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Molecular Mechanisms And Therapeutic Challenges In Breast Cancer Progression And Metastasis

Aliu Olalekan Olatunji[1], Sulaiman Khan[2], Muhammad Majid[3], Hrishik Iqbal[4], [5], Raheela Sarwar[6], Sara khan[7], Ayesha Nazir[8]

[1]Department of Medical Microbiology and Immunology, University of Toledo, USA
Email: aliu_my2004@yahoo.com

[2]Department of Microbiology, Advanced Biomaterials and Tissue Engineering Center, College of Life Science and Technology, Huazhong University of Science and Technology, Wuhan 430074, China, Email: sk9089426@gmail.com

[3]Tianjin Key Laboratory of Molecular Optoelectronic Sciences, Department of Chemistry, School of Science, Tianjin University, Tianjin 300072, China,
Email: majidazam789@gmail.com

[4]Renata PLC, Bangladesh, Email: hrishik.iqbal@renata-ltd.com

[6]Centre of Biotechnology and Microbiology, University of Peshawar
Email: raheela1414@gmail.com

[7]Institute of Integrative Biosciences, CECOS University of IT and Emerging Sciences, Peshawar
Email: Sara.khan@cecos.edu.pk

[8]Pharmacist, Department of Pharmacy, Islamia University Bahawalpur, Pakistan
Email: ayeshapharmacist@hotmail.com

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ABSTRACT

Background: Breast cancer is the most common oncological condition in women worldwide. The mortality rate due to breast cancer is rising, particularly in advanced stages where the disease spreads to vital organs such as the lungs, bone marrow, and liver. Despite extensive research, the cause of the increasing death rate remains unclear.

Objectives: To identify key oncogenes and tumor suppressor genes involved in breast cancer progression and to highlight the molecular and cellular factors that contribute to metastasis and organ selectivity in advanced stages of the disease.

Methods: Review of both basic and clinical studies that have uncovered oncogenes such as HER-2/Neu, cyclins D1, D3, and E, and tumor suppressor genes including p53, ATM, PTEN, BRCA1, and BRCA2. The role of these genes, along with the expression of estrogen and progesterone receptors, in breast cancer diagnosis, prognosis, and treatment strategies was examined.

Results: In early-stage breast cancer, chemotherapy, radiotherapy, and surgery are effective in achieving remission. However, the prognosis for invasive and metastatic breast cancer remains poor, as these forms of the disease are currently incurable. A deeper understanding of the mechanisms behind metastasis and organ-specific dissemination is crucial for improving treatment outcomes.

Conclusions: Advances in the molecular and cellular understanding of breast cancer metastasis could lead to more

effective therapeutic interventions, particularly in addressing organ-specific dissemination. Future research is needed to target the incurable nature of metastatic breast cancer and improve survival rates.
KEYWORDS: tumoural invasiveness, metastasis, microarrays, tamoxifen, target-based therapies

INTRODUCTION

Cancer is one of the three leading causes of death in the world population (2002 Report of the World Health Organization (WHO);. In our country, the death of cancer patients is after cardiovascular diseases and diabetes. In some countries, mammary gland cancer is the leading cause of death among women of reproductive age, and in Mexico, it occupies second place, although in some states in the north of the Republic, it is already in first place. Furthermore, the mortality rate is higher than that of any other oncological disease in women, even cervical cancer (INEGI 2004). Based on these data, it is estimated that between 8 and 11 Mexican women die from it every day. of mammary gland cancer and this figure is increasing (Grajales-Alvarez, Gutiérrez-Mata, et al. 2024).

Fortunately, when cancer is detected in its initial stages, existing therapeutic regimens are very efficient; Unfortunately, this is not the case for invasive stages and the prognosis is poor for patients with metastasis. Therefore, the acquisition of an invasive phenotype, which allows the dissemination of cancer cells, today represents one of the main causes of morbidity and mortality in patients with mammary gland cancer and for oncology patients in general. In developed countries where early detection of diseases such as cervical cancer or mammary gland cancer is very effective, the mortality rate is much lower than the incidence in the population. However, in countries like ours, the lack of adequate early detection programs is reflected in a high mortality rate associated with advanced forms of the disease (Aragón-Franco, Ruiz-Manzano, et al. 2024).

Oncogenes and tumour suppressor genes

Studies carried out during the second half of the last century with viruses that induce tumours in animals defined cancer as a disease caused by altered genes, which allowed the identification of cellular oncogenes and tumour suppressor genes. This advance has allowed us to understand some mechanisms by which a normal cell becomes cancerous and multiplies uncontrollably. The study of these altered genes showed that cancer is a variety of different diseases with phenotypic characteristics and similar behaviours such as uncontrolled proliferation, resistance to apoptosis, and the possibility of invading neighbouring tissues and disseminating to organs distant from their tissue. of origin (Defourny, Caioni et al. 2024).

Retrospective analysis of mutated genes throughout the progression of colon cancer in patient biopsies led to the conclusion that mutations accumulate sequentially over several decades of life, starting as a benign tumour associated with the appearance of two or three mutations in oncogenes or tumour suppressor genes (Defourny, Caioni, et al. 2024).

Oncogenes

Oncogenes are altered versions of normal genes known as proto-oncogenes, whose functions are important in the control of cell proliferation, apoptosis, and cell differentiation. The mechanisms by which they become oncogenes are gene amplification, gene rearrangements, point mutations, and in some cases the participation of viral agents. For example, the Her2 receptor belongs to the epidermal growth factor receptor (EGFR) family. In mammary gland cancer, this gene is usually amplified, generating several copies of the gene and therefore there is an overexpression of this receptor. The result is a gain of function that not only promotes uncontrolled proliferation but also activates protective mechanisms against cell death due to apoptosis. While Her-2 only occurs in 20-25% of patients with mammary gland cancer, in 50% of all different types of human cancer, the ras oncogene is generated by mutation of the ras proto-oncogene (Castillo-Sanchez, Garcia-Hernandez, et al. 2024).

Therefore, protooncogenes are genes that code for elements that normally activate mitogenic signalling pathways. Some mutations generate permanently active gene products; these mutant versions of proto-oncogenes are called oncogenes, with ras and myc being the most common in most human tumours. Ras belongs to the family of small G proteins

(GTPases that exchange GDP for GTP). When bound to GTP, it leads to a proliferative signal evoked by soluble factors such as epidermal growth factor (EGF), platelet-derived growth factor (PDGF), or insulin-like growth factors (IGFs). Oncogenic mutations of Ras interfere with its GTPase activity and therefore prolong its active state and mitogenic signalling in tumour cells (Bornstein-Quevedo, de Anda-González et al. 2024).

Tumour suppressor genes

On the other hand, tumour suppressor genes promote the formation of a tumour when there is a loss or inactivation of it or its protein products. Point mutations or more extensive deletions promote the inactivation of these genes in different human tumours. The most frequent representative of this group of genes is p53, a nucleoprotein whose phosphorylation state ranges between G1 and S and between M and G1. P53 is a tetrameric transcription factor that activates the expression of a large number of genes involved in multiple processes such as cell cycle arrest, senescence, apoptosis, angiogenesis, and DNA repair. One of the genes activated by p53 is the cyclin-dependent kinase inhibitor p21. In response to damage to cellular DNA, p53 is expressed and consequently, p21, which temporarily interrupts the progression of the cell cycle (Retamales, Daneri-Navarro, et al. 2024).

Therefore, cells that contain mutations in p53, which inactivate its function, cannot stop cell cycle progression or DNA replication when it is damaged. The result is that the genetic material is replicated with chromosomal alterations, thus increasing the rate of mutation accumulation. In parallel, mutations with loss of transcriptional function of p53 prevent the activation of cell death by apoptosis that occurs when p53 promotes the expression of proapoptotic proteins such as puma. Studies on the progression of colon cancer showed that early mutations do not necessarily occur in oncogenes, since the gene responsible for the formation of adenomatous polyposis coli (APC) is a tumour suppressor gene. The vast majority of genes mutated in the early stages of this tumour progression correspond to signalling elements of pathways that control cell proliferation (Lujan, Ochoa, et al. 2024).

While ras is not frequently mutated in mammary gland cancer, p53 mutations are very common and are associated with a poor prognosis. Therefore, the detection of mutations in p53 is usually part of the histopathological studies performed on mammary gland cancer biopsies. It is important to highlight that although tumour cells can be mutated in different oncogenes and tumour suppressor genes, the cells present a phenotype very similar to what is called the transformed state. The first to use this term was Peyton Rous, who in 1904 initiated cellular studies of oncogenic transformation associated with avian infection with the Rous sarcoma virus. These studies led David Bishop to the identification of the first oncogene, v-src tyrosine residue kinase, which does not occur in human cancer (Zamzam, Said, et al. 2024).

All transformed cells present aberrant behaviours such as being immortal, presenting uncontrolled proliferation independent of external factors, viability and proliferation independent of their adhesion to a substrate, inhibition of cell death by apoptosis, the ability to promote their vascularization and to invade neighbouring tissues as well as the ability to spread and develop foci of secondary growth or metastasis. As already mentioned, this last phase of tumour progression is the main cause of death related to all forms of cancer (Khoroushi, Neshati et al. 2024).

How many genes are necessary to generate a transformed phenotype? The overexpression of three genes in mammary gland epithelial cells was enough to induce an immortal phenotype with transformed characteristics. The genes introduced were: 1) the catalytic subunit of telomerase, which allows maintaining the length of the telomeres at the end of each replication; 2) the T antigen of the simian virus SV40 that interferes with the functions of the proteins retinoblastoma (Rb) and p53, two brakes of the cell cycle and 3) the oncoprotein H-ras that activates the mitogenic cascade of MAP kinases. Overexpression of these three genes led to amplification of the c-myc proto-oncogene. It is interesting that although none of the three oncogenes introduced correspond to the oncogenes that are normally associated with the development of mammary gland tumours, the tumour phenotype was still generated with a low degree of differentiation, capable of infiltrating and forming tumours in mammary tissue when injected into nude mice (Gashu and Aguade 2024).

Staging, prognosis, and treatment

Mammary gland cancer is stratified into five stages: 0) corresponds to patients with a cancerous growth in situ; I) generally involves a tumour in early stages of vascularization less than 2 cm in diameter, absent from the nodes and without metastasis; II) are patients with a vascularized tumour, with a diameter greater than 2 cm and less than 5 cm, which is present in lymph nodes, but does not yet present metastasis; III) patients with a tumour with a diameter greater than 5 cm and that is already present in supraclavicular nodules and IV) patients who already present foci of metastatic growth. The majority of patients in Mexico arrive at oncology services between stages II and IV. Its prognosis is better if histopathological studies are negative for estrogen and progesterone receptors as well as amplification of the Her2 receptor. It is equally good if the biopsies are negative for mutations in the tumour suppressor genes p53, BRCA1, and BRCA2 (Luo, Zhou et al. 2024).

In contrast to the curative efficacy of chemotherapy, radiotherapy, and surgical procedures when cancer is detected in its early stages the prognosis is poor and can lead to death when detected in invasive or metastatic stages. Although there is extensive knowledge about the genes that give rise to cancer and the functions that are altered, there is still no curative molecular therapy. These types of therapies aimed, for the most part, at selectively interfering with the increased function that is associated with a particular oncogene are called “target therapies.” This lack of curative effects of target therapies most likely reflects the multifactorial genetic nature of oncological diseases. One of these target therapies with encouraging results is the use of humanized monoclonal antibodies against the Her2 receptor, which is overexpressed in 20-25% of invasive forms of mammary gland cancer (Pusztai, Kalashnikova, et al. 2024).

This antibody, whose trade name is trastuzumab or Herceptin, by binding to the Her2 receptor, promotes apoptotic death of mammary gland cancer cells. However, its cytotoxic effects are not sufficient for it to be used as a mono drug, therefore, trastuzumab is used, with very good results, in combination with inhibitors of microtubule function such as taxol or vincristine or with agents that damage DNA such as adriamycin to weaken the tumour before surgery. However, target therapies always reveal a more complex picture when their side effects are evaluated. Thus, for example, trastuzumab produces cardiac alterations, particularly systolic dysfunction, and can also induce pulmonary bronchospasm similar to that of asthma, although to date the molecular bases of these two adverse side effects are not understood (Neagu, Bruno, et al. 2024).

On the other hand, the most effective chemo and radiotherapy treatments remain relatively non-specific to date as they are aimed at poisoning all cells with a high rate of cell division. Since the tumour cells divide more rapidly than the cells of the various epithelia, the tumour cells die, but the epithelial cells are also poisoned, but because they divide more slowly the tumour cells do not die. This explains the multiple side effects such as hair loss or inflammation and dysfunction of the epithelia of the oral cavity and gastrointestinal tract known as mucocitis. The curative potential of chemo and radiotherapy continues to justify their harmful side effects. Therefore, non-specific approaches remain, in most treatments, the most effective way to attack the progression of cancer. These drugs include antimetabolites such as 5'-fluorouridine, agents that cause oxidative damage or DNA alkylation such as cisplatin or adriamycin, and drugs that interfere with microtubules such as taxol or vincristine (Srisawat, Pringproa et al. 2024).

Stages of Breast Cancer

Stage	Characteristics	References
Stage 0	Cancer in situ; no invasion beyond the original tissue.	Luo, Zhou et al. 2024
Stage I	Tumour < 2 cm, no lymph node involvement, no metastasis.	Luo, Zhou et al. 2024
Stage II	Tumour 2-5 cm, present in lymph nodes but no metastasis.	Luo, Zhou et al. 2024
Stage III	Tumour > 5 cm, present in supraclavicular nodes, but no distant metastasis.	Luo, Zhou et al. 2024
Stage IV	Presence of metastatic foci in distant organs.	Luo, Zhou et al. 2024

2. Mechanisms of Oncogene Activation

Mechanism	Description	Examples/References
Gene Amplification	Increased copies of a gene, leading to overexpression.	Her2 gene in mammary gland cancer (Castillo-Sanchez, Garcia-Hernandez, et al. 2024)
Gene Rearrangements	Alteration of gene sequences, often involving chromosomal translocations.	Various types of cancers (Defourny, Caioni et al. 2024)
Point Mutations	Single nucleotide changes result in altered protein function.	Ras oncogene (Bornstein-Quevedo, de Anda-González et al. 2024)
Viral Agents	Viral proteins disrupt normal cellular functions, contributing to cancer development.	SV40 T antigen in mammary gland cells (Gashu and Aguade 2024)

3. Key Tumour Suppressor Genes

Gene	Function	Cancer Types	References
p53	Acts as a transcription factor regulating cell cycle arrest, apoptosis, and DNA repair. Loss of p53 leads to unchecked cell division.	Breast cancer, colon cancer, various others	Retamales, Daneri-Navarro, et al. 2024
APC	Involved in regulating cell proliferation and apoptosis. Mutations often occur early in tumour progression.	Colon cancer	Lujan, Ochoa, et al. 2024
BRCA1/BRCA2	Involved in DNA repair, particularly double-strand break repair. Mutations increase the risk of breast and ovarian cancers.	Breast cancer	Luo, Zhou et al. 2024
Rb	Regulates the cell cycle by inhibiting progression from G1 to S phase. Loss of Rb function promotes uncontrolled cell proliferation.	Retinoblastoma, other cancers	Gashu and Aguade 2024

4. Targeted Therapies for Breast Cancer

Therapy	Mechanism	Usage	Side Effects	References
Trastuzumab (Herceptin)	Binds to Her2 receptor, promoting apoptosis in Her2-positive cancer cells.	Breast cancer (20-25% of cases).	Cardiac issues (systolic dysfunction), pulmonary bronchospasm	Pusztai, Kalashnikova, et al. 2024
Taxol	Inhibits microtubule function, preventing cell division.	Breast cancer, ovarian cancer.	Neuropathy, hair loss	Srisawat, Pringproa et al. 2024
Vincristine	Interferes with microtubule assembly, inhibiting mitosis.	Used in combination with other drugs for solid tumours.	Neuropathy, gastrointestinal issues	Nicolis, De Los Angeles, et al. 2024
Adriamycin (Doxorubicin)	Causes DNA damage by intercalating into DNA strands.	First-line treatment for breast cancer.	Cardiotoxicity, nausea, hair loss	Nicolis, De Los Angeles, et al. 2024

5. Side Effects of Chemotherapy and Radiotherapy

Side Effect	Cause	Examples/References
Hair Loss	Chemotherapy targets rapidly dividing cells, including hair follicles.	Srisawat, Pringproa et al. 2024
Mucositis	Damage to the epithelial cells lining the oral and gastrointestinal tract due to chemotherapy.	Neagu, Bruno, et al. 2024
Cardiotoxicity	Caused by certain drugs like Adriamycin, which can damage heart cells.	Nicolis, De Los Angeles, et al. 2024
Neuropathy	Damage to nerves caused by microtubule-targeting drugs like vincristine and taxol.	Srisawat, Pringproa et al. 2024

As we have already mentioned, in mammary gland cancer, adriamycin, also known as doxorubicin, is the first line of treatment, followed by taxol and vincristine. It is worth mentioning that for mammary gland cancer, radiotherapy is not part of conventional treatments. The development and application of diagnostic procedures and tests that allow early identification are the best approaches to reducing mortality from mammary gland cancer and other oncological diseases. However, in the present and the immediate future, the oncological services of our country will continue to care for patients with advanced stages of the disease who in many cases present metastasis or develop it within the next 5 years after having been subjected to combined treatment regimens. Chemotherapy followed by surgery. For this reason, various groups of Research projects including ours continue to study the molecular and cellular bases of invasion and metastasis (Nicolis, De Los Angeles, et al. 2024).

Tumour progression

Of all the characteristics of the transformed phenotype, a high proliferation rate is the first to appear and is the most common of all of them. It is interesting to note that the majority of solid tumours are derived from epithelial cells, which by their very nature exhibit high rates of cell division. This is the case of lung cancer, the most prevalent oncological disease and with the highest mortality in the world, skin cancer (melanomas), or colon or kidney cancer. They are also derived from secretory epithelia, such as prostate cancer, ovarian cancer, or mammary gland cancer, in the latter the vast majority of tumours are derived from cells of the ductal epithelium and to a lesser extent from the lobular epithelium, this being The latter is responsible for secreting most of the proteins and other components of milk. Other tumours are derived from endocrine epithelia such as pancreatic or thyroid cancer. The high frequency with which tumours originate from epithelial cells is associated with their proliferative potential (Gorobets, Keam et al. 2024)l.

However, tumour cells also originate from other tissues such as sarcomas that are derived from mesenchymal cells or lymphomas, derived from the progenitor cells of the various hematopoietic lineages. Despite having a diverse tissue origin, coming from epithelial or mesenchymal cells, presenting different combinations of oncogenes and tumour suppressor genes, cellular transformation and the progression from contained (benign) growth to Invasive and metastatic (malignant) are surprisingly conserved among different types of cancer and present very similar phenotypes and behaviours. Figure 1 schematically shows the progression of mammary gland cancer from benign neoplastic growth to metastatic growth in distant organs such as the lung, liver, and bone. The tumour initially manifests itself as a focus of abnormal proliferation or neoplasia (new growth) (Lizano, Carrillo-García, et al. 2024).

When the natural organization of the cells in the tissue of origin is lost, different degrees of dysplasia (disordered growth) are identified. All of these stages are treatable and have a good curative prognosis, which is why they are considered "benign." In the second stage, cancer cells acquire the ability to destroy the basal laminae that delimit the space of their tissue of origin and are considered invasive. The tumour mass can increase in volume up to 1 cm^3 without the need to be vascularized, and nourished by diffusion of interstitial fluid. It is important to consider that the detection of a 1 cm mass^3 or less is not easy and is not usually identified in many tumours originating in internal tissues, but it is possible in the mammary gland with careful and frequent exploration. However, from this volume onwards, many of the tumour cells

suffer hypoxia, which induces the production of factors that promote the growth of new vessels, mainly VEGF (vascular endothelial growth factor) and bFGF (basic cell growth factor fibroblasts). These factors and other changes in the environment of the tumour mass favour the vascularization of the tumour, allowing its growth beyond 1 cm.[3]. From this stage onwards, the tumour is considered "malignant" due to its local invasive capacity. The third stage is characterized by the spread of tumour cells via hematogenous or lymphatic routes, a process called metastasis.

This process begins when the cells enter the blood or lymphatic circulation (intravasation), thus being able to reach any part of the body. When circulating through the vessels that supply their target organs, the metastatic cells interact with the endothelium, adhere firmly, and cross the endothelial monolayer through a process called extravasation. Once in the interstitial space of its target organs, invasion occurs and a secondary growth focus is established in the target organ. Adhesion, extravasation, and establishment appear to depend on a functional interaction between the target organ and metastatic cells. It has been It is estimated that only one in every million metastatic cells that enter the bloodstream manages to establish a successful metastatic focus. Therefore, the vast majority of patients who present metastatic forms have a poor prognosis (Mota-López, Barojas-Payán, et al. 2024).

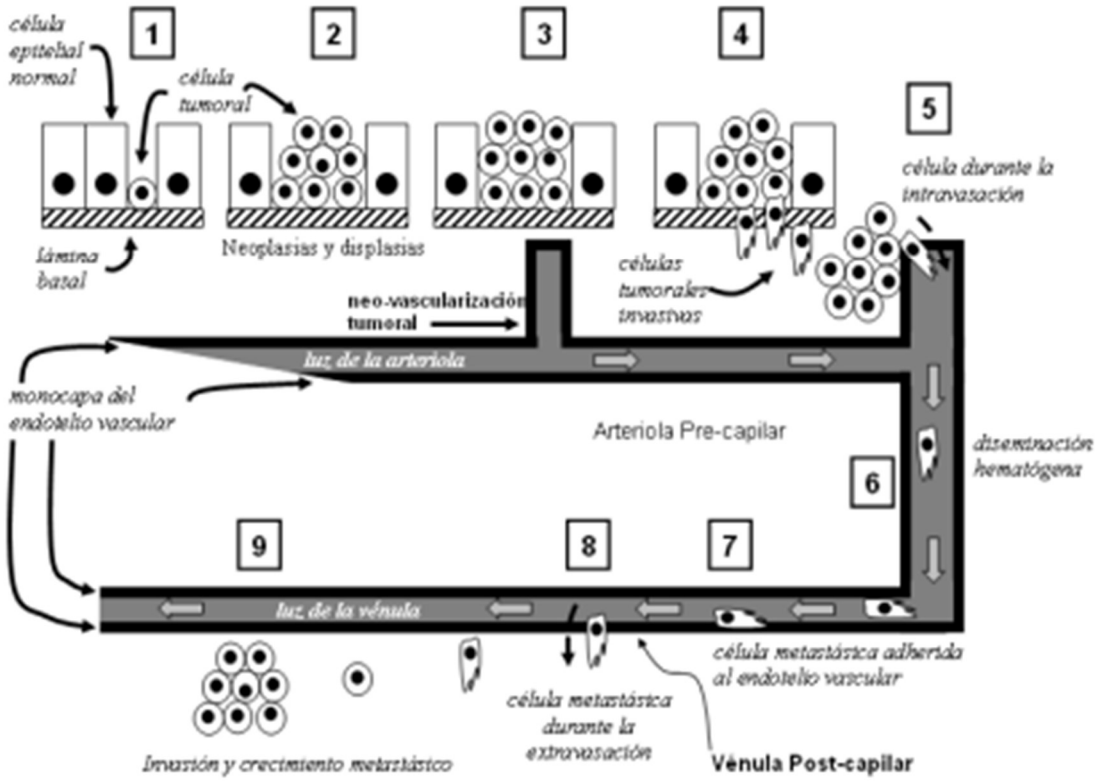

Figure 1 Stages in tumour progression. 1: the appearance of a tumour cell within an epithelium; 2: benign neoplastic growth, contained within its basal lamina; 3: acquisition of invasive capacity site breaking the basal lamina; 4: tumour vascularization; 5: intravasation, tumour cells enter the bloodstream or lymphatic circulation; 6: dissemination through vascular or lymphatic beds; 7: adhesion of metastatic cells to the vascular endothelium of distant target organs; 8: extravasation of the metastatic cell and entry into the target tissue; 9: secondary growth of metastatic cells (Abdul-Nasir, Lee et al. 2024).

It is important to highlight that cancer cells do not present behaviours that are not encoded in the genome, they simply present them outside of the time and place for which they are physiologically programmed. A major question that remains to be resolved is how a relatively small group of mutations in oncogenes and tumour suppressor genes allows the abnormal expression of invasive and metastatic genetic programs, reminiscent of embryonic stages. Thus, for example,

the high rate of proliferation of tumour cells is similar to the accelerated cell division during the early stages of embryonic development or the clonal expansion of B cells that produce antibodies. The ability to invade tissues other than the tissue of origin is similar to the behavior of cytotrophoblast cells during morula implantation, or to the way neutrophils and polymorphonuclear cells infiltrate during an inflammatory reaction. Another example of migration and invasion occurs when cells that are part of the neural crest epithelium migrate to form the structures derived from the branchial arches (Nosalova, Huniadi, et al. 2024).

This phenomenon is similar to what occurs in invasive and metastatic melanomas. Tumour vascularization processes recapitulate what happens when organs and tissues after a heart attack can no longer be nourished by diffusion of the interstitial fluid. Upon entering hypoxia, these tissues promote the formation of new vessels (angiogenesis). In the case of mammary gland cancer, dissemination initially follows the natural flow of lymphatic circulation carrying cancer cells to the axillary lymph nodes (Fig. 2). The high frequency of lung metastasis is also partly explained by this organ is the first to be reached by metastatic cells. However, lung invasion requires a codependent interaction between metastatic cells and lung mesenchyme. Mammary gland cancer cells can also invade cortical bone, bone marrow, or liver (Fig. 2) (Molina, Figueroa et al. 2024).

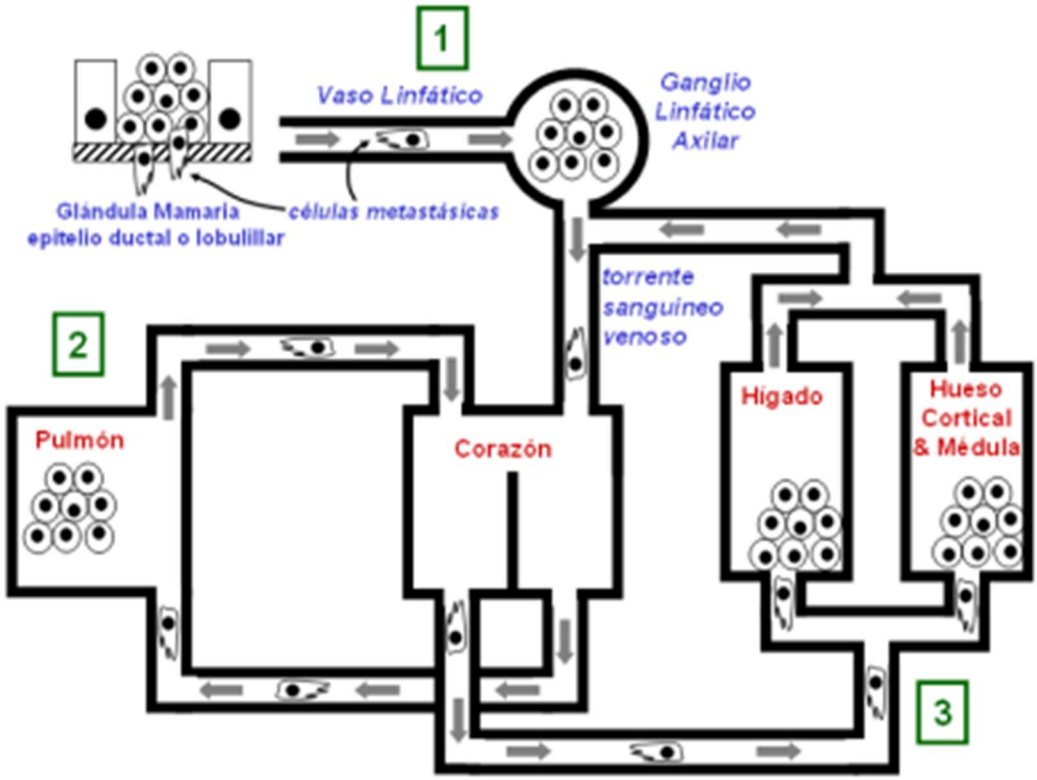

Figure 2. Scheme of the metastatic spread of mammary gland cancer cells.1) Metastatic cells travel through the numerous lymphatic vessels to the axillary lymph nodes. After entering the venous bloodstream they cross the heart and pass through the lung where frequent metastatic growths are generated. 3) If they do not establish themselves in the lung, they cross the heart again and with oxygenated blood reach the liver, cortical bone, or bone marrow (Waldum and Slupphaug 2024).

Basic mechanisms of metastasis

What guides tumour cells so that, regardless of their origin, they follow a very similar tumour progression that culminates in metastasis? This remains a big question that lacks a clear answer. A step before cellular transformation is

immortalization, a product of chromosomal instability that promotes chromosomal aberrations or point mutations. Currently, most of these mutations are considered to be lethal since they occur in genes with essential functions for cellular life: intermediate metabolism, energy generation, cytoskeletal elements, vesicular traffic control elements, protein synthesis, and other components. However, tumour cells that survive are subject to a selection process where the tissue microenvironment offers a series of restrictions and favourable conditions that manifest themselves as the type of extracellular matrix and soluble factors characteristic of the tissue. Therefore, metastasis is considered to occur when the tissue microenvironment of the target organ provides complementary elements to the needs of the tumour cells (Dj, Alimova et al. 2024).

A novel element has been the discovery that tumour cells also secrete factors specific to the invaded tissue, establishing a codependency relationship between metastatic cells and the invaded tissue. In the case of bone metastasis by mammary gland cancer cells, it is clear that the expression of several components of the bone matrix, such as osteopontin, type I collagen, and regulators of osteoclast maturation such as osteocalcin and osteoprotegerin are conditioning factors. Malignancy and metastasis to bone. In conclusion, it is clear that there is communication and codependency between metastatic cells and the organs they invade, but there is still a long way to go before we have a clear understanding of the functioning of these relationships and their importance in the development of metastases. This concept has its origin in the "seed and soil" hypothesis, proposed in 1889 by the English surgeon Stephen Paget which highlights that the distribution of metastases is not due to a "random phenomenon." ", but the tumour cells (the "seed") present an "affinity" or tropism and specific dependence on the environment of their target organs (the "earth") (Carrión-Estrada, Aguilar-Rojas, et al. 2024).

This hypothesis was refuted by James Swing (1928), who explained metastasis based on the anatomical structure of the vascular system, a position that prevailed until the 1970s with the studies of Sugarbaker (1979). From then on, it is considered that regional metastases can be attributed to anatomical or mechanical considerations such as efferent venous circulation or lymphatic drainage towards regional lymphoid nodes and nodes, as occurs in mammary gland cancer, while metastases Distant organs are processes that occur in an organ-specific manner and require functional interactions (Abduxalilova, Azimova, et al. 2024).

The classic view of tumour progression postulated that both the acquisition of a metastatic phenotype and the characteristics that determine invasion of a particular organ are established late when the tumour acquires malignant characteristics. In recent years, the research groups of Friend, Golup, and Massagué have found evidence indicating that both the metastatic potential and the tropism towards one organ seem to be determined in the early stages of progression when it is still a benign tumour. Nowadays it is considered that metastatic potential is defined in early stages during cellular transformation, but that its manifestation depends largely on the genetic background of the affected individual. This scenario then contemplates the so-called susceptibility genes, which, without being causal elements of metastatic development, can facilitate the process (Culha, Davarci, et al. 2024).

There have been significant advances in the study of the molecular bases of organ-specific metastasis in the case of mammary gland cancer. Comparative analysis of the expression pattern of cancer cells using the microarray technique has shown that metastatic cells express a hundred genes that seem to be associated with the invasive phenotype and specific organ tropism. Thus, for example, the overexpression of different combinations of epiregulin (EREG), metalloproteinases types 1 and 2 (MMP1, MMP2) or vascular adhesion protein (VCAM), along with another dozen genes in gland cancer tumours stage I breast cancer appear to be predictive of lung metastasis. In contrast, overexpression of interleukin 11 (IL-11), a chemokine receptor (CXCR4), metalloproteinase 1 (MMP1), and fibroblast growth factor type 5 (FGF5) along with another small group of genes predicts a metastasis to bone. How these types of results can find practical application in the clinic remains to be determined (Sánchez, Cesarman-Maus, et al. 2024).

The specificity for certain organs is not only due to the capacity for interaction between tumour cells and the vascular endothelium but also involves the expression of attracting factors such as chemokines and the expression of their

receptors on tumour cells. For example, the expression of chemokine receptors such as CXCL12/CXCR4 and CCL21/CCR7 has been found in metastatic cells (Obregón-Mendoza, Meza-Morales, et al. 2024).

Currently, the search for a molecular signature that predicts a metastatic phenotype the type of organ that will be invaded and the cellular mechanisms of adhesion and extravasation will lead to a better understanding of the different phases of metastasis. It is expected that these types of studies will allow the establishment and development of better therapeutic strategies and the development of drugs, either to limit or prevent the expansion of tumour cells to distant organs (Carrión-Estrada, Aguilar-Rojas, et al. 2024).

Signalling pathways, oncogenes, and tumour suppressor genes

As already mentioned, most of the genes altered in tumour cells serve as elements in the signalling pathways that control cell proliferation. Due to the type of function, they play in these pathways, they have been divided into two large families: oncogenes, which act as cell cycle accelerators, and tumour suppressor genes, which act as brakes (Kasianchyk, Velazquez, et al. 2024).

Oncogenes and mitogenic pathways

There are a wide variety of factors that activate them through receptors with seven transmembrane domains, as occurs with the oncogene associated with Kaposi's sarcoma. Proliferation is also stimulated through receptors with tyrosine kinase domains, such as Her2, and even through nuclear receptors such as estrogen receptors, both important examples in mammary gland cancer (Fig. 3). It is enough for one of the elements of the mitogenic pathway to present a mutation with gain of function for the pathway downstream of these proteins to be activated, maintaining a proliferative stimulus even without more elements being mutated. When analyzing mutated genes in mitogenic signalling pathways, an unexpected pattern emerges: not all gene products of transduction pathways can be mutated with oncogenic consequences (Barrera-Juarez, Halun-Trevino, et al. 2024).

The experimental gain-of-function mutation of genes such as Grb2 (growth-factor receptor binding protein 2), SOS (son of sevenless), or mitogenic stimulus-dependent kinases (MAPKs) instead of inducing an oncogenic phenotype are lethal (Fig. 3). In mammary gland cancer, the Her2 or alpha-type estrogen receptor (ER)a) is usually overexpressed. In contrast, other genes of the mitogenic pathways such as the coupling proteins Grb2 and SOS or the enzymes of the mitogen-activated kinase cascade (MAPK), have never been identified as oncogenes in any type of cancer. Ras and Raf, intermediate signalling elements between the receptor and MAP kinases, have been identified as oncogenes, although in mammary gland cancer, they are not frequent mutations. Among the mitogenic ones, there is also the phosphatidylinositol 3-phosphate kinase (PI3K) that phosphorylates the phospho-inositides generated by phospholipase C gamma (PLC).c) and which in turn leads to the activation of the Akt kinase. The PI3K/Aktque pathway activates survival pathways dependent on the transcription factor NF-kB and inactivates apoptotic pathways by phosphorylating caspase-9 and proteins such as BAD that normally neutralize anti-apoptotic proteins such as $BCLX_L$ by forming heterodimers with them. Akt kinase frequently presents gain-of-function mutations in mammary gland cancer that interfere with apoptosis and express survival genes (Agramonte, Miranda, et al. 2024).

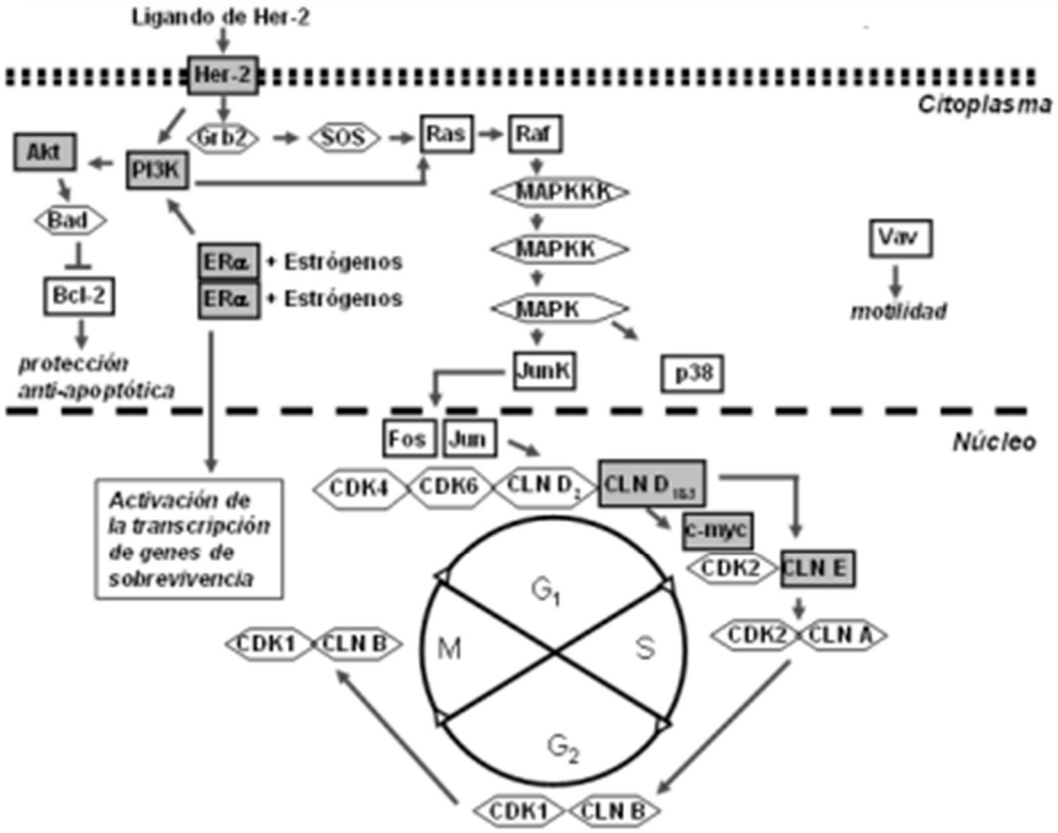

Figure 3. Scheme of the signalling of the mitogenic, motility, and apoptosis pathways. The mitogenic pathway of the family represented by Her2, a member of the epidermal growth factor family receptors, is presented. All oncogenes are framed in rectangles. Oncogenes that are frequently mutated in mammary gland cancer are found in grey rectangles. Elements of mitogenic pathways that are not proto-oncogenes are framed in white hexagons. Inhibitory effects are indicated with a line and a vertical bar. The double dashed line at the top represents the cell membrane, and the dashed line at the bottom represents the nuclear membrane. Inside the nucleus, the cell cycle is represented. The oncogenes Vav and Bcl-2 associated with cell motility and protection against cell death by apoptosis are also shown, respectively (Cataldo, Aravena et al. 2024).

All mitogenic pathways converge in the activation of the MAP kinase cascade that leads to the activation of enzymes such as Jun transcription factor kinase (JUNK) or p38 that activate the expression of the cell cycle thanks to the activation of the genes that code for cyclins D1, D2, and D3. The different D cyclins bind to the cyclin-dependent kinases (CDKs) CDK4 and CDK6 that control the progression of the G phase of the cell cycle. This promotes the expression of cyclin E which binds to CDK2. The cyclin-E/CDK2 complex phosphorylates the retinoblastoma protein (Rb), which releases the transcription elongation factor E2F, allowing the expression of the genes necessary to synthesize triphosphorylated deoxy-nucleotides necessary for the replication of genetic material. The cyclin-E/CDK2 complex promotes the synthesis of cyclin-A, which, together with CDK2, directs the S phase and part of the G2 phase (Djohan and Wang 2024).

In turn, the cyclin-A/CDK2 complex promotes the expression of cyclin B, which, together with CDK1, directs the last M phase with which the cell cycle ends (Figures 3 and 4). It is understandable then that the overexpression of cyclins D1, D3, and E is associated with the development of mammary gland cancer. However, neither cyclin D2 nor the cyclin-dependent kinases CDK4, CDK6, or CDK2 have been identified as oncogenes in this type of cancer. It is considered that all elements of the mitogenic pathway that do not participate as oncogenes, such as Grb2, SOS, MAPs, or cyclin D2, as well as CDKs, have other functions in addition to their role in cell cycle control by which their gain-of-function mutations

are letha (Riano, Contreras-Chavez, et al. 2024)l.

Tumour suppressor genes and antiproliferative pathways

Figure 4 presents anti-myogenic pathways that explain the mechanism by which loss-of-function mutations in tumour suppressor genes contribute to uncontrolled proliferation and greater accumulation of mutations. For example, the phosphatase PTEN (Phosphatase and tensin homolog), a tumour suppressor gene associated with inherited forms of mammary gland cancer, is the only gene that has been identified as an antagonist of the pathway activated by PI3K kinase. In mammary gland cancer, PTEN mutations abrogate its function, allowing the PI3K/Akt pathway to not be efficiently turned off (Herrera-Torres, Parra-Torres et al. 2024).

Transforming growth factor beta (TGF-b) is representative of a large family of factors with antiproliferative activity that is based on the fact that it leads to the expression of inhibitors of cyclin/CDK complexes. Among the inhibitors that are induced by this pathway are the proteins p21 and p27 (Fig. 4). On the TGF-pathway type I and II receptors and with the signalling elements Smad4 and Smad2 have been identified as tumour suppressor genes involved in the development of mammary gland cancer. The dysfunction of this pathway results in the inhibitors of the cyclin/CDK complexes that control the start of the cell cycle not being expressed, therefore, the cells lack a cycle brake and divide uncontrollably (Li, Zhou, et al. 2024).

The cell cycle is interrupted when there is DNA damage; this effect results mainly from the expression of the p53 protein, which in turn promotes the expression of the CDK inhibitor p21. This blockage of the cycle gives time for the different repair systems of the genetic material to come into action. Radiation generates DNA double-strand breaks, the repair of which requires a series of radiation-induced proteins (RAD). The DNA damage repair system generated by DNA breaks requires the RAD52 family proteins, which repair the breakthrough homologous recombination with the unaffected chromatid. The sensors of DNA breaks are the proteins ATM and NBS1, then RAD52 and RAD51 associate with the damaged DNA and attract a variety of proteins from the same RAD family to repair. Among the proteins that are required for this repair process are the proteins encoded by the tumour suppressor genes BRCA1 and BRCA2 (BReast CAncer gene 1 and 2 respectively). These two genes are associated with hereditary forms of mammary gland cancer and in particular, BRCA2 is associated with mammary gland cancer, while BRCA2 is with ovarian cancer. The mutated ataxia telangiectasia (ATM) gene is also associated with inherited forms of mammary gland cancer but not with the associated proteins RAD51 or RAD52 (Ramírez-Santos, Calzada et al. 2024).

Therefore, the different transduction pathways involve both oncogenes and mutated tumour suppressor genes that have been identified as genes associated with the development of cancer (Wang, Albers et al. 2024).

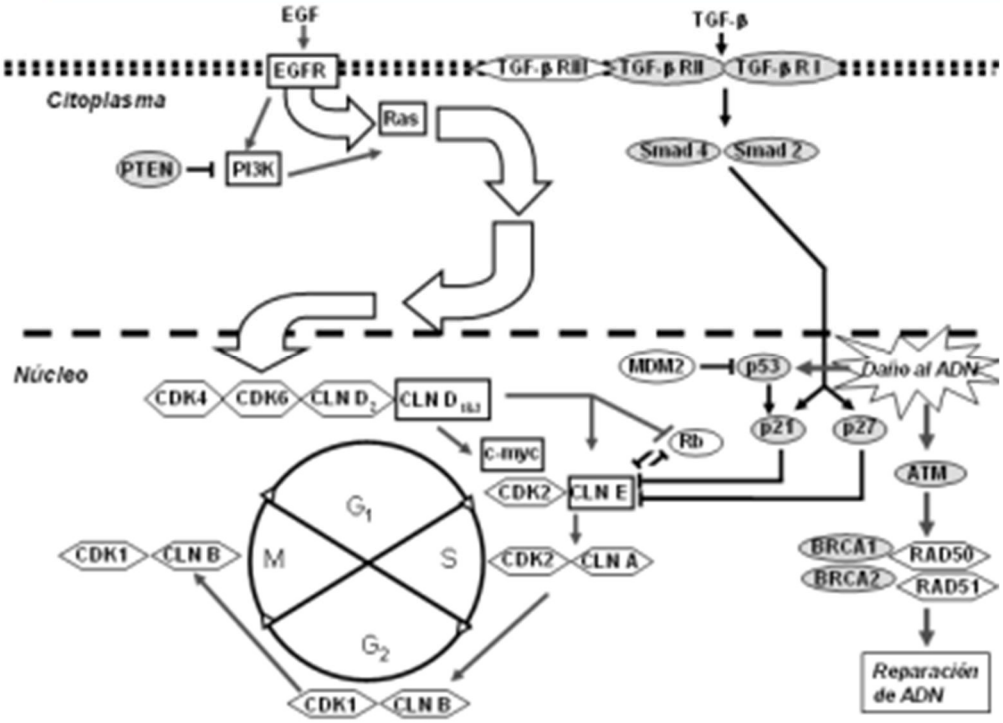

Figure 4. Scheme of the signalling of the TGF-antimitogenic pathway. b. The mitogenic pathway is represented by the flow of arrows from the epidermal growth factor (EGF) to the cell cycle. The antimitogenic pathway of TGF- is represented on the right side of the diagram. b. Tumour suppressor genes that are frequently mutated in mammary gland cancer are found in grey ovals. Also shown is the tumour suppressor gene PTEN that antagonizes the effects of PI3K (top left of the diagram). Inhibitory effects are indicated with a line and a vertical bar. The double dashed line at the top represents the cell membrane, and the dashed line at the bottom represents the nuclear membrane. Inside the nucleus, the cell cycle is represented. Also shown are the tumour suppressor genes that participate in the repair of DNA damage: ATM, BRCA1, BRCA2, and RAD52 and 51 (Beniwal, Dahiya, et al.).

Intercellular adhesion molecules

Cells that have invasive and metastatic capabilities present alterations in the expression of different classes of adhesion molecules that mediate cell anchoring to their microenvironment. The affected proteins include 1. cell-cell adhesion molecules (CAMs), mainly members of the immunoglobulin superfamily and the cadherin family, whose function is to regulate cell-cell interactions, and 2. integrins, which are responsible for cell-extracellular matrix (ECM) interactions. All of these adhesion interactions converge on regulatory signalling pathways in the cell. One of the adhesion molecules commonly altered in melanomas and other types of tumours (for example, pancreatic, mammary gland, gastric, and colorectal cancer, among others) is E-cadherin, a Ca-dependent homotypic molecule^{2+}, responsible for cell-cell interactions (Shao and Di 2024).

This protein occurs ubiquitously in epithelial cells (hence its classification as type “E”). E-cadherin expression or function has been observed to be decreased or lost in many human carcinomas, as an early change during the development of metastatic progression. This decrease makes it easier for tumour cells to free themselves from the adhesion contacts of neighbouring cells and separate from the tissue and the primary tumour mass. Studies in vitro, have indicated that deletions of the domain cytoplasmic E-cadherin result in a functional loss of cell-cell adhesion and an increase in cell motility. On the other hand, studies indicated that in the majority of tumours of epithelial origin, the function of E-cadherin is lost through mechanisms that include mutations in the coding region of the gene, inactivation of the promoter

by hypermethylation, or by proteolysis of the extracellular domain and/ or cytoplasmic protein (Luís 2024).
Through their intracellular domain, cadherins interact with the actin cytoskeleton through adapters such as alpha and beta catenins. Beta-catenin in particular plays a central role as it acts as a transcription factor. When cells lose intercellular contact, beta-catenin is released and translocates to the nucleus where it promotes gene expression and proliferation. This explains why mutations in the beta-catenin gene are also associated with this type of tumour. Beta-catenin plays a particularly important role in the WNT receptor/lipoprotein receptor system signalling pathway in the development of colon cancer. Overexpression of E-cadherin in cultured melanoma cells and transgenic mouse models decreases the invasive and metastatic capacity of the tumour, while its inactivation increases both capacities. Due to this, it has been proposed that E-cadherin functions as a suppressor of invasion and metastasis in epithelial cancers, and its functional elimination represents a necessary step in the acquisition of this capacity. Despite what was expected, mutations in E-cadherin are rare in different types of cancer, including mammary gland cancer, therefore changes in its expression are considered to be epigenetic changes or transient adaptations of invasive cells (Rybinska, Mangano et al. 2024).
On the other hand, changes in the expression of integrins and their affinity for molecules of the immunoglobulin superfamily or components of the ECM, for example, laminin, collagen, fibronectin, and vitronectin, are also evident in invasive and metastatic cells. Integrins are heterodimeric proteins consisting of two subunits (and) linked together in a non-covalent manner. Each subunit has an extracellular domain, a transmembrane domain, and a noncatalytic cytoplasmic domain. In some tumours, the expression of certain integrins increases, while in others it decreases. In colon and mammary gland cancer, a reduction in the expression and an altered distribution of integrin subunits has been observed (a1, a6, b1, b4, thea5b1). These subunits act as receptors for collagen, fibronectin, and laminin (Nehzati, Hefelfinger et al. 2024).
The different microenvironments invaded influence the responses of malignant cells. According to this, the successful colonization of these new sites, both distant and local, requires an adaptation that is achieved through changes in the spectrum of subunits and integrins, which are expressed by the invading cells. Carcinoma cells facilitate invasion through a change in the expression of their integrins. Thus, for example, the change in integrinsa1b2 that binds to the constitutive matrix of the basal lamina changes to integrinsa3b1 andainb3 preferentially to new extracellular matrix components generated by extracellular proteases of invasive cells. Overexpression of normal family integrinsb2 in tumour cells blocks the formation of metastasis, highlighting the importance of the type of integrins expressed by the metastatic cell for its dissemination (Galal, Al-Rimawi, et al. 2024).

The role of matrix metalloproteases in invasion and metastasis

In recent years, interest in identifying those molecules involved in the proteolytic degradation of the extracellular matrix has increased considerably. During the invasion process, tumour cells have to cross the interstitial matrix that is composed of glycoproteins, proteoglycans, and filamentous proteins. One of the main findings has been the participation of various cascades of proteolytic reactions in the invasion and metastasis processes. Four classes of proteases participate in these cascades: serine-, cysteine-, aspartyl-, and matrix metalloproteases (MMPs), the latter being the most studied, due to their participation in the initial step of the degradation of the extracellular matrix (Rojas-Armas, Palomino-Pacheco, et al. 2024).
The breakdown of the basal laminae and the invasion of the interstitial space requires proteases of various types, which have been studied for many years in cells of various types of cancer. The vast majority of proteases are synthesized and secreted in the form of inactive zymogens, an exception is the metalloproteinases (MMPs) that contain the sequence RXKR (Arg-X-Lys-Arg) such as stromelysin-3 and MT-MMPs. All Other inactive zymogens are activated in the extracellular environment by a plasminogen activator system or by another member of the MMP family. Active MMPs are under strict regulation by tissue inhibitors of MMPs (TIMPs) or bya$_2$-plasma macroglobulin in a 1:1 stoichiometry. The balance between activators and inhibitory peptides of proteases present in the extracellular environment normally determines the maintenance and repair processes of extracellular matrices (Sun, Huang et al. 2024).

The first observations about the importance of MMPs in invasion and metastasis were made by Liotta reporting that an enzyme secreted by melanoma cells was capable of degrading collagen, a component of the basal laminae. This discovery was followed by numerous studies that indicate a correlation between the expression of MMPs in tumours and their ability to invade and generate metastasis; Therefore, an increase in the expression of MMP-2 (gelatinase A, 72 kDa) and MMP-9 (gelatinase B, 92 kDa) has been demonstrated in different human tumours. Both MMPs have their highest activities about that of type IV collagen, the main constituent of the basal laminae. It is interesting that although there are 9 MMPS, it has been MMP-2 and MMP-9 that are most frequently overexpressed in invasive cells. Other proteins that present an increase in different tumours are interstitial collagenases, stromelysin 2 and 3, matrilysin, and MT1-MMP (Bhandari, Gilligan et al. 2024).

All of these enzymes are capable of degrading extracellular matrix molecules (for example, laminin, fibronectin, and vitronectin, among others), proteoglycans, glycoproteins, and various types of collagen. Furthermore, invasive tumour cells also express metalloproteases associated with the cell membrane that activate gelatinase B and function as receptors for gelatinase A, efficiently inducing the proteolysis of matrix proteins throughout the area where the cells make contact (pericellular zone). In some cases, the expression level of these MMPs has been correlated with the degree of tumour progression or clinical status. Initially, it was believed that the main role of MMPs was to facilitate the breakdown of physical barriers of the tissue, thus promoting the invasion and entry of tumour cells into the blood and/or lymphatic circulation (Bania, Adamou, et al. 2024).

However, it has recently been shown that MMPs and their inhibitors participate in other stages of tumour progression. Expression of stromelysin-1 (MMP-3) in the epithelial mammary gland is sufficient to induce the development of invasive mesenchymal-like tumours and this transition can be blocked by TIMP-1. Recently it has been possible to set up a preparation of mesenteric veins where a microscope lens allows images of circulating cells to be recorded, either by visible light microscopy or even fluorescence microscopy. This technique called intravital videomicroscopy, has allowed us to show that beta MMPs are also important in the creation and maintenance of an environment that contributes to the initiation and growth of primary tumours such as metastatic foci... This effect may be mediated by the processing and release of growth factors associated with the extracellular matrix, such as TGF- or basic FGF or the RAGE receptor. Receptor for advanced glycation It isnd products) (Khajoei, Azadeh et al. 2024).

Serine proteases

Within the MMPS family, there are serine proteases that in turn include plasminogen activators. These are directly and indirectly involved in the degradation of the extracellular matrix. Plasminogen activators are proteases that specifically convert inactive plasminogen to active plasmin, an enzyme that has broad substrate specificity. Through plasmin, plasminogen activators can indirectly degrade a wide variety of proteins, including fibrin, fibronectin, type IV collagen, vitronectin, and laminin. Plasmin also can activate latent collagenase and pro-plasminogen activators. There are two types of plasminogen activators, urokinase-type plasminogen activator (uPA) and tissue-type plasminogen activator (tPA). The urokinase-type is directly involved in the degradation of extracellular matrix proteins during physiological and pathological tissue remodelling processes (Castañeda-Sánchez, Chimal-Vega, et al. 2024).

On the other hand, tissue-type plasminogen is an enzyme that is involved in the dissolution of clots in blood vessels and the maintenance of vascular homeostasis. However, the role that tPA plays in cancer development is controversial. This tissue type of plasminogen is known to be absent in glioblastoma metastasis, as well as in colon, lung, and breast tumours. In the case of uPA, an increase in its activity has been detected in primary tumours as well as in melanoma metastases. The distribution of uPA on the cell membrane is not homogeneous, being found mainly in the so-called invasive front, which corresponds to the lamellipodia that extend the tumour cells as they advance (Khosravaninezhad, Zavareh, et al.). On the other hand, in many tumours the proteases that degrade the extracellular matrix are not produced by tumour cells but by stromal cells and inflammatory cells. These proteases, once released, can be manipulated by tumour cells. In this way, tumour cells can induce the expression of uPA and its subsequent binding to the surface receptor uPAR producing

the proteolytic activation of plasminogen. This protease, as already mentioned, is capable of degrading various components of the extracellular matrix directly or indirectly through the activation of metalloproteases, which subsequently degrade collagens and other proteins of the interstitial matrix and basement membranes, such as laminin and fibronectin (Zambrano-Román, Padilla-Gutiérrez, et al. 2024).

Active Locomotion

A requirement for tumour cells to invade the surrounding tissue and extracellular matrix (ECM) is to have the ability to spread to other tissues, also called "active locomotion." To do this, tumour cells use migration mechanisms similar, if not identical, to those that occur in normal cells during physiological processes such as embryonic morphogenesis, wound healing, and immune cell trafficking. Recent studies indicate that oxygen deprivation could increase the motility capacity of tumour cells. It has been found that hypoxia increases the expression of genes associated with cell migration, such as c-Met, a receptor protein that increases cell motility and invasion through binding to its ligand, hepatocyte growth factor (HGF). The vav oncogene, which acts as a scaffolding protein, to which different signalling effectors bind, activates the small G proteins Rac and CD48, which increase the turnover of the actin cytoskeleton, an essential step for active locomotion. In the mammary gland, cancer vav is not frequently mutated (Cadena-Iñiguez, Santiago-Osorio, et al. 2024).

Intravasation, arrest and extravasation

After successfully crossing the extracellular matrix, tumour cells enter the vascular system to spread to new organs, a step called intravasation. This step requires a coordinated sequence of proteolysis and active locomotion. Recent evidence indicates the existence of important differences in the intravasation of metastatic and non-metastatic cells within a primary tumour. It has been observed that metastatic cells orient and elongate towards blood vessels, while non-metastatic cells associate randomly, and their elongation is independent of the position of the blood vessels. This suggests that cell orientation may be induced by chemoattraction to blood vessels. Structural analysis of primary tumours suggests that the direct entry of tumour cells into blood vessels is confined to small veins; this vascular network is called postcapillary microvasculature Other vessels, such as the great veins, can also be invaded, but arterial invasion is a rare event (Trinh 2024).

There are reports where it has been shown that in some tumours (for example, sarcomas), blood is transported through vascular clefts, which are lined by tumour cells, rather than by an endothelium. In these tumours, invasion does not require prior degradation of the basal laminae. However, the tumour dissociation process should be supported by the action of proteolytic enzymes. In some anatomical sites and/or in some dedifferentiated tumours, the basal laminae may be very thin and devoid of collagen. For example, in the lung, the combined thickness of the alveolar epithelium, basal lamina, and capillary endothelium is only 100mm. Furthermore, the tumour neovasculature tends to be discontinuous and present openings (fenestrated endothelium), which is why it is weak and easily haemorrhages, due in part to the overproduction of VEGF (Palos, Zhou, et al. 2024).

Furthermore, intravasation into these vessels may require much less degradation than intravasation into normal vessels. Tumour cells can also enter the blood circulation in the lymphatic-venous connections, after having entered the lymphatic capillaries. Interestingly, none of these structures present basal laminae. Sugino and his group showed that, in some models, metastatic cells can gain access to blood vessels by intravasation of "tumour cell nests" surrounded by vascular endothelial cells, followed by intravascular growth of the tumour without penetration of the vascular wall. In different studies, it has been found that the efficiency of vascular invasion has a great impact on the course of metastatic progression. That is, patients in whom invasion of blood or lymphatic vessels is detected during surgery have a worse prognosis than patients without vascular invasion (Zhang, Yan et al. 2024).

After having entered the vasculature, aggregated or individual tumour cells evade different mechanisms of the immune response (for example, the action of T and B lymphocytes, neutrophils, macrophages, and NK killer cells), and of the

vascular environment, such as turbulence or the complement system. Blood or lymphatic flow passively draws metastatic cells to distant organs and tissues where they form secondary lesions. As already mentioned at the beginning, it is proposed that the cells are arrested in the postcapillary veins of the target organs. Metastatic cells adhere to endothelial cells (ECs) and the subendothelial basal lamina, which may be exposed (Ma, Shi, et al. 2024).

Recent observations performed with intravital microscopy suggest that metastases originate from the intravascular growth of tumour cells adhered to the endothelium rather than from extravasated cells [65-68]. These results highlight the importance of intercellular adhesion in tumour metastasis. However, for this to be carried out, the endothelium is required to go from its basal or resting state to its activated state. This phenotypic change, normally present in the inflammatory reaction, allows expression on the surface of apical endothelial adhesion molecules necessary for heterotypic tumour cell-endothelial interaction and which serve as the basis for tumour extravasation (Xing, Li et al. 2024).

After the tumour cell-endothelium interaction, metastatic cells extend along the vascular wall to subsequently extravasate into the parenchyma of the target organs where they will finally proliferate through sequential steps of proteolysis, cell-substrate adhesion, and active locomotion. These processes are carried out in a similar way as they were carried out during the processes of intravasation and interaction with the extracellular matrix (Al-Qadasi, Yahia et al. 2024).

Mammary gland cancer

From the observations made by Beatson in 1896 on the regression of mammary gland cancer in patients undergoing removal of the ovaries, the hormonal dependence of the disease became clear. Subsequent studies revealed that hormonal dependence is not a widespread phenomenon in mammary gland cancer, and only between 25 and 40% of tumours respond favourably to the removal of the ovaries. This led to the search for biological markers that would allow us to identify this group of patients. with forms of cancer dependent on estrogen and/or progesterone, with which immunohistochemical assays were developed for the identification of estrogen receptors (ER) and progesterone receptors (PgR). From this moment on, the histopathological identification of these receptors in mammary gland cancer has been a very important tool in diagnosis, prognosis, and treatment (Wang, Shang, et al. 2024).

There are two isoforms of the estrogen receptor called alpha (595 amino acids) and beta (530 amino acids). Compared to the ER-alpha isoform, ER-beta lacks 53 amino acids at its amino terminus and 12 at its carboxyl terminus. Normally, the alpha isoform is expressed in the female sexual organs including the mammary gland, while the beta isoform is only significantly expressed in the ovary and the male sexual organs, and some areas of the central nervous system. The alpha isoform is the one commonly found in patients with hormone-dependent forms of mammary gland cancer. Figure 5A schematizes the structure of the estrogen receptor with its binding domains (Mendoza, Nefte et al. 2024).

Estrogen receptors act both at the transcriptional level, promoting the expression of genes that mediate long-term effects such as the sustained expression of caspase inhibitors such as an inhibitor of apoptosis protein (IAP-1), as well as at the cytoplasmic level, activating kinase-dependent signalling cascades that mediate immediate responses such as activation of the mitogenic pathway. The function as a transcription factor depends on the interaction with its ligand in the cytoplasm, which favours the binding to estrogen response elements (EREs) in DNA and also its interaction with co-transcription activators such as SRC-1, SRC-2, or SRC-3Steroid Receptor Co activator), CEBP/p160 (CCAAT/enhancer binding protein). Figure 5B schematizes the binding of an ER dimer to its ERE and its interaction with coactivators or SERM (selective estrogen receptor modulator) (Ch'ng 2024).

These coactivators recruit acetyltransferases that acetylate histone lysine residues (HATs) and SWI/SNF chromatin remodelling complexes. In parallel, these co-activators decrease the binding of histone deacetylases (HDACs; histone de-acetylase complexes). All of this results in a relaxation of the chromatin, favouring the union of general transcription factors and RNA polymerase II, thereby increasing the frequency of transcription initiation. It is interesting to note that mutations in the BAF57 protein associated with mammary gland cancer have recently been identified that reduce the interaction between ER-beta and SWI/SNF complexes. The BAF 57 protein is part of the structural core of the SWI/SNF

chromatin remodelling complexes (Cruz-Ramos, Trapero-Corona et al. 2024).

The cytoplasmic effects of estrogen receptors include increased cell proliferation and are dependent on the activation of 3-phosphatidylinositol. Kinase (PI3K) and the mitogen-dependent kinases (MAPKs). These cytoplasmic effects require the ER coregulator called proline-, glutamic acid-, and leucine-rich protein type 1 (PELP1/MNAR), which mediate the interaction between the ER and its cytoplasmic effectors such as PI3K (77). Hormonal dependence appears to be a complex phenomenon that includes not only a mitogenic stimulus but also the expression of genes that allow evasion mainly of apoptotic stimuli (Schmidt 2024).

Originally, the identification of the estrogen receptor is useful in oncological practice and its presence indicates a poor prognosis. However, today this has changed thanks to the use of antiestrogens such as tamoxifen in patients with mammary gland cancer, which usually has favourable effects contributing to tumour regression. The administration of anti-estrogens is not effective if they are administered for prolonged periods (Basumatary and Talukdar 2024).

The development of estrogen antagonists led to the application of tamoxifen and its derivatives. These compounds bind to the ligand binding site and allow receptor binding to response elements, but block the interaction with coactivators, so these compounds prevent or block the expression of estrogen-dependent genes. It is still unknown whether there is interference with cytoplasmic effects, but it is clear that it interferes with the activation of mitogen-dependent kinases and therefore with cell proliferation. The structures of estradiol and tamoxifen are shown in Figure 5C (Bueno-Urquiza, Godínez-Rubí et al. 2024).

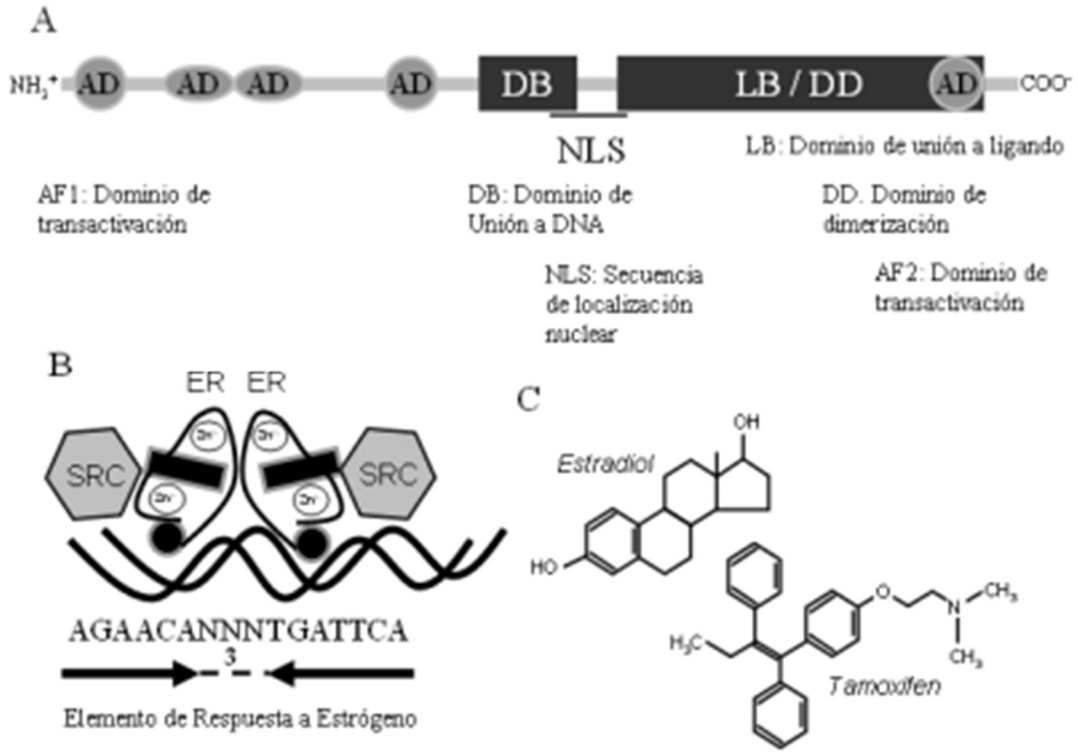

Figure 5. A) Structure of the estrogen receptor indicating the different protein domains that constitute it. B) Scheme showing the binding of an estrogen receptor dimer linked to its consensus sequence in DNA and its interaction with steroid hormone receptor coactivators (SRCs). The estrogen response element corresponds to the DNA sequence to which the estrogen receptor binds. In the nucleotide sequence, N corresponds to any of the four nucleotides. C) Developed formulas of estradiol and its antagonist, tamoxifen (Vuong, Gue et al.)

New therapies in mammary gland cancer

Conventional chemotherapy and radiotherapy followed by surgical procedures are effective in stages I and II but lose efficiency with more advanced stages. Therefore, new therapeutic strategies have been sought, supported by the molecular knowledge that has been generated in recent years. The overexpression of the growth factor receptor Her-2, as a marker of poor prognosis, has led to the search for possible mechanisms of inhibition of this system. On the one hand, receptor-neutralizing antibodies have been generated that prevent its activation (trastuzumab). These antibodies are applied as a new complementary therapy to taxol or vinblastine to weaken the tumour before its surgical removal (Aguilar-Martínez, Campos-Viguri, et al. 2024).

An alternative strategy has consisted of generating inhibitors of both the HER2-Neu kinase domain and the PDGF receptor kinase domain, which is also activated in this type of cancer. Another therapeutic perspective is the inhibitors of farnesyl- and geranyl-transferases such as R115777, which are required for the activity of the ras oncogene during mitogenic stimuli, and the use of neutralizing antibodies to vascular growth factor (VEGF) such as bevacizumab or Avastin. We will have to wait for the results of ongoing studies with these possible target therapies to define their therapeutic value in mammary gland cancer (Barber, McCullough, et al. 2024).

Conclusion

Mammary gland cancer is a growing public health problem in our country. Mammary gland cancer cells are overwhelmingly derived from ductal or lobular epithelia. As in the rest of oncological diseases, early detection usually has a good prognosis if you receive chemo- and/or radio treatment. Appropriate therapy; Current surgical procedures also have a high probability of cure. The high mortality rate of mammary gland cancer in our country is mainly due to invasive and metastatic forms of the disease. Some hereditary forms are associated with the overexpression of cyclins D1, D3, and E. One of the oncogenes associated with the development of the disease is the HER2/Neu receptor of the epidermal factor receptor family. Mutated forms of ras and amplification of c-myc are often found in advanced forms of the disease. It is also associated with tumour suppressor genes such as p53, ATM, BRCA1, BRCA2, and PTEN.

Despite great advances in understanding the molecular bases associated with cancer development, there are still few useful applications in treatment. For example, the expression of the estrogen receptor, which originally resulted in a poor prognosis, may now have a better prognosis thanks to the use of antagonists such as tamoxifen. Patients with HER2/neu amplification can today be treated with antibodies neutralizing the mitogenic activity of the receptor. At this time, the tools with the greatest impact seem to be in the field of public health, such as the design of campaigns aimed at the detection and early care of mammary gland cancer, thus preventing its progression to invasive forms that are very difficult to treat or to forms of metastatic diseases that are considered incurable.

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