HOX Genes in Breast Cancer: from Molecular Insights to Precision Diagnostics and Emerging Therapies

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Abstract

This review explores the multifaceted role of HOX gene family in breast cancer progression, metastasis, and treatment resistance. It highlights how dysregulated HOX genes influence tumorigenesis, hormone therapy resistance, and subtype-specific aggressiveness. Emphasis is placed on their potential as diagnostic biomarkers and therapeutic targets, including the use of HOX-interacting peptides, gene editing, and nanotechnology. The article also examines limitations of current diagnostic tools and showcases recent advances such as photodynamic therapy and immunotherapy. Understanding HOX gene dynamics may revolutionize early detection and facilitate the development of personalized, targeted treatment strategies for breast cancer.

Keywords: *HOX gene, breast cancer, gene family, therapy, diagnostic biomarkers.*

I. INTRODUCTION

The distribution of fat and hair throughout the body, as well as the processes of embryogenesis and oncogenesis, are all influenced by a broad family of transcription factors called the Homeobox (HOX) genes [1–4]. The human HOX gene family is comprised of 39 genes that are distributed across 4 chromosomes (7p15, 17q21.2, 12q13, and 2q31) [5]. The 39 HOX genes are divided into four clusters: HOXA, HOXB, HOXC, and HOXD [6]. Vaquerizas et al. provided a description of the homeobox, a well-conserved DNA sequence present in every HOX gene [7]. Vertebrate embryonic development is controlled by the unique expression pattern of the HOX genes, which includes mutations, and their reliant mechanism [8, 9]. Elevated HOX protein expression has been linked to cancer [2]. Furthermore, it has been demonstrated that the HOXC gene family is significantly expressed in a number of solid tumours, including lung, prostate, and colon cancer [6, 11]. The HOXA and HOXB gene families express themselves identically because breast cancer develops from ectoderm. If the origin of the germ layer and the expression level of the HOX gene in cancer are related, more investigation is required to ascertain this. Furthermore, Cobain et al. noted that breast cancer is a multifaceted disease with a variety of subtypes that are connected to various clinical outcomes [1]. The discovery

of efficient medicines has been hampered by the combative nature of breast cancer, which includes its high incidence of metastasis, multifactorial occurrence, and limited options for detection and prognosis. Therefore, one may consider breast cancer to be a complex, multifactorial disease with both hereditary and chance origins. Only 20% of patients may have a family history of breast cancer, although genetics plays a major role in this.

This study aims to provide a comprehensive examination of the function of each of the 39 HOX genes in breast cancer along with recent advancements in detection and treatment. This review primarily intends to address many research gaps and issues about the involvement of HOX genes in breast cancer. HOX genes play a role in both normal development and cancer. They are also related to the onset and progression of breast cancer. Novel diagnostic techniques for identifying breast cancer based on HOX gene function and potential therapeutic approaches are also discussed, as well as the shortcomings of current breast cancer treatment and diagnostic approaches and how they can be addressed with the help of HOX gene knowledge.

2.0 UNDERSTANDING HOX GENE FUNCTIONS IN THE CONTEXT OF BREAST CANCER PROGNOSIS AND THERAPY

Breast cancer is the most common type of cancer in humans and the most dangerous and fatal for women, according to Inman et al. [12]. Following childbirth, the female mammary gland undergoes a series of hormonal and transcription factor-regulated alterations, including those encoded by the HOX cluster (A, B, C, and D) during pregnancy, lactation, and involution [13]. Surprisingly, the development of breast cancer is often associated with HOX gene regulation [13]. The expression levels of eight out of ten genes in the HOXB cluster are changed in breast cancer, which influences the aggressiveness of the illness and its resistance to hormone treatment. This highlights the importance of HOXB genes as potential targets for therapy to overcome the negative effects of tamoxifen resistance. Emphasise. cancer treatment [13]. HOX genes' role in breast cancer treatment must be understood in order to develop effective treatment strategies. Despite some residual variations in the characterisation of HOX gene expression in cancer, their expression patterns may vary for each kind of cancer and can be used as a "fingerprint" to classify cancer types prior to perforation of the original tumour. It is believed to exist circulating tumour cells (CTCs), per Inman et al. (2015) [12]. The utilisation of HOX genes as therapeutic targets has shown encouraging results; a short peptide (HXR9, which has recently been replaced by HTL001) affects the activity of HOX paralogs 1–9 and inhibits their binding to ATS cofactors. It, necrosis (or necrosis coupled), induces apoptosis [12]. This peptide really induces leukemic cell death and has anticancer properties against breast, mesothelioma, ovarian, meningioma, prostate, and non-small cell lung cancers. It has been found that dysregulated HOX genes either cause or contribute to breast cancer development. Research has shown that dysregulation of 35 out of 39 human HOX genes occurs and/or has a role in the development of breast cancer [12]. By altering expression levels in breast cancer, Lewis et al. have shown that the HOXB gene particularly influences aggressiveness and resistance to hormone therapy [13]. For example, HOXB13 is a transcription factor that is essential for the development of the mammary gland and has a favorable effect on hormone receptors in a subset of breast cancers [13]. Overexpression of HOXB13 is associated with tamoxifen resistance as well as enhanced tumour growth, invasion, and metastasis.

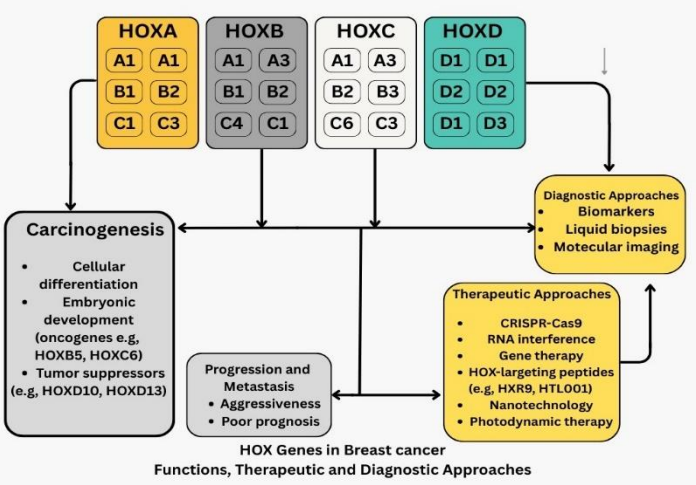

Figure 1*-Overview of HOX gene clusters (A–D), their involvement in carcinogenesis, progression, and metastasis of breast cancer. This figure also illustrates associated diagnostic and therapeutic approaches such as biomarkers, liquid biopsies, photodynamic therapy, and HOX-targeting peptides.*

2.1 ROLES IN NORMAL BREAST DEVELOPMENT

The knowledge of HOX genes in breast cancer is essential for creating effective therapeutic strategies. Eight out of ten genes in the HOXB cluster have changed expression levels, which impact the aggressiveness of the illness and its resistance to hormone treatment. These changes have been related to the formation of breast cancer on several occasions [13]. This highlights the importance of HOXB genes as viable targets for therapeutic intervention to mitigate the negative effects of tamoxifen resistance.

The use of HOX genes as therapeutic targets has shown promising results; a short peptide (HXR9, recently replaced by HTL001) affects the activity of HOX paralogs 1--9 and prevents them from binding to ATS cofactors, which causes necrosis and apoptosis in circulating tumour cells (CTCs) [12]. In addition to triggering leukemic cell death, this peptide has demonstrated anticancer benefits in a variety of cancer types, including breast, mesothelioma, ovarian, meningioma, prostate, non-small cell lung, and melanoma.

Moreover, research has shown that dysregulation of 35 out of 39 human HOX genes results in breast cancer formation and/or contributes to its development [12]. In particular, overexpression of the transcription factor HOXB13 has been associated with tamoxifen resistance, enhanced tumour growth, invasion, and metastasis [13]. This transcription factor is essential for the development of the mammary gland.

Comprehending the role of HOX genes is crucial for creating effective breast cancer therapy regimens. Despite some residual variations in the characterisation of HOX gene expression in cancer, their expression patterns may vary for each kind of cancer and can be used as a "fingerprint" to classify cancer types before perforation of the original tumour [13].

2.2 SPECIFIC HOX GENES IMPLICATED IN BREAST CANCER PROGRESSION

Zhang et al. noted that one of the HOX genes that promotes the growth of breast cancer through the Wnt/β-catenin pathway is HOXB5 [18]. The scientists found that the expression of HOXB5 was much higher in breast cancer tissue when compared to neighbouring normal tissue. Furthermore, they found that HOXB5 knockdown reduced the migration, invasion, and proliferation of breast cancer cells. Moreover, the researchers showed that HOXB5 promotes the activation of the Wnt/β-catenin pathway by upregulating the production of β-catenin. These results suggest that HOXB5 may be a promising target for the treatment of breast cancer. Together with HOXB5, Zhao et al. also found that acute myeloid leukaemia (AML) was associated with abnormal expression of HOXA5 and HOXA9 [17]. Although this study did not target breast cancer specifically, it does demonstrate that HOX genes may have a role in the development of several cancer types. In a similar vein, overexpression of HOXC9 has been connected to both the onset of gastric cancer and poor patient survival [17]. This work demonstrates that HOX genes can be utilised as prognostic markers for cancer, even if it does not specifically examine breast cancer.

In conclusion, the dysregulation of specific HOX genes, such as HOXB5, HOXB7, and HOXB13, has been connected to the progression of breast cancer. Understanding the roles played by these specific HOX genes in breast cancer may lead to the development of novel therapeutic targets and improved diagnostic methods. More

research into the particular functions of these HOX genes and the dysregulated pathways in breast cancer might lead to the development of novel and more effective treatment strategies.

2.3 MECHANISMS OF HOX GENE DYSREGULATION IN BREAST CANCER

There are important therapeutic ramifications from comprehending the processes of HOX gene dysregulation in breast cancer, especially with regard to the creation of targeted treatments. Lewis et al. noted that there is evidence connecting the dysregulation of HOX genes to several facets of breast cancer progression, such as tumour formation, invasion, metastasis, and resistance to hormone treatment [13]. Targeted medicines to interfere with these processes and maybe stop or reverse the growth of breast cancer can be created by understanding the precise mechanisms causing the deregulation of HOX genes.

Therapeutic intervention targets may be identified, for example, by identifying certain signalling pathways or molecular interactions that result in the deregulation of HOX genes. The goal of targeted therapy is to normalise the expression and function of HOX genes by modifying these pathways or interactions. Furthermore, by comprehending the genetic and epigenetic mechanisms causing dysregulation of the HOX gene, targeted epigenetic treatments or gene-based interventions to rectify the aberrant expression of HOX genes in breast cancer cells can be developed.

More individualised and successful treatment plans may result from the development of targeted medicines based on the dysregulation of certain HOX genes, such as HOXB5 and HOXB13. More precise and focused therapy methods might result from, for instance, customising therapeutic drugs to suppress the overexpression of HOXB5 or HOXB13 depending on the molecular profile of each patient's breast cancer.

In conclusion, knowledge of the processes behind HOX gene dysregulation in breast cancer lays the groundwork for the creation of tailored treatments meant to restore the abnormal expression and functionality of HOX genes. Clinical results and quality of life may eventually be improved by these targeted medicines, which may provide patients with breast cancer with more efficient and customised therapy alternatives.

3.0 DIAGNOSTIC APPROACHES FOR BREAST CANCER

Breast cancer is such a varied disease that diagnosis of it requires the application of both traditional and innovative technologies. Lehmann et al. noted that mammography is the most often used imaging modality for breast cancer screening [24]. It is a cost-effective and timely method of early detection of breast cancer. However, mammography is not always a good approach to detect breast cancer in people with dense breast tissue. In this case, other imaging modalities include ultrasonography and magnetic resonance imaging (MRI). In addition to imaging methods, biomarkers can also be used to diagnose breast cancer. Human epidermal growth factor receptor 2 (HER2), Ki-67 expression, and hormone receptor status are a few of the signs used in the diagnosis of breast cancer. These biomarkers can provide information about the tumor's aggressiveness as well as how well it will respond to hormone or chemotherapy treatments. Multigene testing is another state-of-the-art method for breast cancer diagnosis. Lehmann et al. noted that multigene testing can provide information on the likelihood of a recurrence and the potential for a response to therapy [24]. However, its use is limited by the high cost and lack of insurance coverage for multiple gene testing. Using circulating tumour cells (CTCs) is another innovative method of identifying breast cancer. Alix-Panabières and Pantel noted that circulating tumour cells can provide information regarding the likelihood of a relapse and the potential for a therapeutic response [23]. However, it might be difficult to locate CTCs because to their low circulation volume.

In conclusion, the identification of breast cancer requires a combination of traditional and state-of-the-art methods.

Breast cancer can be detected by a number of imaging techniques, including mammograms, ultrasounds, and MRIs. HER2 expression, Ki-67 expression, and hormone receptor status are a few of the markers used in breast cancer detection. Among the advanced methods for identifying breast cancer include multigene analysis and circulating tumour cells. These methods show promise in identifying breast cancer in its early stages, but further study is needed to determine their use.

3.1 LIMITATIONS OF EXISTING DIAGNOSTIC APPROACHES

Lehmann et al. discussed the shortcomings of current diagnostic techniques and found that mammography is not always effective in identifying breast cancer in women with thick breast tissue [24]. Furthermore, the ability to predict treatment response is limited for indicators such Ki-67 expression, HER2 status, and hormone receptor status. Multigene testing is expensive and not covered by insurance, despite its potential. Additionally, because circulating tumour cells (CTCs) are uncommon in blood, it might be challenging to identify them [23]. Furthermore, Pfeifer et al. emphasised that the sensitivity and specificity of point-of-care diagnostic instruments are limited, potentially resulting in false-positive or false-negative outcomes [22].

The shortcomings of the available diagnostic tools for breast cancer highlight the need for more study and technical developments to overcome these obstacles. Even though mammography is a commonly used technology, women with thick breast tissue may not benefit from it as much, which might result in false-negative findings. Future studies could concentrate on creating sophisticated imaging methods that are especially designed to get around the drawbacks of dense breast tissue, like better contrast-enhanced mammography or investigating new imaging modalities that provide greater sensitivity and specificity for this patient group.

Treatment decisions can benefit greatly from the information provided by biomarkers, such as Ki-67 expression, HER2 status, and hormone receptor status. However, further study is needed to find new biomarkers or improve the ones that already exist because of their limitations in capturing the whole spectrum of breast cancer subtypes and predicting therapy response. In order to improve the predictive and prognostic utility of biomarker testing, this might entail investigating the possibilities of liquid biopsy-based biomarkers or integrating multi-omics techniques to give a more thorough molecular characterisation of breast cancer.

The necessity for development on scalable and affordable methods for molecular profiling and liquid biopsy-based diagnostics is underscored by the high prices and restricted accessibility of multigene testing as well as the difficulties in identifying and interpreting circulating tumour cells (CTCs). Subsequent investigations may concentrate on the advancement of novel technologies that facilitate the effective and sensitive identification of CTCs, in addition to the establishment of simplified and economical multigene testing systems to increase their availability to a wider range of patients.

Research into the development of these technologies to increase their accuracy and dependability is also necessary due to the sensitivity and specificity limits of point-of-care diagnostic instruments. This could entail investigating novel biomarker panels or biosensing technologies that provide improved sensitivity and specificity in the point-of-care setting, as well as integrating artificial intelligence and machine learning algorithms to improve the diagnostic performance of point-of-care devices.

Moreover, further research should focus on finding novel biomarkers, exploring advanced imaging techniques for dense breast tissue, enhancing the sensitivity and accessibility of molecular profiling technologies, and improving the diagnostic performance of point-of-care tools through scientific research and technological innovation in order to overcome the limitations of current breast cancer

diagnostic methods. These initiatives might completely change the way that breast cancer is diagnosed and treated, providing more precise, affordable, and easily available methods for early diagnosis and individualised treatment choices.

4.0 RECENT THERAPEUTIC APPROACHES ON BREAST CANCER

Because breast cancer is a major concern to women's health and is growing more widespread globally, researchers are closely monitoring this issue. While not all traditional treatment techniques are safer, some have had a substantial influence on patients' lives, such as radiation, chemotherapy, surgery, and drugs [25–27]. Despite the remarkable developments in recent years, all traditional treatment approaches have limited cellular absorption, toxicity, and specificity [28]. These medications have a transient and acute harmful effect on normal patient cells. In drug-based chemotherapy, even taxanes and anthracyclines show little therapeutic efficacy [26, 30]. Scientists are closely monitoring this matter since breast cancer is growing more then substantial shift away from the use of traditional treatment and towards photodynamic therapy, immunotherapy, gene therapy, nanotechnology, and computational drug discovery has improved therapeutic possibilities for breast cancer care [32].

Current treatment modalities for breast cancer comprise a wide range of tactics meant to enhance patient results and tackle the disease's complexity. These strategies include cutting-edge methods like gene therapy, immunotherapy, nanotechnology, and computational drug discovery in addition to conventional modalities like surgery, radiation, and chemotherapy. As the field of oncology's therapeutic interventions evolves, each strategy offers a new chance to improve the efficacy and accuracy of breast cancer treatment.

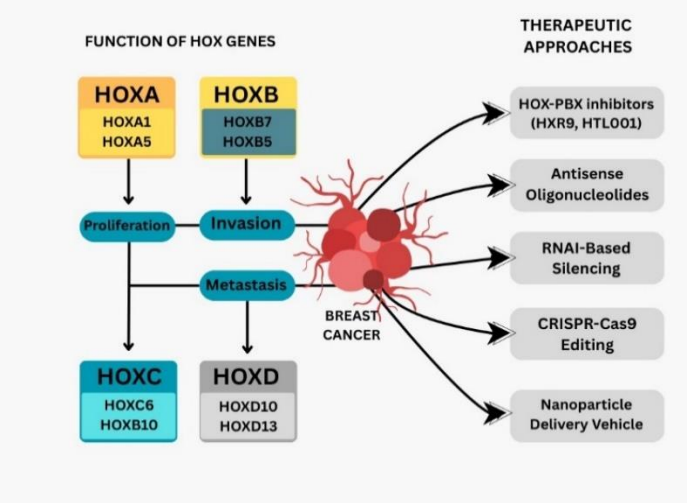

Figure 2- *Roles of specific HOX gene clusters in breast cancer progression and therapeutic targeting. HOXA and HOXB clusters contribute to proliferation and invasion; HOXC and HOXD clusters are implicated in metastasis. Therapeutic strategies include HOX-PBX inhibitors, RNAi-based silencing, CRISPR-Cas9 editing, and nanoparticle delivery systems.*

4.1 Hyperthermia or Thermotherapy

Hyperthermia was one 20th-century oncological strategy that employed warmth to manage cancer. Necrosis of cancer cells occurs when the temperature of cancer tissue is artificially raised in hyperthermia. Wust et al. and Yagawa et al. have suggested that heat exhaustion may impede the growth of tumours and make them more vulnerable to radiation and anticancer drugs [33, 35]. Rubio et al. claim that heat inhibits DNA damage repair and decreases the survival rate of cancer cells. Breast cancer is treated using a range of ablations, including as laser, ethanol, radiofrequency, cryoablation, and the more modern microwave ablation [36]. The application of computer modelling in the treatment of breast cancer hyperthermia is the most recent advancement [36]. Research has shown that using heat in addition to chemotherapy and radiation therapy can improve local control of breast cancer [37]. Following radiation and chemotherapy, thermotherapy inhibits the growth of damaged breast cancer cells [35]. Although promising, hyperthermia as a cancer treatment is now best utilised in combination with other medicines rather than as a treatment on its own. Hyperthermia can cause pain, edoema, burns, blood clots, infections, and skin conditions [38].

4.2 Photodynamic Therapy

Photodynamic therapy is an advanced light-based treatment that uses nontoxic photosensitizer and laser light to kill cancer cells. Agostinis et al. and Banerjee et al. described PDT's anticancer effectiveness as mediated by three processes: 1. Direct lethal effect on cancer cells; 2. Indirect effect on tumour vasculature; and 3. Activation of systemic immunity. When the proper energy and wavelength of light are combined with the drug, molecular oxygen is produced, which destroys the targeted cancer cells [40, 41]. Because photosensitizers are very selective and have little systemic toxicity, they are a useful tool for targeting cancer cells. Clinical trials for Photofrin, Metvix, Levulan, Foscan, Visudyne, and Laserphyrin are officially acknowledged as treatments for breast cancer [42]. Photosensitizers target receptors including estradiol, human epidermal growth factor receptor, and gonadotropin-releasing hormone receptor in breast cancer [43]. Before administering photodynamic treatment for breast cancer, one must consider skin sensitization since PDT allows photosensitizer to be distributed more widely in tumour cells than intravenous injection [45].

4.3 Immunotherapy

Immunotherapy has been shown to aid in the battle against cancer by boosting the immune system's capacity to fend against the illness. The hypothesis that there is a connection between cancer growth and the immune system (in its three stages: elimination, equilibrium, and escape) is gaining traction. Immunotherapy addresses many immune system regulatory checkpoints to treat breast cancer [46]. Molecular immunotherapy, cellular immunotherapy, and vaccination therapy are all forms of immunotherapy that the FDA has approved [47]. The three types of immunotherapies include checkpoint inhibitors, bivalent antibodies, and adoptive T cell transfer [48]. Compared to chemotherapy and radiation therapy, immunotherapy is more focused. Despite immunotherapy's targeted function in the treatment of breast cancer, there are still certain questions about targeting, safety, and effectiveness that need to be further investigated [49].

4.4 Gene Therapy

Numerous unique platforms enabled by gene therapy have made it feasible to target several genes in breast cancer. The genetically unstable environment of tumour cells is the driving force behind the use of gene therapy in the treatment of breast cancer. Cross and Burmester described gene therapy as involving the injection of modified genetic material into diseased cells in a way that prevents the cancerous cells from proliferating and eventually results in their death [50]. Delivering genes and controlling their expression in cancer cells is a difficult issue in cancer care [51]. Gene therapy involves the following steps: 1. Oncogene suppression; 2. Immune response stimulation; 3. Introduction of suicide genes; and 4. Protecting bone marrow with drug resistance genes [52]. Therapeutic gene expression needs to be strictly controlled in order to control the desired gene product [51]. Indeed, increasing studies on gene therapy highlight its potential, along with the toxicity vectors, immunity, and several technological obstacles that still impede the successful treatment of breast cancer [53]. Improved vector delivery techniques could provide a new angle on the most promising treatment modalities [54].

4.5 Dynamics of BH3 Profiling

The prediction of a certain medication's clinical result BH3 profiling is a novel technique for quantifying death signals induced by a specific medication. By examining the BCL-2 family, DBP predicts the susceptibility to chemotherapy [55]. The cytotoxicity prediction capacity of BH3 profiling is validated by five different drug-treated breast cancer cell lines [55]. By comparing the many death signals caused by chemotherapy treatments, DBP will make it possible to utilise effective drugs for precision medicine [57].

4.6 Nanotechnology

The use of nanotechnology opens up new and fascinating possibilities for the diagnosis and treatment of severe diseases like cancer. The primary barrier to successful treatment for breast cancer is the potentially harmful effects

of conventional methods, which nanotechnology seeks to mitigate. Over the past 10 years, targeting metastatic breast cells has led to the creation of numerous nanoparticles that hold tremendous promise for targeted drug delivery. In order to create smart active fabricate multifunctional devices (SAFMD) that can transport medications, cross the biological barrier, and reach the desired cell, these NPs' primary physiological job is to control molecules at the nanoscale [28]. When drug-based chemotherapy (DBC) is used for an extended period of time, the monoclonal antibody trastuzumab causes unfavourable cardiac abnormal function. To treat these cardiac issues and other physiological anomalies, oncologists must create novel drug delivery methods (nanoparticles) [26, 58–60]. Consequently, a unique strategy for treating breast cancer known as nanotechnology has been identified as a remedy for each of these problems. The human body's most vulnerable organs are the liver, brain, lungs, and bone; these tissues are home to cancer stem cells (CSCs) and tumour mimicking cells (TICs) [61, 62]. Tumour formation, including leukaemia and breast cancer, is dependent on the Notch, Hedgehog, and Wnt signalling pathways in stem cells [63, 64]. The treatment of breast cancer has so shown potential using Notch target therapy [65]. Despite notch-target therapy's numerous outstanding applications in diagnosis and treatment, some of its limitations need to be addressed in order to fulfil this medical challenge. Hussain et al. described nanotechnology as the process of improving the sizes and shapes of nanoparticles down to the nano range (1–100 nm) [66]. Two innovative turning points in the "era of nanomedicine" include PEGylated liposomal doxorubicin and the FDA-approved nano platform [67–69]. Nanoparticles with large surface area/volume ratios and microscopic surface areas have unique biological activity that allows them to target mutant cells [70–72].

Metallic nanoparticles, such as those made of silver, gold, uranium, titanium, and zinc, are more effective because they have a greater surface area and powerful antifungal, antibacterial, anti-diabetic, and anticancer effects [73, 74]. Silver nanoparticles are the most often used metallic nanoparticles due to their strong membrane polarity and lesser toxicity [75, 76]. Both organic (polymeric, liposomes, and micelles) and inorganic (silica, iron oxide) nanoparticles have advantages over one another in the pharmaceutical treatment period [78, 79]. Studies on the advanced nanotechnology-based treatment of breast cancer are making target-based medicine administration and discovery increasingly important. Many nanoparticles (NPs) are utilised for encapsulation, malignant cell absorption, or binding (electrostatic, covalent) in order to avoid problems when aiming at cells [80]. Numerous drugs with good solubility and bioavailability have shown maximum catalytic activity on the MCF-7 cell line, according to data provided [81]. The non-toxicity of nanoparticles on several breast cell lines, such as MDA-MB-231, SkBr-3, and MCF-7, has been the subject of numerous research [83–85]. Doxorubicin (DOX) is used as a chemotherapeutic mediator in combination with nanoparticles to deliver drugs. The most well-known method for tastefully treating cancer is "active targeting." In order to ligate with NPS/drugs and connect with the specific localised receptor on malignant cells, this approach uses a variety of ligands. Peptide ligands, such as glycine, beta-alanine, and gamma-aminobutyric acid, are mostly used in nanotechnology to boost biological activity. Active targeting, which takes place in the microenvironment (matrix, blood vessel), is superior than passive targeting in terms of toxicity, cellular absorption, and specificity [82].

With the promise of more effective treatment, less systemic toxicity, and tailored drug delivery, nanotechnology has become a viable tool for improving breast cancer therapy. It is important to recognise the obstacles and constraints linked to the utilisation of nanotechnology in the treatment of breast cancer.

The possibility of off-target consequences and unexpected biological interactions when introducing nanoparticles into the body is a major concern [79]. Concern and research are still being conducted on the biodistribution and clearance of nanoparticles as well as their long-term safety profile. Furthermore, in order for nanotechnology-based medicines

to be widely used in clinical settings, practical issues with scalability and cost-effectiveness must be resolved [80].

In addition, resistance to therapies based on nanoparticles and the possibility of nanoparticle accumulation in certain tissues or organs are crucial factors to take into account when implementing nanotherapeutic techniques for breast cancer in clinical settings [87, 94].

To tackle these obstacles, further investigation is needed into the creation of biocompatible and targeted nanoparticles. Additionally, extensive preclinical and clinical research is needed to assess the efficacy and safety of nanotechnology-based therapeutics in the treatment of breast cancer [28, 87].

The area of nanotechnology in breast cancer therapy can continue to advance towards the creation of safe, efficient, and focused therapeutic modalities with the potential to have a major influence on patient outcomes by acknowledging and aggressively overcoming these obstacles [32, 95].

5.0 CONCLUSION

This article discusses what has been learned about the HOX gene family and how it affects breast cancer as well as what can be used as a treatment and a means of diagnosing it. The HOX genes assist in the development and metastasis of breast cancer and when the genes malfunction, they are associated with aggressive cancers that are difficult to treat [12, 13].

We've learned a lot about HOX genes in breast cancer, but even so, we've got a lot more to discover. For instance, we must conduct more research on exactly how HOX genes initiate and contribute to the development of breast cancer [18, 96]. In addition, we must conduct more research on whether drugs targeting HOX genes may treat breast cancer and what their effects might be [12, 32].

Additionally, there is a need to develop improved and more accurate tests for breast cancer. This may involve enhancing the existing tests, discovering new markers, and utilizing sophisticated imaging methods [24, 87].

The future studies should investigate novel imaging techniques, identify novel biomarkers, render molecular profiling technologies more sensitive and accessible, and enhance point-of-care diagnostic technologies through science and technology [22, 95]. These studies need to address the shortcomings and limitations of the existing breast cancer diagnosis and treatment techniques [28, 94]. By identifying and attempting to resolve these issues, we can continue to create safe, effective, and targeted therapies that have the potential to significantly influence patient outcomes [32, 87].

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REFERENCES

[1] E. F. Cobain, K. J. Milliron, and S. D. Merajver, “Updates on breast cancer genetics: clinical implications of detecting syndromes of inherited increased susceptibility to breast cancer,” Semin. Oncol., 2016.

[2] Z. Luo, S. K. Rhie, and P. J. Farnham, “The enigmatic HOX genes: Can we crack their code?,” Cancers (Basel), vol. 11, no. 3, p. E323, 2019, doi: 10.3390/cancers11030323.

[3] M. Turcotte et al. “Genetic contribution to waist-to-hip ratio in Mexican children and adolescents based on 12 loci validated in European adults,” Int. J. Obes. (Lond), vol. 43, pp. 13–22, 2019, doi: 10.1038/s41366-018-0055-8.

[4] F. Liu et al. “Meta-analysis of genome-wide association studies identifies 8 novel loci involved in shape variation of human head hair,” Hum. Mol. Genet., vol. 27, no. 4, pp. 559–575, 2018, doi: 10.1093/hmg/ddx416.

[5] L. Li et al. “HOX cluster-embedded antisense long non-coding RNAs in lung cancer,” Cancer Lett., vol. 450, pp. 14–21, 2019, doi: 10.1016/j.canlet.2019.02.036.

[6] S. Bhatlekar, J. Z. Fields, and B. M. Boman, “Role of HOX genes in stem cell differentiation and cancer,” Stem Cells Int., vol. 2018, p. 3569493, 2018, doi: 10.1155/2018/3569493.

[7] J. M. Vaquerizas, S. K. Kummerfeld, S. A. Teichmann, and N. M. Luscombe, “A census of human transcription factors: Function, expression and evolution,” Nat. Rev. Genet., vol. 10, no. 4, pp. 252–263, 2009, doi: 10.1038/nrg2538.

[8] J. Gordon, "Hox genes in the pharyngeal region: How Hoxa3 controls early embryonic development of the pharyngeal organs," Int. J. Dev. Biol., vol. 62, no. 10-11-12, pp. 775–783, 2018, doi: 10.1387/ijdb.180284jg.
[9] M. Mallo, "The vertebrate tail: A gene playground for evolution," Cell. Mol. Life Sci., 2019, doi: 10.1007/s00018-019-03311-1.
[10] S. Bhatlekar, J. Z. Fields, and B. M. Boman, "HOX genes and their role in the development of human cancers," J. Mol. Med. (Berl), vol. 92, no. 8, pp. 811–823, 2014, doi: 10.1007/s00109-014-1181-y.
[11] Y. Yao et al. "HOXC13 promotes proliferation of lung adenocarcinoma via modulation of CCND1 and CCNE1," Am. J. Cancer Res., vol. 7, no. 9, pp. 1820–1834, 2017.
[12] J. L. Inman, C. Robertson, J. D. Mott, and M. J. Bissell, "Mammary gland development: cell fate specification, stem cells and the microenvironment," Development, vol. 142, no. 6, pp. 1028–1042, 2015.
[13] M. T. Lewis, "Homeobox genes in mammary gland development and neoplasia," Breast Cancer Res., vol. 2, no. 3, pp. 158–169, 2000.
[14] C. J. Watson and T. K. Walid, "Mammary development in the embryo and adult: a journey of morphogenesis and commitment," Development, vol. 135, no. 6, pp. 995–1003, 2008.
[15] H. Macias and L. Hinck, "Mammary gland development," Wiley Interdiscip. Rev. Dev. Biol., vol. 1, no. 4, pp. 533–557, 2012.
[16] L. M. Woods, B. Rachet, N. Cooper, and M. P. Coleman, "Predicted trends in long-term breast cancer survival in England and Wales," Br. J. Cancer, vol. 96, no. 7, pp. 1135–1138, 2007.
[17] P. Zhao et al. "Aberrant expression of HOXA5 and HOXA9 in AML," Asian Pac. J. Cancer Prev., vol. 16, no. 9, pp. 3941–3944, 2015.
[18] J. Zhang, S. Zhang, X. Zhang, F. Zhang, and L. Zhao, "HOXB5 promotes the progression of breast cancer through wnt/beta-catenin pathway," Pathol. Res. Pract., vol. 224, p. 153117, 2020.
[19] W. Li, C. Li, Q. Xiong, X. Tian, and Q. Ru, "MicroRNA-10b-5p downregulation inhibits the invasion of glioma cells via modulating homeobox B3 expression," Exp. Ther. Med., vol. 17, no. 6, pp. 4577–4585, 2019.
[20] M. A. Mansour and T. Senga, "HOXD8 exerts a tumor-suppressing role in colorectal cancer as an apoptotic inducer," Int. J. Biochem. Cell Biol., vol. 88, pp. 1–13, 2017.
[21] L. Marra et al. "Deregulation of HOX B13 expression in urinary bladder cancer progression," Curr. Med. Chem., vol. 20, no. 6, pp. 833–839, 2013.
[22] M. E. Pfeifer, "Quo vadis point-of-care diagnostics? Report II of the SWISS SYMPOSIUM in point-of-care diagnostics 2017," CHIMIA Int. J. Chem., vol. 72, no. 1-2, pp. 80–82, 2018, doi: 10.2533/chimia.2018.80.
[23] C. Alix-Panabières and K. Pantel, "Challenges in circulating tumour cell research," Nat. Rev. Cancer, vol. 14, no. 9, pp. 623–631, 2014, doi: 10.1038/nrc3820.
[24] B. D. Lehmann et al. "Identification of human triple-negative breast cancer subtypes and preclinical models for selection of targeted therapies," J. Clin. Invest., vol. 121, no. 7, pp. 2750–2767, 2011, doi: 10.1172/JCI45014.
[25] F. A. Haggar and R. P. Boushey, "Colorectal cancer epidemiology: incidence, mortality, survival, and risk factors," Clin. Colon Rectal Surg., vol. 22, no. 4, pp. 191–197, 2009, doi: 10.1055/s-0029-1242458.
[26] H. Barabadi et al. "Emerging theranostic biogenic silver nanomaterials for breast cancer: a systematic review," J. Cluster Sci., vol. 30, no. 2, pp. 259–279, 2019, doi: 10.1007/s10876-018-01491-7.
[27] A. M. Allahverdiyev et al. "Current aspects in treatment of breast cancer based of nanodrug delivery systems and future prospects," Artif. Cells Nanomed. Biotechnol., vol. 46, no. sup3, pp. S755–S762, 2018, doi: 10.1080/21691401.2018.1511573.
[28] K. D. Miller et al. "Cancer treatment and survivorship statistics, 2016," CA Cancer J. Clin., vol. 66, no. 4, pp. 271–289, 2016, doi: 10.3322/caac.21349.
[29] H. Barabadi et al. "Emerging theranostic silver nanomaterials to combat colorectal cancer: a systematic review," J. Cluster Sci., vol. 31, no. 2, pp. 311–321, 2020, doi: 10.1007/s10876-019-01668-8.
[30] H. Barabadi et al. "Emerging theranostic gold nanomaterials to combat colorectal cancer: a systematic review," J. Cluster Sci., vol. 31, no. 4, pp. 651–658, 2020, doi: 10.1007/s10876-019-01681-x.
[31] H. Barabadi et al. "Emerging antineoplastic gold nanomaterials for cervical cancer therapeutics: a systematic review," J. Cluster Sci., 2019.
[32] A. Wicki, D. Witzigmann, V. Balasubramanian, and J. Huwyler, "Nanomedicine in cancer therapy: challenges, opportunities, and clinical applications," J. Control. Release, vol. 200, pp. 138–157, 2015, doi: 10.1016/j.jconrel.2014.12.030.
[33] P. Wust et al. "Hyperthermia in combined treatment of cancer," Lancet Oncol., vol. 3, no. 8, pp. 487–497, 2002, doi: 10.1016/S1470-2045(02)00818-5.
[34] H. Alexander, "Isolation perfusion," Cancer: Principles Pract. Oncol., vol. 1, p. 2, 2001.
[35] Y. Yagawa, K. Tanigawa, Y. Kobayashi, and M. Yamamoto, "Cancer immunity and therapy using hyperthermia with immunotherapy, radiotherapy, chemotherapy, and surgery," J. Cancer Metastasis Treat., vol. 3, no. 10, p. 218, 2017, doi: 10.20517/2394-4722.2017.35.
[36] M. Rubio, A. V. Hernandez, and L. L. Salas, "High temperature hyperthermia in breast cancer treatment," Hyperthermia, pp. 83–100, 2013.
[37] B. Uysal, "Hyperthermia and breast cancer: A short review," 2017.
[38] S. Jha, P. K. Sharma, and R. Malviya, "Hyperthermia: role and risk factor for cancer treatment," Achiev. Life Sci., vol. 10, no. 2, pp. 161–167, 2016, doi: 10.1016/j.als.2016.11.004.

[39] J. Płonka and M. Latocha, "Photodynamic therapy in the treatment of breast cancer," Pol. Merkuriusz Lek., vol. 33, no. 195, pp. 173–175, 2012.
[40] P. Agostinis et al. "Photodynamic therapy of cancer: an update," CA Cancer J. Clin., vol. 61, no. 4, pp. 250–281, 2011, doi: 10.3322/caac.20114.
[41] S. M. Banerjee et al. "Photodynamic therapy in primary breast cancer," J. Clin. Med., vol. 9, no. 2, p. 483, 2020, doi: 10.3390/jcm9020483.
[42] M. J. Lamberti, N. B. R. Vittar, and V. A. Rivarola, "Breast cancer as photodynamic therapy target: Enhanced therapeutic efficiency by overview of tumor complexity," World J. Clin. Oncol., vol. 5, no. 5, pp. 901–907, 2014, doi: 10.5306/wjco.v5.i5.901.
[43] T. H. Oude-Munnink et al. "Molecular imaging of breast cancer," Breast, vol. 18, pp. S66–S73, 2009, doi: 10.1016/S0960-9776(09)70276-0.
[44] M. Lapeš, J. Petera, and M. Jirsa, "Photodynamic therapy of cutaneous metastases of breast cancer after local application of meso-tetra-(para-sulphophenyl)-porphin (TPPS4)," J. Photochem. Photobiol. B, vol. 36, no. 2, pp. 205–207, 1996, doi: 10.1016/S1011-1344(96)07373-3.
[45] M. A. D'Hallewin et al. "Photodynamic therapy with intratumoral administration of Lipid-Based mTHPC in a model of breast cancer recurrence," Lasers Surg. Med., vol. 40, no. 8, pp. 543–549, 2008, doi: 10.1002/lsm.20662.
[46] L. A. Emens, "Breast cancer immunobiology driving immunotherapy: vaccines and immune checkpoint blockade," Expert Rev. Anticancer Ther., vol. 12, no. 12, pp. 1597–1611, 2012, doi: 10.1586/era.12.147.
[47] M. Liu and F. Guo, "Recent updates on cancer immunotherapy," Precis. Clin. Med., vol. 1, no. 2, pp. 65–74, 2018, doi: 10.1093/pcmedi/pby011.
[48] J. Song, Z. Teng, and W. Cao, "Characteristics of Immunobiology in the Tumor Microenvironment-Development of Immunotherapies," Hindawi, 2019, doi: 10.1155/2019/1513964.
[49] M. Sambi, L. Bagheri, and M. R. Szewczuk, "Current challenges in cancer immunotherapy: multimodal approaches to improve efficacy and patient response rates," J. Oncol., 2019.
[50] D. Cross and J. K. Burmester, "Gene therapy for cancer treatment: past, present and future," Clin. Med. Res., vol. 4, no. 3, pp. 218–227, 2006, doi: 10.3121/cmr.4.3.218.
[51] G. U. Dachs, G. J. Dougherty, I. J. Stratford, and D. J. Chaplin, "Targeting gene therapy to cancer: a review," Oncol. Res., vol. 9, no. 6-7, pp. 313–325, 1997.
[52] S. Takahashi, Y. Ito, K. Hatake, and Y. Sugimoto, "Gene therapy for breast cancer. -Review of clinical gene therapy trials for breast cancer and MDR1 gene therapy trial in Cancer Institute Hospital," Breast Cancer, vol. 13, no. 1, pp. 8–15, 2006, doi: 10.2325/jbcs.13.8.
[53] G. Kouraklis, "Progress in cancer gene therapy," Acta Oncol., vol. 38, no. 6, pp. 675–683, 1999, doi: 10.1080/028418699432815.
[54] C. M. McCrudden and H. O. McCarthy, "Current status of gene therapy for breast cancer: progress and challenges," Appl. Clin. Genet., vol. 7, pp. 209–220, 2014.
[55] M. Certo et al. "Mitochondria primed by death signals determine cellular addiction to antiapoptotic BCL-2 family members," Cancer Cell, vol. 9, no. 5, pp. 351–365, 2006, doi: 10.1016/j.ccr.2006.03.027.
[56] J. Montero and A. Letai, "Dynamic BH3 profiling-poking cancer cells with a stick," Mol. Cell. Oncol., vol. 3, no. 3, p. e1040144, 2016, doi: 10.1080/23723556.2015.1040144.
[57] A. C. Faber et al. "Differential induction of apoptosis in HER2 and EGFR addicted cancers following PI3K inhibition," Proc. Natl. Acad. Sci. USA, vol. 106, no. 46, pp. 19503–19508, 2009, doi: 10.1073/pnas.0905056106.
[58] J. J. Lee, L. Saiful-Yazan, and C. A. Che-Abdullah, "A review on current nanomaterials and their drug conjugate for targeted breast cancer treatment," Int. J. Nanomedicine, vol. 12, pp. 2373–2384, 2017, doi: 10.2147/IJN.S127329.
[59] S. Jeibouei et al. "Personalized medicine in breast cancer: pharmacogenomics approaches," Pharm. Genomics Pers. Med., vol. 12, pp. 59–73, 2019, doi: 10.2147/PGPM.S167886.
[60] H. Barabadi, K. D. Kamali, and F. J. Shoushtari, "Emerging theranostic silver and gold nanomaterials to combat prostate cancer: a systematic review," J. Cluster Sci., 2019, doi: 10.1007/s10876-019-01588-7.
[61] V. Plaks, N. Kong, and Z. Werb, "The cancer stem cell niche: how essential is the niche in regulating stemness of tumor cells?," Cell Stem Cell, vol. 16, no. 3, pp. 225–238, 2015, doi: 10.1016/j.stem.2015.02.015.
[62] K. Shibuya et al. "Targeting the facilitative glucose transporter GLUT1 inhibits the self-renewal and tumor-initiating capacity of cancer stem cells," Oncotarget, vol. 6, no. 2, pp. 651–661, 2015, doi: 10.18632/oncotarget.2892.
[63] N. Takebe, L. Miele, P. J. Harris, and W. N. Hait, "Targeting Notch, Hedgehog, and Wnt pathways in cancer stem cells: clinical update," Nat. Rev. Clin. Oncol., vol. 12, no. 8, pp. 445–464, 2015, doi: 10.1038/nrclinonc.2015.61.
[64] D. L. Abravanel et al. "Notch promotes recurrence of dormant tumor cells following HER2/neu-targeted therapy," J. Clin. Invest., vol. 125, no. 6, pp. 2484–2496, 2015, doi: 10.1172/JCI74883.
[65] V. Mamaeva et al. "Inhibiting notch activity in breast cancer stem cells by glucose functionalized nanoparticles carrying γ-secretase inhibitors," Mol. Ther., vol. 24, no. 5, pp. 926–936, 2016, doi: 10.1038/mt.2016.42.
[66] Z. Hussain, J. A. Khan, and S. Murtaza, "Nanotechnology: An Emerging Therapeutic Option for Breast Cancer," Crit. Rev. Eukaryot. Gene Expr., vol. 28, no. 2, pp. 163–175, 2018, doi: 10.1615/CritRevEukaryotGeneExpr.2018022771.

[67] V. Varadharaj et al. "Antidiabetic and antioxidant activity of green synthesized starch nanoparticles: an in vitro study," J. Cluster Sci., 2019.
[68] A. Khatua et al. "Phytosynthesis, characterization and fungicidal potential of emerging gold nanoparticles using Pongamia pinnata leave extract: a novel approach in nanoparticle synthesis," J. Cluster Sci., vol. 31, no. 1, pp. 125–131, 2020, doi: 10.1007/s10876-019-01624-6.
[69] R. Balachandar et al. "Plant-mediated synthesis, characterization and bactericidal potential of emerging silver nanoparticles using stem extract of Phyllanthus pinnatus: a recent advance in phytonanotechnology," J. Cluster Sci., vol. 30, no. 6, pp. 1481–1488, 2019, doi: 10.1007/s10876-019-01591-y.
[70] B. Ajitha, Y. A. K. Reddy, H.-J. Jeon, and C. W. Ahn, "Synthesis of silver nanoparticles in an eco-friendly way using Phyllanthus amarus leaf extract: Antimicrobial and catalytic activity," Adv. Powder Technol., vol. 29, no. 1, pp. 86–93, 2018, doi: 10.1016/j.apt.2017.10.015.
[71] S. Bamrungsap et al. "Nanotechnology in therapeutics: a focus on nanoparticles as a drug delivery system," Nanomedicine (Lond), vol. 7, no. 8, pp. 1253–1271, 2012, doi: 10.2217/nnm.12.87.
[72] S. Satpathy, A. Patra, B. Ahirwar, and M. Delwar Hussain, "Antioxidant and anticancer activities of green synthesized silver nanoparticles using aqueous extract of tubers of Pueraria tuberosa," Artif. Cells Nanomed. Biotechnol., vol. 46, no. sup3, pp. S71–S85, 2018, doi: 10.1080/21691401.2018.1489265.
[73] P. V. Rao et al. "Phytochemicals and biogenic metallic nanoparticles as anticancer agents," Oxid. Med. Cell. Longev., 2016, doi: 10.1155/2016/3685671.
[74] P. Khandel et al. "Biogenesis of metal nanoparticles and their pharmacological applications: present status and application prospects," J. Nanostructure Chem., vol. 8, no. 3, pp. 217–254, 2018, doi: 10.1007/s40097-018-0267-4.
[75] K. Kanagamani et al. "Antimicrobial, cytotoxicity and photocatalytic degradation of norfloxacin using Kleinia grandiflora mediated silver nanoparticles," J. Cluster Sci., vol. 30, no. 6, pp. 1415–1424, 2019, doi: 10.1007/s10876-019-01583-y.
[76] E. R. Carmona, N. Benito, T. Plaza, and G. Recio-Sanchez, "Green synthesis of silver nanoparticles by using leaf extracts from the endemic Buddleja globosa hope," Green Chem. Lett. Rev., vol. 10, no. 4, pp. 250–256, 2017, doi: 10.1080/17518253.2017.1360400.
[77] J. Cao et al. "A7RC peptide modified paclitaxel liposomes dually target breast cancer," Biomater. Sci., vol. 3, no. 12, pp. 1545–1554, 2015, doi: 10.1039/C5BM00161G.
[78] A. C. Anselmo and S. Mitragotri, "A review of clinical translation of inorganic nanoparticles," AAPS J., vol. 17, no. 5, pp. 1041–1054, 2015, doi: 10.1208/s12248-015-9780-2.
[79] A. C. Anselmo and S. Mitragotri, "Nanoparticles in the clinic," Bioeng. Transl. Med., vol. 1, no. 1, pp. 10–29, 2016, doi: 10.1002/btm2.10003.
[80] R. Cheng, F. Meng, C. Deng, H.-A. Klok, and Z. Zhong, "Dual and multi-stimuli responsive polymeric nanoparticles for programmed site-specific drug delivery," Biomaterials, vol. 34, no. 14, pp. 3647–3657, 2013, doi: 10.1016/j.biomaterials.2013.01.084.
[81] R. L. Siegel, K. D. Miller, and A. Jemal, "Cancer statistics, 2016," CA Cancer J. Clin., vol. 66, no. 1, pp. 7–30, 2016, doi: 10.3322/caac.21332.
[82] H. Maeda, K. Tsukigawa, and J. Fang, "A Retrospective 30 Years After Discovery of the Enhanced Permeability and Retention Effect of Solid Tumors: Next-Generation Chemotherapeutics and Photodynamic Therapy-Problems, Solutions, and Prospects," Microcirculation, vol. 23, no. 3, pp. 173–182, 2016, doi: 10.1111/micc.12228.
[83] J. T. Lear et al. "Multiple cutaneous basal cell carcinomas: glutathione S-transferase (GSTM1, GSTT1) and cytochrome P450 (CYP2D6, CYP1A1) polymorphisms influence tumour numbers and accrual," Carcinogenesis, vol. 17, no. 9, pp. 1891–1896, 1996, doi: 10.1093/carcin/17.9.1891.
[84] N. Allocati, M. Masulli, C. Di Ilio, and L. Federici, "Glutathione transferases: substrates, inihibitors and pro-drugs in cancer and neurodegenerative diseases," Oncogenesis, vol. 7, no. 1, p. 8, 2018, doi: 10.1038/s41389-017-0025-3.
[85] S. Akhtar, I. Mahjabeen, Z. Akram, and M. A. Kayani, "CYP1A1 and GSTP1 gene variations in breast cancer: a systematic review and case-control study," Fam. Cancer, vol. 15, no. 2, pp. 201–214, 2016, doi: 10.1007/s10689-015-9849-1.
[86] M. C. Larsen et al. "Characterization of CYP1B1 and CYP1A1 expression in human mammary epithelial cells: role of the aryl hydrocarbon receptor in polycyclic aromatic hydrocarbon metabolism," Cancer Res., vol. 58, no. 11, pp. 2366–2374, 1998.
[87] Y. Ma, J. Huang, S. Song, H. Chen, and Z. Zhang, "Cancer-targeted nanotheranostics: recent advances and perspectives," Small, vol. 12, no. 36, pp. 4936–4954, 2016, doi: 10.1002/smll.201600635.
[88] T. V. Verissimo et al. "In vitro cytotoxicity and phototoxicity of surface-modified gold nanoparticles associated with neutral red as a potential drug delivery system in phototherapy," Mater. Sci. Eng. C, vol. 65, pp. 199–204, 2016, doi: 10.1016/j.msec.2016.04.030.
[89] R.-M. Yang et al. "Hyaluronan-modified superparamagnetic iron oxide nanoparticles for bimodal breast cancer imaging and photothermal therapy," Int. J. Nanomedicine, vol. 12, pp. 197–206, 2016, doi: 10.2147/IJN.S121249.
[90] S. J. Jang et al. "In-vitro anticancer activity of green synthesized silver nanoparticles on MCF-7 human breast cancer cells," Mater. Sci. Eng. C, vol. 68, pp. 430–435, 2016, doi: 10.1016/j.msec.2016.03.101.
[91] D. Radenkovic, H. Kobayashi, E. Remsey-Semmelweis, and A. M. Seifalian, "Quantum dot nanoparticle for optimization of breast cancer

diagnostics and therapy in a clinical setting," Nanomedicine (Lond), vol. 12, no. 6, pp. 1581–1592, 2016, doi: 10.1016/j.nano.2016.02.014.

[92] X. Zhou et al. "Dual-responsive mesoporous silica nanoparticles mediated codelivery of doxorubicin and Bcl-2 SiRNA for targeted treatment of breast cancer," J. Phys. Chem. C, vol. 120, no. 39, pp. 22375–22387, 2016, doi: 10.1021/acs.jpcc.6b06759.

[93] Q. Zeng et al. "Carbon dots as a trackable drug delivery carrier for localized cancer therapy in vivo," J. Mater. Chem. B Mater. Biol. Med., vol. 4, no. 30, pp. 5119–5126, 2016, doi: 10.1039/C6TB01259K.

[94] V. Thakur and R. V. Kutty, "Recent advances in nanotheranostics for triple negative breast cancer treatment," J. Exp. Clin. Cancer Res., vol. 38, no. 1, p. 430, 2019, doi: 10.1186/s13046-019-1443-1.

[95] Q. Mu, H. Wang, and M. Zhang, "Nanoparticles for imaging and treatment of metastatic breast cancer," Expert Opin. Drug Deliv., vol. 14, no. 1, pp. 123–136, 2017, doi: 10.1080/17425247.2016.1208650.

[96] N. Chung et al. "HOX gene analysis of endothelial cell differentiation in human bone marrow-derived mesenchymal stem cells," Mol. Biol. Rep., vol. 36, pp. 227–235, 2007.

[97] E. M. Carpenter, "Hox genes and spinal cord development," Dev. Neurosci., vol. 24, no. 1, pp. 24–34, 2002.

[98] M. Kmita et al. "Early developmental arrest of mammalian limbs lacking HoxA/HoxD gene function," Nature, vol. 435, pp. 1113–1116, 2005.

[99] Y. Liu et al. "microRNA-520a-3p inhibits proliferation and cancer stem cell phenotype by targeting HOXD8 in non-small cell lung cancer," Oncol. Rep., vol. 36, no. 6, pp. 3529–3535, 2016, doi: 10.3892/or.2016.5149.

[100] Y. Cui et al. "HOXD1 functions as a novel tumor suppressor in kidney renal clear cell carcinoma," Cell Biol. Int., vol. 45, pp. 1246–1259, 2021, doi: 10.1002/cbin.11568.