXB9 as a controller of a more aggressive phenotype in cancer cells (Sha et al. 2015; Xue et al. 2017).

HOXB9 impacts the recruitment and stimulation of diverse immune cells, such as myeloid-derived suppressor cells (MDSCs), monocytes, macrophages, and cancer-associated fibroblasts (CAFs) within the tumor microenvironment. The immune cells are drawn to the tumor environment due to proinflammatory substances caused by HOXB9, and they play a role in suppressing the immune response (Contarelli et al. 2020; Liu et al. 2023; Pai and Sukumar 2020; Rastogi et al. 2023). The overexpression of HOXB9 in 42% of human breast cancers is consistent with the dysregulation of other HOX genes; however, the functional and molecular implications of modifications in other HOX genes in cancer remain little understood. Examining HOXB9-dependent phenotypes implies that dysregulated HOXB genes could play a role in reprogramming cancer cells to become more mesenchymal and possibly more invasive, achieving through tumor production and secretion of various growth factors that modify the surrounding environment to promote tumor growth (Hayashida et al. 2010).

HOXB9 is a crucial transcription factor that plays a significant role in cancer by affecting several aspects, such as tumor growth, resistance to anti-angiogenic treatments, metastasis, and the modification of the tumor microenvironment. Gaining a comprehensive understanding of the complex regulatory mechanisms associated with HOXB9 is essential for developing precise therapeutic techniques in

the field of cancer, especially in the quest for more potent anti-angiogenic medicines.

Impact of HOXB9 on cancer-associated signaling pathways

HOXB9, a constituent of the HOX gene family, has been linked to intricate impacts on signaling pathways that have crucial functions in the formation and advancement of cancer. The specific processes by which HOXB9 affects these pathways depend on the setting and can differ among various forms of cancer (Feng et al. 2021b). The following is a comprehensive analysis of the impact of HOXB9 on crucial signaling pathways associated with cancer:

Wnt/β-Catenin Signaling Pathway HOXB9 has been documented to act as a suppressor of the Wnt/β-catenin pathway under specific circumstances. It can disrupt stabilizing and moving β-catenin to the nucleus, an essential step in Wnt signaling (Xiong et al. 2019).

HOXB9 exerts a tumor-suppressive impact by blocking the Wnt/β-catenin signaling pathway, which is often linked to increased cell growth and the advancement of tumors (Yu et al. 2020).

Transforming Growth Factor-Beta (TGF-β) Signaling Pathway HOXB9 can interact with components of the TGF-β signaling pathway, impacting its downstream signaling cascades (Xiong et al. 2020).

The impact of HOXB9 on TGF-β signaling can lead to the stimulation of EMT, a critical mechanism for spreading cancer to other parts of the body (Chiba et al. 2022).

Notch Signaling Pathway The function of HOXB9 in the Notch signaling system seems to rely on specific circumstances, and its impact may differ across various types of cancer (Shenoy et al. 2022a).

HOXB9 has sometimes been linked to the activation of Notch target genes, leading to increased cell proliferation and survival (Kwon et al. 2015).

PI3K/Akt/mTOR Pathway HOXB9 has been associated with stimulating the phosphatidylinositol 3-kinase (PI3K)/protein kinase B (AKT)/mammalian target of rapamycin (mTOR) pathway in some cancer scenarios. This activation can enhance cell viability, proliferation, and resistance to programmed cell death, contributing to cancer cells' oncogenic capacity (Song et al. 2022).

ERK/MAPK Signaling Pathway HOXB9 has been documented to activate the ERK/MAPK signaling pathway in some cancer contexts. HOXB9 activation of this pathway can result in enhanced cellular proliferation and survival, promoting the advancement of malignancy (Gonçalves et al. 2020).

Nuclear Factor-kappa B (NF-κB) Pathway HOXB9 has been linked to the suppression of the NF-κB pathway. HOXB9's suppression of nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) may play a role in controlling the expression of genes related to inflammation, apoptosis, and immunological responses, impacting the tumor microenvironment (Yu et al. 2020).

HOXB9's impact on signaling pathways in cancer is complex and dependent on multiple factors, such as the specific cellular environment and the tumor's molecular characteristics. The influence of HOXB9 on signaling pathways depends on the context, which emphasizes the complexity of its regulatory functions in cancer and the necessity for additional research to determine the exact mechanisms involved in different types of cancer (Shenoy et al. 2022a).

Dual role of HOXA9 and HOXB9 in cancer

HOXA9 and HOXB9 have attracted interest because of their multifaceted functions in the complex field of cancer biology. These genes are components of the broader HOX network that regulates cells' spatial and temporal arrangement during embryonic development. HOXA9 and HOXB9 have been linked to multiple aspects of cancer start, progression, and response to treatment, in addition to their developmental roles (Contarelli et al. 2020).

The abnormal expression of HOXA9 and HOXB9 has been detected in various types of cancer, such as hematological tumors, breast cancer, ovarian cancer, and head and neck squamous cell carcinoma (HNSCC). These genes can have positive and negative effects on the development of tumors, depending on the specific conditions and environment within the cells. Their participation in crucial biological mechanisms such as cell growth, movement, infiltration, and resistance to medical treatments highlights their importance in cancer research (de Bessa Garcia et al. 2020; Kelly et al. 2016; Platais et al. 2016).

To fully comprehend the dual function of HOXA9 and HOXB9 in cancer, it is imperative to thoroughly investigate their molecular mechanisms and interactions within complex signaling cascades. Understanding the individual actions of these genes in different contexts is crucial for developing precise therapeutic approaches that can exploit their potential as either oncogenes or tumor suppressors (Contarelli et al. 2020).

Leukemia

The complicated participation of HOXA9 and HOXB9 in leukemia is characterized by their dual role in promoting and preventing carcinogenesis. These effects are

context-dependent and vary among various subtypes of leukemia.

HOXA9 is commonly up-regulated in many types of blood cancers, such as acute myeloid leukemia (AML) and acute lymphoblastic leukemia (ALL), and its increased expression is generally linked to an unfavorable prognosis. HOXA9 acts as a transcription factor that controls the expression of genes related to cell cycle regulation, self-renewal, and differentiation. It forms complexes with co-factors like MEIS1 to regulate the expression of target genes. The regulatory function adds to its capability to enhance the proliferation of leukemic cells and their ability to renew themselves by regulating crucial regulators of the course of the cell cycle and the renewal of hematopoietic stem cells (Collins and Hess 2016b; Paul et al. 2020; Symeonidou and Ottersbach 2021).

Moreover, HOXA9 also hinders the regular process of hematopoietic differentiation, leading to the buildup of undifferentiated leukemic blasts. This obstruction enhances the combative characteristic of leukemia. HOXA9 regulates transcription and interacts with enzymes that modify chromatin, such as histone and DNA methyltransferases. This interaction causes changes in the structure of chromatin and the expression of genes. These interactions highlight the diverse involvement of HOXA9 in influencing the molecular characteristics of blood cancers, offering an understanding of the mechanisms that contribute to its connection with the advancement of leukemia and unfavorable prognosis (Blecua et al. 2020).

HOXB9's tumor-suppressive role in leukemia

HOXB9's role in leukemia varies depending on the setting, demonstrating both oncogenic and tumor-suppressive effects. The impact of leukemia is determined by the amount of its expression and its unique interactions within the cellular microenvironment (Braekeleer et al. 2014; Drabkin et al. 2002).

It has been shown that in specific subtypes of leukemia, there is an anti-proliferative effect caused by inhibiting the growth of leukemic cells. This effect is closely related to regulating cell cycle checkpoints involving the gene HOXB9. The anti-proliferative ability is a component of HOXB9's broader regulatory function in signaling pathways essential for cell survival and growth. It can significantly impact the delicate equilibrium between self-renewal and differentiation by interacting with pathways such as Wnt/β-catenin and Notch (Almasmoum et al. 2021; Kwon et al. 2015; Winkler 2010).

Furthermore, the influence of HOXB9's function in leukemia extends beyond cell-intrinsic processes. The activity of this entity seems to be affected by the leukemic microenvironment, where its regulatory function might be altered through interactions with stromal cells and extracellular matrix components. The significance of HOXB9 in leukemia progression is further complicated by its interactions with the microenvironment. The intricate relationship between HOXB9, signaling pathways within cells, and the microenvironment specific to leukemia collectively influences the diverse range of its participation in the disease, providing a nuanced comprehension of its impact on cell growth and the broader context of disease advancement (Brotto et al. 2020).

To comprehend the dual function of HOXA9 and HOXB9 in leukemia, a comprehensive examination of their molecular mechanisms and connections with the complex signaling networks in leukemia cells and their surroundings is necessary. The intricate nature of the situation emphasizes the necessity for precise therapeutic approaches that consider the distinct molecular characteristics of different forms of leukemia; this is crucial to effectively regulate the functions of HOXA9 and HOXB9 for therapeutic advantage (Brotto et al. 2020).

Solid tumors

HOXA9 in solid tumors

HOXA9 has been recognized as a tumor suppressor in several types of solid tumors, such as breast, ovarian, and cervical malignancies. The expression of HOXA9 is frequently reduced in these situations, and increasing HOXA9 levels has been linked to the suppression of cancer cell growth and the initiation of programmed cell death (apoptosis) (Alvarado-Ruiz et al. 2016; Bhatlekar et al. 2014; Shenoy et al. 2023).

HOXA9 regulates apoptosis and autophagy processes in tumor cells by controlling the transcription of v-rel avian reticuloendotheliosis viral oncogene homolog A (RELA), a vital element of the NF-κB pathway. When HOXA9 is not present, RELA becomes more active, activating important molecules related to programmed cell death (apoptosis) and the self-degradation process (autophagy) at the level of gene transcription. More precisely, the upregulation of RELA levels leads to activating the anti-apoptotic protein Bcl-XL. Concurrently, the study demonstrated that the autophagic process is affected, increasing autophagic molecules such as autophagy-related gene 2 (ATG2), ATG3, and ATG12 (Han et al. 2019).

HOXA9 exerts a substantial influence in inhibiting EMT and the spread of cancer cells to other body parts in different forms of cancer. HOXA9 in cervical cancer (CC) acts as a tumor suppressor by inhibiting cell proliferation and migration when its expression is lowered. Reintroducing HOXA9 leads to a reduction in these aggressive cellular activities and an enhancement of the epithelial phenotype. Significantly, an increase in HOXA9 results in activating the newly

discovered EMT inhibitor, grainyhead-like 2 (GRHL2), establishing a mechanical connection to preventing EMT in CC cells. When CC cells express HOXA9 and are infected with E6 or E7-HPV 18 oncoproteins, there is a noticeable reduction in cell proliferation, motility, colony formation, and metabolism, demonstrating that HOXA9 has a role in inhibiting the progression of CC (Alvarado-Ruiz et al. 2016; Mehrazarin et al. 2015; Torres-Reyes et al. 2014). The proper expression of HOXA9, HOXB9, and HOXD9 in adult mammary glands indicates that these genes play a direct role in the development of mammary tissue postpartum. Searching for these HOX genes' misexpression in mammary carcinomas might be fruitful since their loss-of-function mutations result in mammary gland hypoplasia during pregnancy (Chen et al. 2020).

Additionally, in colorectal cancer cells (CRC), overexpression of HOXA9 promotes the self-renewal and overpopulation of SCs. Techniques aimed at regulating HOX expression could focus on cancerous stem cells and create more potent treatments for colorectal cancer (Bhatlekar et al. 2018b). Furthermore, dysregulated HOXA4, HOXA9, and HOXD10 gene signaling leads to SC overpopulation and cancer development. These gene signals are primarily found in SCs. For instance, the link between HOXA9 and the aldehyde dehydrogenase (ALDH) gene family suggests that there are regulatory mechanisms between HOXA9 and RA signaling in both malignant and benign colonic stem cells (Bhatlekar et al. 2019; Xu and Wellik 2011).

Decreased levels of HOXA9 transcripts in breast cancer are linked to the spread of cancer cells to other parts of the body and the severity of the disease. Reintroducing HOXA9 in breast cancer cells results in elevated tumor-suppressor breast cancer gene 1 (BRCA1) expression, inhibiting malignant activity. Moreover, in the context of breast cancer (BC), the suppression of the high mobility group AT-hook 2 (HMGA2)-ten-eleven translocation 1 (TET1)-HOXA9 pathway impedes the progression of tumors, the process of cancer cells entering blood vessels, the infiltration of cancer cells into surrounding tissues, and the spread of cancer to other parts of the body (Gilbert et al. 2010; Sun et al. 2013).

HOXB9 in solid tumors

HOXB9 exhibits multifaceted functions in solid tumors, exerting its impact through multiple molecular processes that lead to distinct biological consequences and clinical observations in various cancer types. In breast cancer, HOXB9 serves as the target gene of the E2F1 transcription factor, resulting in an overexpression of VEGFA, bFGF, IL-8, and angiopoietin-like protein 2 (ANGPTL2). This chemical interaction contributes to the augmentation of EMT. The biological consequence of this process is the formation of highly vascularized tumors that have a propensity to create lung metastases. Clinically, the link between HOXB9 overexpression, higher tumor grade, and poor survival highlights the role of HOXB9 in determining the aggressive aspects of breast cancer (Chiba et al. 2012; Hayashida et al. 2010; Seki et al. 2012; Shrestha et al. 2012; Zhussupova et al. 2014).

Colorectal cancer is characterized by elevated VEGFA, bFGF, TGF-β, and IL-8 expression in HOXB9, which promotes EMT. The acetylated version of HOXB9 is notably involved in inhibiting cancer progression. The molecular action significantly enhances cell migration and invasion, resulting in substantial biological effects. The clinical observation of increased HOXB9 expression is associated with distal metastases and resistance to bevacizumab, highlighting the significant clinical consequences of HOXB9 in colorectal cancer (Carbone et al. 2017; Hoshino et al. 2014; Huang et al. 2014; Wan et al. 2016).

HOXB9 significantly stimulates the expression of E2F transcription factor 3 (E2F3) in endometrial cancer by directly focusing on its promoter. This molecular interaction has profound biological implications, particularly by augmenting cell migration and contributing to the advancement of cancer. High expression of HOXB9 is clinically correlated with a high histological grade and an increased probability of lymph node metastases, highlighting the clinical significance of HOXB9 in endometrial cancer (Wan et al. 2018).

HOXB9 plays a crucial role in gastric cancer by inhibiting the phosphorylation of Akt and the activity of NF-κB, leading to the induction of EMT. This molecular mechanism results in a significant biological impact, particularly the suppression of the growth and movement of stomach cancer cells. From a clinical perspective, the observed relationship between reduced expression and excessive expression of HOXB9 is associated with lymph node metastases and unfavorable survival rates, underlying the dual effect of HOXB9 on the clinical outcomes of patients with gastric cancer (Kato et al. 2019; Zhang et al. 2019).

HOXB9 plays a crucial function in glioma by stimulating the TGF-β1/ Mothers against the decapentaplegic homolog 2 (SMAD2) signaling pathway. This molecular activity has significant biological consequences, such as promoting cell growth, movement, the creation of spherical structures, and an increased ability to produce tumors. The clinical analysis reveals a strong association between the excessive expression of HOXB9 and the spread of cancer cells to the lymph nodes, as well as a negative impact on the survival rate of patients with glioma, highlighting the crucial role of HOXB9 in determining the clinical outcomes of glioma patients (Fang et al. 2014).

HOXB9 is essential in promoting EMT in hepatocellular cancer. It achieves this by activating the TGF-β1/ SMAD2 signaling pathway and simultaneously controlling pro-angiogenic proteins. This molecular activity leads to notable biological consequences, such as the stimulation

of cell growth, movement, and infiltration in the context of hepatocellular carcinoma. The clinical significance of the increased expression of HOXB9 is associated with vascular invasion and unfavorable prognosis, highlighting its impact on the clinical outcomes of patients with hepatocellular carcinoma (Chiba et al. 2017; Li et al. 2014; Sha et al. 2015).

HOXB9 plays a crucial role in lung cancer as the gene is targeted by the WNT/TCF4 pathway, which GalNAc-T14 activates through Wnt signaling. Additionally, HOXB9 undergoes acetylation mediated by PCFA. The complex molecular mechanisms described here have specific impacts on biological systems. HOXB9 facilitates cell invasion and plays a role in chemotactic invasion and colony development. Significantly, the acetylated variant of HOXB9 has a reduced ability to stimulate cell migration and tumor proliferation. The clinical observation of increased expression of HOXB9 in lung cancer is associated with a high grade of tumor and an adverse prognosis, indicating its importance in impacting the clinical outcomes of patients with this cancer (Kwon et al. 2015; Nguyen et al. 2009; Wan et al. 2016; Zhan et al. 2015).

HOXB9 has a crucial function in oral squamous carcinoma by facilitating EMT via the TGF-β1/SMAD2/Slug signaling pathway. This molecular activity leads to notable biological consequences, including the augmentation of cell motility and invasion in oral squamous cancer. From a clinical perspective, elevated levels of HOXB9 are linked to a higher histological grade and shorter overall survival, revealing the significance of HOXB9 in impacting the clinical outcomes of persons with oral squamous carcinoma (Sun et al. 2017; Xue et al. 2017).

HOXB9 is the specific gene targeted by miR-192 in ovarian and renal cancer. This molecular interaction results in a clear and specific biological impact, especially the promotion of tumor blood vessel formation in the context of ovarian and renal cancer. The regulatory association between HOXB9 and miR-192 highlights the importance of HOXB9 in modulating angiogenesis-related processes in these specific kinds of cancer (Wu et al. 2016).

HOXB9 plays a crucial role in pancreatic cancer, characterized by heightened expression of VEGFA, bFGF, IL-8, and ANGPTL2, resulting in an enhanced EMT process. These molecular processes lead to notable biological impacts, as HOXB9 stimulates growth, movement, and invasion and maintains resistance to anti-VEGF inhibition in the microenvironment of pancreatic cancer. The acetylated version of HOXB9 can reduce tumor growth, which adds complexity to the regulatory mechanisms controlled by HOXB9 in pancreatic cancer. In a clinical setting, the excessive expression of HOXB9 is linked to a reduced overall survival rate, highlighting its significance as a prognostic factor in pancreatic cancer (Carbone et al. 2017; Sun et al. 2020).

HOXB9 plays a crucial function in prostate cancer by promoting EMT and controlling pro-angiogenic factors. From a clinical perspective, the excessive expression of HOXB9 is associated with the invasion of blood vessels and an unfavorable prognosis, underscoring its importance in impacting the clinical outcomes of patients with prostate cancer. The complex molecular mechanisms of HOXB9 in prostate cancer highlight its potential as a significant contributor to the advancement and prognosis of this specific kind of cancer (Xu et al. 2020).

HOXB9 plays a complicated and context-dependent role in solid tumors, affecting several biological processes that contribute to the convoluted landscape of cancer progression and clinical consequences in different forms of cancer (Martinou et al. 2021, 2022).

Drug resistance

The simultaneous participation of HOXA9 and HOXB9 in drug resistance introduces further intricacy to their significance in cancer biology. The involvement of these homeobox genes in drug resistance is well-established, with their effects being both promotive and inhibitory. However, their roles can fluctuate depending on the cancer type and therapeutic circumstances (Contarelli et al. 2020; Ju et al. 2017; Shenoy et al. 2023).

HOXA9 in promoting drug resistance

HOXA9 has been linked to the promotion of medication resistance in some types of cancer. HOXA9 potentially enhances resistance by controlling the expression of genes associated with drug efflux, DNA repair, and anti-apoptotic pathways. It can generate a cellular milieu that impairs the effectiveness of chemotherapy drugs (Göllner et al. 2017; Miyamoto et al. 2021).

HOXA9 in inhibiting drug resistance

On the other hand, data indicates that HOXA9 might have a function in increasing the sensitivity of cancer cells to specific treatments. HOXA9 can potentially increase the vulnerability of cancer cells to chemotherapy by controlling the pathways responsible for cell cycle arrest and apoptosis. It has the potential to inhibit medication resistance mechanisms (Liu et al. 2014).

HOXB9 in promoting drug resistance

HOXB9 has a role in developing drug resistance in tumors, specifically in its effect on resistance to bevacizumab, a medication that inhibits VEGF. Tumors exhibiting HOXB9-positive expression exhibited resistance to bevacizumab treatment,

whereas this therapeutic drug successfully treated animals harboring HOXB9-negative tumors. Suppressing the expression of HOXB9 in mice resistant to bevacizumab led to a notable decrease in the levels of crucial molecules, including ANGPTL2, chemokine ligand 1 (CXCL1), IL8, and TGFβ1. This intervention reversed the transformation of cells into a mesenchymal phenotype and decreased the infiltration of CD11b+cells. As a result, the sensitivity to bevacizumab was ultimately restored (Carbone et al. 2017).

Moreover, the predictive significance of HOXB9 was emphasized in individuals who received an initial chemotherapeutic treatment that included bevacizumab. Those with a tumor that does not express the HOXB9 gene had a notably more extended period without disease progression (progression-free survival, or PFS) than those with cancer that express the HOXB9 gene when treated with this specific treatment plan (Hoshino et al. 2014).

HOXB9 in inhibiting drug resistance

On the other hand, there are situations in which HOXB9 might play a part in making cancer cells more responsive to treatment. HOXB9 potentially regulates pathways related to drug metabolism, apoptosis, and DNA damage response, therefore impacting the reaction of cancer cells to chemotherapy (Yuniati et al. 2019). The roles of HOXA9 and HOXB9 in drug resistance are highly dependent on the specific setting, similar to their involvement in cancer growth. The unique cellular and molecular contexts and the type of anticancer treatment used can determine the genes' role as promoters or inhibitors of drug resistance (Brotto et al. 2020).

Interaction with Drug Response Pathways:

HOXA9 and HOXB9 have the potential to interact with essential pathways that play a role in drug response, including pathways associated with DNA damage repair (such as the BRCA pathway), apoptosis (such as the Bcl-2 family), and drug transport (such as ABC transporters). Modulation of drug sensitivity or resistance can occur through their influence on various pathways (Brotto et al. 2020; Duan et al. 2015; Li et al. 2019a).

Understanding the dual functions of HOXA9 and HOXB9 in drug resistance is essential for developing precise treatment approaches. Additional investigation is required to clarify the exact circumstances in which these genes play a role in drug resistance and to pinpoint new treatment approaches that can regulate their actions in a specific situation.

HOXA9 and HOXB9 interaction with immune cells

The interplay between HOXA9 and HOXB9 with immune cells is an intricate and diverse feature of the tumor microenvironment, exerting a pivotal influence on modulating the immune response to cancer. HOXA9 and HOXB9 have been found to influence the behavior of immune cells, affecting the equilibrium between immune responses that are anti-tumor and those that are pro-tumor. This analysis explores the intricate dynamics of the interaction between HOXA9 and HOXB9 with immune cells (Duan et al. 2022; Morgan et al. 2022).

Interaction of HOXA9 with immune cells

Macrophages

HOXA9 significantly influences the phenotype and function of tumor-associated macrophages (TAMs) in ovarian cancer, changing the immune microenvironment. TAMs are well-known for promoting angiogenesis, tissue remodeling, and suppressing anti-tumor immune responses. An elevated presence of tumor-associated macrophages (TAMs) was detected in mouse models of ovarian cancer that expressed HOXA9 when administered intraperitoneally (i.p.). Remarkably, the presence of HOXA9 in ovarian cancer cells stimulated the movement of peritoneal macrophages toward the cancer cells and caused these macrophages to develop traits typical of TAMs (Ko et al. 2014).

The observed TAM-like characteristics included increased M2 markers, specifically CD163 and CD206, and immunosuppressive cytokines such as IL-10 and chemokine ligand 17. Simultaneously, there was a decrease in the expression of the immunostimulatory cytokine IL-12. The stimulation of TAMs by HOXA9 was mainly due to the joint influence of HOXA9-induced tumor-derived TGF-β2 and CCL2 levels (Ko et al. 2014).

T cells

HOXA9 displays a fluctuating expression pattern during T-cell maturation, contributing to distinct phases of cellular differentiation. Curiously, the level of HOXA9 expression significantly decreases upon entering the thymus (in CD34 + CD1- cells) despite its crucial role in forming T-cells. However, when T cells reach the stage of commitment to the T-cell lineage (CD34 + CD1 + cells), the expression of HOXA9 is again increased. The expression

profile indicates that HOXA9 is not essential in the initial multipotential progenitor cells in the thymus, but it becomes crucial when these cells develop into the T-cell lineage (de Bock and Cools 2018, Taghon et al. 2003).

Examining HOXA9 expression at various phases of human T-cell development demonstrates that it is mainly expressed during the first stages, corresponding to its crucial function in early differentiation. It is worth mentioning that mouse thymocytes lack the HOXA9 gene, which prevents T-cell development after entering the thymus and exhibits decreased expression of the IL-7 receptor. This receptor is a vital cytokine involved in the initial stages of T-cell formation. The correlation between the expression pattern of HOXA9 and IL-7-dependent phases indicates its role in controlling the IL-7 receptor during the maturation of human T-cells. Nevertheless, the absence of HOXA9 expression during the latter stages of T-cell development suggests that this gene may not be necessary for the ultimate maturation of human T cells (Cieslak et al. 2020; Collins and Hess 2016b).

HOXA9 can impact the functioning of T cells in the tumor microenvironment. It can lead to a decrease in the expression of major histocompatibility complex class I (MHC-I), which lowers the ability of cytotoxic T lymphocytes to recognize cancer cells and helps the cancer cells evade the immune system. HOXA9 expression has been associated with promoting T cell exhaustion, a condition characterized by the loss of effector activities and reduced responsiveness to antigens in T cells, enhancing the tumor's ability to evade the immune system (Zhou et al. 2020).

Dendritic Cells (DCs)

HOXA9 plays a diverse and intricate role in dendritic cell (DCs) functioning. HOXA9 is mainly known for its role in hematopoiesis, preserving the stem cell characteristics in hematopoietic stem cells (HSCs) (Ramos-Mejía et al. 2014). It seems that HOXA9 affects the formation of dendritic cells (DCs) through multiple pathways.

HOXA9's influence on DCs is related to its connection with toll-like receptor (TLR)-mediated activities in plasmacytoid dendritic cells (pDCs). HOXA9 is believed to activate TLR7 and 9 in pDCs, essential for generating significant quantities of type I interferons (IFNs). This involvement can occur through either direct or indirect means. This phenomenon can be attributed to gene regulation, and it is suggested that HOXA9 might be involved in the process of differentiating precursor cells in the bone marrow (BM), as the absence of HOXA9 resulted in the presence of immature precursors lacking maturity.

Concerning the growth of DCs, the cytokine receptor FMS-like tyrosine kinase 3 (FLT3) and its ligand FLT3L play a vital role, and the impact of HOXA9 on Flt3 has been proven. Moreover, experiments in a laboratory setting utilizing bone marrow cells lacking the HOXA9 gene and stimulated with Flt3L showed a drop in the overall number of cells and a tendency towards reduced production of a specific type of dendritic cells called pDCs. These findings indicate that HOXA9 plays a function in forming dendritic cells in a controlled environment. The presence of modified proliferation ability and a transition towards the cDC fraction in knockout cultures suggests the intricate nature of HOXA9's participation, potentially suggesting the presence of compensatory mechanisms. HOXA9 plays a role in regulating Flt3 and affecting the formation of DCs. However, its specific function is complex and depends on the situation. It may involve compensatory mechanisms and significantly impact cell proliferation rather than cell differentiation (Collins and Thompson 2018; Gwin et al. 2013).

Interaction of HOXB9 with immune cells

Macrophages

HOXB9 has been linked to promoting M2-like polarization of macrophages, releasing immunosuppressive cytokines, and forming a microenvironment that supports tumor growth (Jonkers et al. 2020).

T cells

HOXB9 can impede the activation of cytotoxic T lymphocytes by modulating the expression of co-stimulatory molecules on antigen-presenting cells, hindering the inhibition of efficient immune responses against tumors (Pai and Sukumar 2020).

Natural Killer (NK) cells

HOXB9 has been linked to suppressing NK cell activity, essential for eradicating cancer cells. This suppression enhances the tumor's ability to evade the immune system (Kim et al. 2012).

Dual role and context-dependence

The interaction between HOXA9 and HOXB9 and immune cells demonstrates a dual function strongly influenced by the specific circumstances. The genes' effect on the immune system, whether it promotes suppression or stimulation, is primarily determined by the exact type of tumor, its stage, and the cues from its microenvironment (Bondos et al. 2020).

Therapeutic implications

Comprehending the complex interaction of HOXA9, HOXB9, and immune cells is essential for developing precise immunotherapies. Manipulating the activities of these genes may strengthen the body's immune responses against tumors and enhance the effectiveness of immunotherapeutic treatments. Ultimately, the interplay between HOXA9 and HOXB9 and immune cells plays a crucial role in shaping the immunological characteristics of the tumor microenvironment. Additional investigation is necessary to understand the exact mechanisms and discover therapeutic approaches that utilize these connections to enhance cancer immunotherapy (Feng et al. 2021a; Maffuid and Cao 2023; Yi et al. 2023).

Conclusion

Ultimately, our thorough investigation examined the complex field of biomedical research, specifically highlighting the crucial functions of HOXA9 and HOXB9 in cancer. We explored the intricate realm of these transcription factors, delving into their underlying biology and examining their effects on signaling networks, gene regulation, and clinical consequences in different types of cancer. For example, there are regulatory mechanisms between HOXA9 and RA signaling in malignant and benign colonic stem cells. Also, the roles of HOXA9 and HOXB9 in drug resistance are highly dependent on the specific setting, similar to their involvement in cancer growth. The study emphasized the context-dependent impact of HOXB9 on the course of cancer and its connection to drug resistance. Additionally, it highlighted the involvement of HOXA9 in shaping the microenvironment of tumors. This analysis highlights the possibility of specific therapies and emphasizes the importance of a detailed understanding of HOXA9 and HOXB9 in the intricate field of cancer biology.

Abbreviations HOX: Homeobox; TALE: Three amino acid loop extension; CCND1: Cyclin D1; CDK6: Cyclin-dependent kinase 6; VEGF: Vascular endothelial growth factor; CAFs: Cancer-associated fibroblasts; EMT: Epithelial-mesenchymal transition; CRC: Colorectal cancer; SC: Stem cell; PTEN: Phosphatase and TENsin homolog deleted on chromosome 10; CIP1: Cyclin-dependent kinase inhibitor p21; WAF1: Wildtype p53-activated fragment 1; PBX: Pre-B cell leukemia transcription factor; MEIS1: Myeloid ecotropic viral integration site 1; MAPK: Mitogen-activated protein kinase; ERK: Extracellular signal-regulated kinase; TCF4: Transcription factor 4; WNT: Wingless-related integration site; GalNAc-T14: N-acetyl-galactosaminyl-transferases 14; bFGF: Fibroblast growth factor; MDSCs: Myeloid-derived suppressor cells; TGF-β: Transforming growth factor-β; PI3K: Phosphatidylinositol 3-kinase; AKT: Protein kinase B; mTOR: Mammalian target of rapamycin; NF-κB: Nuclear factor kappa-light-chain-enhancer of activated B cells; HNSCC: Head and neck squamous cell carcinoma; SCC: Squamous cell carcinoma; AML: Acute myeloid leukemia; ALL: Aacute lymphoblastic leukemia; RELA: V-rel avian reticuloendotheliosis viral oncogene homolog A; ATG: Autophagy-related gene; GRHL2: Grainyhead-like 2; ALDH: Aldehyde dehydrogenase; BRCA1: Breast cancer gene 1; TET1: Ten-eleven translocation 1; HMGA2: High-mobility-group protein AT-hook 2; ANGPTL2: Angiopoietin-like protein 2; E2F3: E2F transcription factor 3; SMAD: Mothers against decapentaplegic homolog 2; CXCL1: Chemokine ligand 1; PFS: Progression-free survival; TAM: Tumor-associated macrophage; MHC: Major histocompatibility complex; DC: Dendritic cell; TLR: Toll-like receptor; IFN: Type I interferons; BM: Bone marrow; FLT3: FMS-like tyrosine kinase 3; FLT3L: FMS-like tyrosine kinase 3 ligand; NK: Natural killer

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