Molecular Subtypes of Breast Cancer and CDk Dysregulation

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6.1 Introduction

BC is a varying disease with a wide range of cell composition, molecular changes and clinical manifestations. The prognosis and response of cancer treatment is influenced by many characteristics which are: histological grade, tumour type and size, LN metastasis, ER, PR, and HER-2. BC is the most commonly seen cancer around the globe (Siegel et al. 2020). Approximately, 250,000 new BC cases were reported in the United States (US) in 2014, accounting for approximately 14% of all new cancer diagnoses (Economopoulou et al. 2015). In Great Britain, more than 50,000 cases of BC were confirmed, which is about 15% of all new cancer cases. BC is a broad term that includes a variety of disorders with distinct histological features, dissemination patterns, treatment responses, sufferers' outcomes and imaging features. BC affects females of all age groups, killing around 42,000 people in the USA in 2019 and dying from cancer in females, despite decades of research and advances in drug and diagnostic imaging (Khan et al. 2022). This is the second most usual cause. In spite of the fact that mortality due to BC has reasonably lowered as a result of currently accessible treatments, it is estimated that over 450,000 people die each year from the disease (Al-Rikabi and Husain 2012). The molecular subset of BC is a strong prognostic and predictor, depending on histological grade and LN metastasis. Therefore, categorising BC into molecular subtypes is a crucial part of treatment decisions. Long-established immunohistochemistry (IHC) markers like ER, HER-2, PR are important for molecular subtyping (Fig. 6.1) (Johnson et al. 2021). GE profiling using complementary DNA microarrays has emerged as a new tool for therapeutically essential molecular classification. The BC can be grouped

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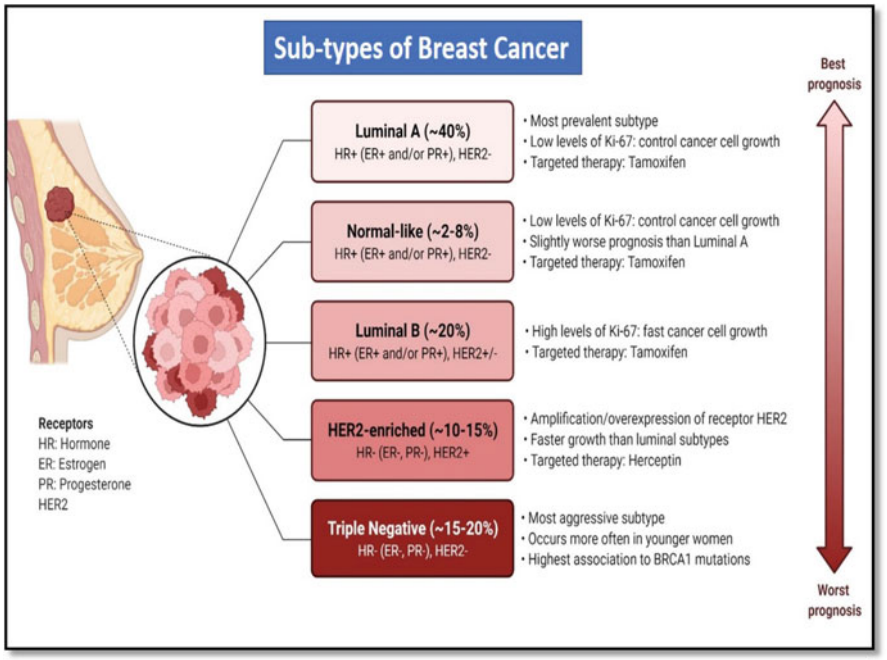

Fig. 6.1 Molecular subtypes of breast carcinoma

into molecular subtypes on behalf of GE patterns: luminal like, HER-2 enriched and basal like. The most often and common kind of BC is luminal-like tumours, which account for 60–70% of all cancers. The ER and various genes dominated by the epithelium cells that bound the lumen of TDLU of the duct where more BC develop are highly expressed. The oncogene Erb-B2 (HER-2) is present in low quantity more often (Goyal and Trivedi 2020).

BC patients with HER-2-enriched tumours constitute around 15% of total cases (Fig. 6.2). These are characterised by Erb-B2 oncogene overexpression and also modest levels of ER expression. Basal cell-like tumours make up for about 12–16% of all BCs and dominate numerous of the matching genes as TDLU basal myoepithelial cells (Johnson et al. 2021). They frequently do not express ER, as do many of the genes involved in estrogen receptor expression. According to a study by the American Cancer Society, around 73% of BC diagnoses in the USA are Luminal A, around 11% are Luminal B, around 12% are Triple Negative, and around 4% are HER-2 enriched. Further studies have shown that subgroups are associated with different clinical features. The E-R+ luminal subtype, for example, is currently divided into a couple of subgroups, A and B, and having each a distinct prognosis (Van't Veer et al. 2002).

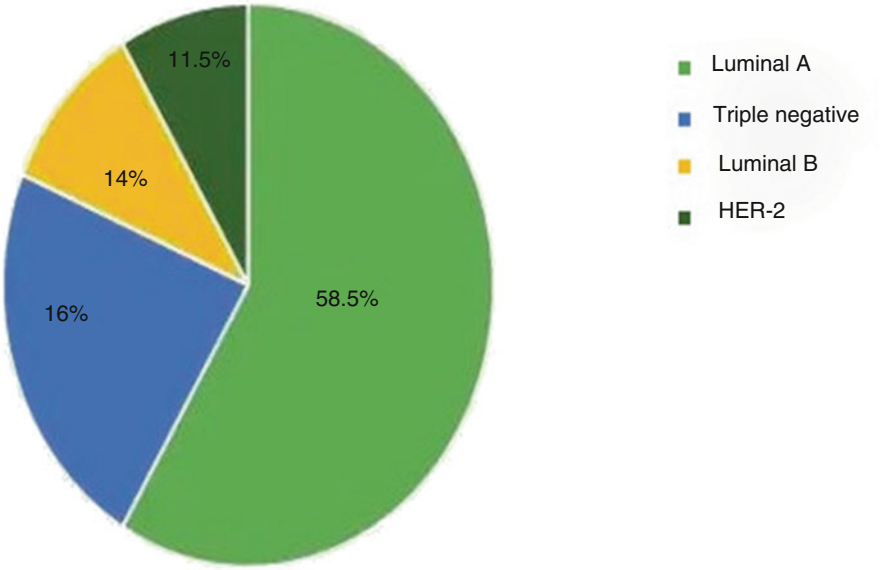

Fig. 6.2 Statistical data of molecular subtypes of Brest carcinoma in KAUH (2012–2018)

6.2 Genetic Expression

The estrogen receptor expression is a distinguishing feature of the luminal subtype. The term "luminal" derives from the resemblance linking the genes dominated by the tumours and the genes dominated by luminal breast epithelium cell (Perou et al. 2000). ER, PR, and more genes connected with Estrogen receptor stimulation are expressed in a majority of luminal cancers. BC luminal subtypes are the most common and can be classified into two groups A and B. GE patterns and clinical diagnosis of A and B luminal breast tumours differ significantly (Sørlie et al. 2003).

6.2.1 Luminal A

HER-2-negative tumours are also called luminal A tumours. It is a protein that the human body produces constantly on regular basis. BC with standard levels of HER-2 protein is called HER-2 negative. From a genetic point of view, HER-2 plays a crucial part in repairing of healthy mammary cells and also cell formation. Unlike Luminal-A tumours, luminal-B tumours are not that common and account for around 20% of all malignancies, compared to 40% for luminal A tumours (Anurag et al. 2020). These tumours are well-differentiated cancers and include morphologically undefined renal tubules, mucinous, classical lobular carcinomas and neuroendocrine carcinomas. Luminous BC has progesterone receptors as well as estrogen, is HER-2-

negative, and contains small amount of the protein Ki67, which regulates the rate of cancer cell development. These malignancies grow slower, have a lower grade and have a better diagnosis than other types of cancer. People with HR + are characterised by ER or PR-positive hormone receptors. Estrogen and progesterone are present so cancers that are ER and/or PR + develop faster. Medication which depresses the levels of ER and PR in the human body is effective against this type of BC (Gao and Swain 2018).

6.2.2 Luminal B

Luminal B-like BC is estrogen receptor-positive, HER-2-positive, and contains arbitrary amounts of Ki67 protein. It can also be positive or negative for the progesterone receptor. These tumours grow faster and are slightly less diagnosed than type A tumours. Luminal B tumours differ from luminal A tumours in that they express more proliferative and/or cell-cycle genes and have less PR expression (Prat et al. 2015). The Ki67 protein, IHC markers of growing nuclear antigen and cell proliferation are importantly expressed in luminal-B tumours which is not the case in luminal A cancer. In contrast to luminal A tumours, luminal B cancers have a high frequency of p53 mutations (Sørlie 2004). Luminal B tumours are poorly differentiated and usually highly malignant.

6.2.2.1 Clinical Implications and Management

Several researches have conveyed that ER+ cancers- luminal-A and B subtypes have two unique outcomes. Those suffering from luminal-B tumour had notably brief survival and ill health free survival than those with luminal A BC. Luminal-A tumours have the best diagnosis of all BC subtypes, but luminal-B, HER-2-rich, and basal subtypes do not show good clinical outcomes (Lahsaee 2018). Patients with luminal-B BC are poorly diagnosed with respect to luminal-A tumours due to overexpression of cell cycle and proliferative genes in these cancers (Sørlie 2004). A molecular subtype approach to BC treatment was accepted by the St Gallen expert consensus group in 2011 (Goldhirsch et al. 2011). IHC markers are used in these treatment algorithms to deliver comprehension into a tumour inherent molecular subtype and to guide therapy. We describe substitutes of four molecular types of BC, semi-quantitative IHC expression of Ki-67, HER-2, PR, and ER is currently employed (Qi et al. 2021). Luminal-B cancers are characterised from luminal-A tumours in clinical practise by a soaring Ki-67 expression (around 14%), soaring histologic grade and lower PR expression (under 20%). IHC surrogates, on the other hand, do not necessarily reflect the genuine intrinsic molecular subtype. Luminal-A and B tumours are recognised as HER-2- by IHC, ER+, PR+, and all HER-2+ tumours are classed as “HER-2 subtype” in any case of HR status. The “luminal B HER-2+” subtype includes tumours that are ER+, PR+, and HER-2+. Hormone therapy should be part of the treatment plan for all those suffering from luminal BC (Fig. 6.3).

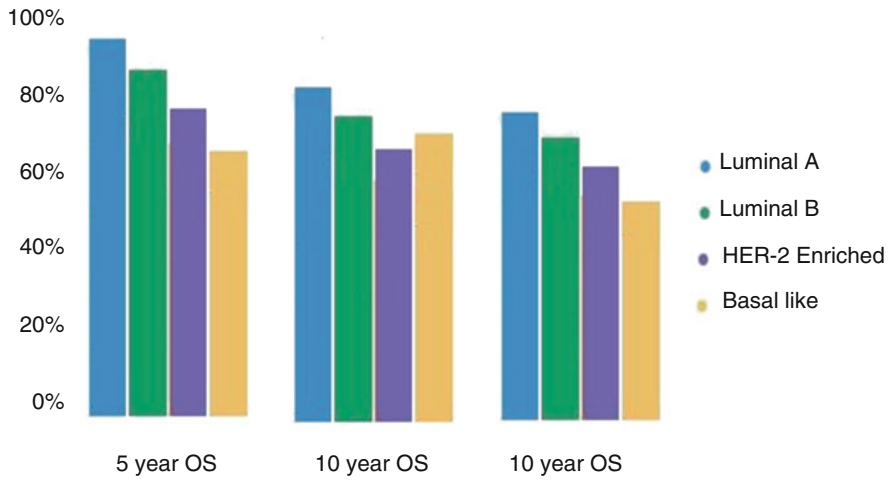

Fig. 6.3 Patients with invasive breast cancer are grouped by molecular subtype in the results

6.2.3 HER-2 Enriched Subtype

Genetic Expression E-R-negative, P-R-negative, and HER-2-positive. BCs are rich in HER-2. Tumours rich in HER-2-are usually successfully treated with targeted therapies that target the HER-2 protein, but develop earlier than luminal tumours and have a poor prognosis. HER-2 is transmembrane receptor (tyrosine kinase receptor) that holds together to extracellular signals and initiates a cascade that regulates cell proliferation, survival and differentiation. Between 12% and 20% of all BCs highly express the HER-2 protein and/or exhibit amplification of the HER-2 gene, leading to aggressive tumour development and poor clinical diagnosis (Tang and Tse 2016). The HER-2 oncogene is a known BC prognostic factor associated with shortening DFS and OS (Sørlie et al. 2003). Peru used HER-2 oncogene overexpression, specific gene selection overexpression, and low ER expression to classify HER-2-rich molecular subtypes. However, overexpression of proliferative genes such as Ki67 and proliferative nuclear antigens is not seen in the HER-2-enriched subtype. Nonetheless, HER-2-rich tumours have a worse prognosis than luminal malignancies, demonstrating the importance of the HER-2 oncogene. Surprisingly, proliferative genes such as Ki67 and proliferating nuclear antigens are not upregulated in HER-2-rich subtypes. However, HER-2-rich tumours have a worse prognosis than luminal cancer, emphasising the importance of the HER-2 oncogene. Tumours expressing HER-2 are E-R and P-R negative, but HER-2 positive. HER-2-positive BC cells have an abnormally high number of copies of the HER-2 gene and produce the HER-2 protein receptor found in BC cells. When the HER-2 receptors are functioning properly, they control how healthy breast cells regenerate, grow, and heal. As the cell proliferates, the receptors divide the cell and encourage it to proliferate rapidly and out of control. This is because cells overdose human epidermal growth factor 2, a substance that promotes cell development. Excessive

Table 6.1 Clinical and immunohistochemical surrogates for molecular subtypes of breast cancer

Subtype	ER	PR	HER-2	Ki-67	Histological grade	Multiparameter molecular test results
Luminal A	+	≥20%	Can be positive	<14%	Generally, 1or 2	Favourable prognosis, i.e., lower recurrence scores
Luminal B	+(generally lower relative to luminal A	<20%	Can be positive	>14%	Generally, 3	Unfavourable prognosis, i.e., higher recurrence scores
HER-2	–	–	+	Any	Generally, 3	
Basal	–	–	–	Any	Generally, 3	

HER-2-positive genes in BC tissue are often examined to determine if patients will benefit from targeted therapy options that prevent HER-2 from promoting the development of cancer cells (Kim and Koo 2020).

Symptoms of HER-2-positive BC are quite common to those of other types of BC. Lumps in the breast, changes in breast shape, pain, edema, and abnormal drainage are some of the common symptoms of BC. Many females with HER-2-positive BC first receive neoadjuvant chemotherapy with drugs that directly target HER-2. Some females, especially females with small tumours, undergo surgery first, followed by adjuvant therapy, including both chemotherapy and HER-2-targeted therapy. Endocrine therapy may also be given to females whose cancer is "hormone receptor positive", that is, females who need estrogen to grow. Doctors can perform tests to determine if BC falls into this category (Oh and Bang 2020) (Table 6.1).

6.2.3.1 Clinical Implications and Management

Detecting HER-2 positivity in BC gives critical diagnostic and forecastic information that helps guide HER-2-directed therapy and enhances clinical outcomes. Clinically, HER-2 positiveness is explained as full and robust membrane staining in fewer than 10% of cells by IHC. All IHC 3+ tumours are HER-2+, all IHC 1+ tumours are HER-2-, and all IHC 2+ tumours are ambiguous. Reflex HER-2 testing with fluorescent in situ hybridisation is triggered when the results are ambiguous (FISH). The ratio of HER-2 gene amplification to the chromosomes 17 probe defines the FISH results (CEP17). E-R, P-R, HER-2+ is the most often utilised IHC surrogate for the HER-2-enriched subtype (Table 6.1). However, the outcome of IHC and FISH, which clinically define tumours as HER-2+, do not necessarily match the outcomes of GEPs, which characterise tumours as HER-2-enriched, and HER-2+ illness is heterogeneous. "HER-2+" is used all over this review to refer to tumours that are useful for HER-2 expression by IHC, whereas "HER-2-enriched" refers to cancers identified by GEP(Godoy-Ortiz et al. 2019).

One of the most important outcomes in the treatment of BC is the success of anti-HER-2 therapies for females with early and advanced HER-2 + BC. Trastuzumab

(Herceptin, Genentech, San Francisco, CA) is the most commonly used anti-HER-2 therapy, but studies have shown that other anti-HER-2 drugs such as pertuzumab, neratinib, lapatinib and T-DM1 are also effective (Upton et al. 2021). In 2005, the first study where chemotherapy was compared to trastuzumab in patients with surgical HER-2 + disease showed improved DFS and about 33% reduction in mortality risk in patients receiving trastuzumab (Ahmed et al. 2015). Trastuzumab in combination with chemotherapy has a longer time to disease progression, a longer duration of response, and a lower one-year mortality rate in females with metastatic HER-2 + cancer than chemotherapy alone years later in 2012. It has been found to be associated with high median survival. In spite of continued advances in anti-HER-2 treatment, the prognosis for HER-2 + disease is poor. Because people with HER-2 + disease have a very broad clinical outcome, oncologists need diagnostic techniques to lead treatment. The traditional approach to females with HER-2 + malignancies is Neoadjuvant chemotherapy who can be operated on by IHC because the response to the therapy provides diagnostic and forecastive information (Pereira et al. 2019).

6.2.4 Triple-Negative or Basal-Like BC

Estrogen receptor-negative, progesterone receptor-negative, and HER-2-negative BCs are known as triple-negative or basal cell-like BCs. The chances of Triple-negative BC in young females with the BRCA1 mutation is more. Females with triple-negative BC are considered more aggressive than Luminal-A or Luminal-B BC (van Barele et al. 2021).

6.2.4.1 Genetic Expression

Many BC genes are dominated by either of the two types of epithelium cells, basal cells or luminal cells found in human breast tissue, according to Perou et al. (2000). High expression of keratin 5, keratin 17, integrin B4, laminin, and growth-related genes is a GE feature of basal epithelial cells, and thus basal-like BC (BLBC) subtypes. The p53 gene is mutated in most BLBC cancers. Most other genes co-expressed with ER are absent in these malignancies (Sørlie 2004). Basal-type BC accounts for about 15% of all invasive BCs and is usually high-grade, large at detection, and subject to local and distant recurrence (Tang and Tse 2016). Basal cell-like subtypes are the most usual of triple-negative BC (TNBC), accounting for around 70–80% of all TNBC cases. Triple-negative BC is a diverse group of tumours and the persisting 20–30% of TNBC can be divided into at least six distinct subgroups based on GEP (Teschendorff et al. 2007). TNBC is defined as the absence of IHC expression of ER, PR, or HER-2. TNBC is defined as a tumour in which less than 1% of the nucleus expresses ER and PR and HER-2 expression is 0 to 1 + or IHC2 + and FISH negative (Johnson et al. 2021). E-R, P-R, and HER-2 are the most commonly used IHC surrogate in BLBC. The majority of TNBC is ductal carcinoma that is not morphologically characterised. However, adenoid cystic carcinoma, secretory cancer, metaplastic cancer, and medullary thyroid cancer are also different

forms of TNBC (Tang and Tse 2016). Several ongoing studies have shown many TNBCs as in all endogenous subtypes. It suggests that it can be subdivided into subtypes. In addition, the basal cell-like group is the most unique of the four endogenous subtypes of BC. BC tumours are thought to be derived from common luminal progenitor cell lines.

6.2.4.2 Clinical Implications and Management

Basal cell-like TNBC has absence of IHC expression, a major biomarker suitable for selected therapies, Estrogen receptor, progesterone receptor and HER-2. As a result, treatment of basal cell-like TNBC has not been selected, leaving chemotherapy as the only dependent and neoadjuvant treatment option. TNBC shows a better relationship between post-NACT pCR and better DFS and OS, as well as HER-2 + cancer. All TNBC tumours larger than 5 mm and/or with LN metastasis should receive neoadjuvant chemotherapy. Patients with residual lesions after completion of NACT may benefit from adjuvant chemotherapy to improve DFS and OS. BLBC is highly sensitive to chemotherapy because of its absence of ER expression, soaring grade, soaring proliferation index. Most neoadjuvant studies show that BLBC has a higher pCR among others. In spite of the 80% pCR rate reported by BLBC, the diagnosis remains abysmal. In spite of the relatively high pCR, the relatively abysmal diagnosis is called the "triple negative paradox".

6.3 Other Subtypes Under Investigation

Since the publication of Peruvian paper in 2000, further studies have revealed greater molecular heterogeneity in BC. Several new subtypes have been suggested, including (i) Claudin-low, (ii) Molecular Apocrine, and (iii) luminal HER-2 subtypes (Tang and Tse 2016). Expression of claudin 1, 3, 4, 7, 8 is low in claudin BC. These tumours are usually TNBC with a abysmal diagnosis. Molecular apocrine BC is defined by androgen receptor expression without ER expression and is often TNBC or HER-2. Ultimately, the "luminal HER-2" group is a new luminal-like subtype that exhibits E-R expression and is HER-2-positive by IHC in about 50% of patients. Compared to traditional intraluminal BC, these tumours are more malignant, have low P-R expression, relapse early, have more LN metastases, and are more responsive to endocrine therapy. In addition, it will be lower compared to ER, PR, and HER-2 + tumours.HER-2 intraluminal BC has a further aggressive clinical course identified by localised and early recurrence.

6.4 CDK Dysregulation in BC

The tumour microenvironment contains a number of elements that aid cancer growth and hinder anti-tumour responses (Mehraj et al. 2021). It has been hypothesised that targeting these cancer-promoting elements in the tumour microenvironment could be a powerful immunotherapeutic method for cancer treatment. Cyclin-Dependent

Table 6.2 Different cyclins and CDKs which take part in cell cycle

Phase	Cyclin	CDK
G0	C	CDK3
G1	D, E	CDK4, CDK2, CDK6
S	A, E	CDK2
G2	A	CDK2, CDK1
M	B	CDK1

Kinases (CDKs) have been proposed as a novel prospective target for cancer therapy among the different tumour supportive variables (Sofi et al. 2022). In conjunction with cyclins, these factors play an important role in cell cycle progression. CDK dysregulation has been linked to enhanced cell proliferation in diverse of malignancies, encompassing BC. As a result, the development and usage of CDK inhibitors in the treatment of BC has been linked to promising results. However, it is unknown which CDK inhibition method is the most successful for BC treatment (Deng et al. 2018). Because selective CDK1 blockade, either alone or in combination with other therapies, has been linked to effective anti-cancer effects, CDK1 may be the best CDK target for BC therapy.

Cyclins and CDKs play important roles in regulating cell cycle transition because they are required for cell cycle G1, S, G2, and M phase progression. To control the activity of cyclins and CDK inhibitors, CDK, a serine/threonine kinase, binds with both of these molecules. CDK activity is often dysregulated in cancer cells and is a promising target for cancer treatment. Human cells have 20 CDKs and 29 cyclins (Malumbres and Barbacid 2009). Cell cycle transition and cell division are directly regulated by CDK1, CDK2, CDK3, CDK4, CDK6, and CDK7, while cell cycle-related gene transcription is mediated by CDK 7–11 (Ding et al. 2020). At different times during the cell cycle, several cyclin-dependent kinases (CDKs) have diverse functions. In a certain cell environment during G1 phase, CDK4 and CDK6 assemble into a complex with one of the three D-type cyclins (D1, D2, or D3) (Table 6.2).

6.5 Role of CDK4/6 in Cell Cycle Control

The G1, G2, S, and M stages of mammalian cell cycle are traditionally classified into four different stages. The interaction of different cyclins with their cognate CDKs tightly controls the ordered movement between these phases at checkpoints. CDK is a well-conserved family of threonine protein kinases/serine with at least 12 loci known to encode them. Various regulatory CDKs containing three interphase CDKs (CDK_2, CDK_4, CDK_6), single-threaded split CDK (CDK_1, formerly called as CDC_2), and CDK7, component of the CDK activation complex, and transcription CDKs are all members of this family (CDK8, CDK9). Cyclins are a large family of proteins that are divided into four types (A, B, D, and E types of cyclins) Unlike CDKs and serve as regulatory subunits for the CDK cyclin holoenzyme. In spite of the vast quantity of CDKs and cyclins, only some of them are significantly included in the development of BC. Suppression of cell cycle progression is usually

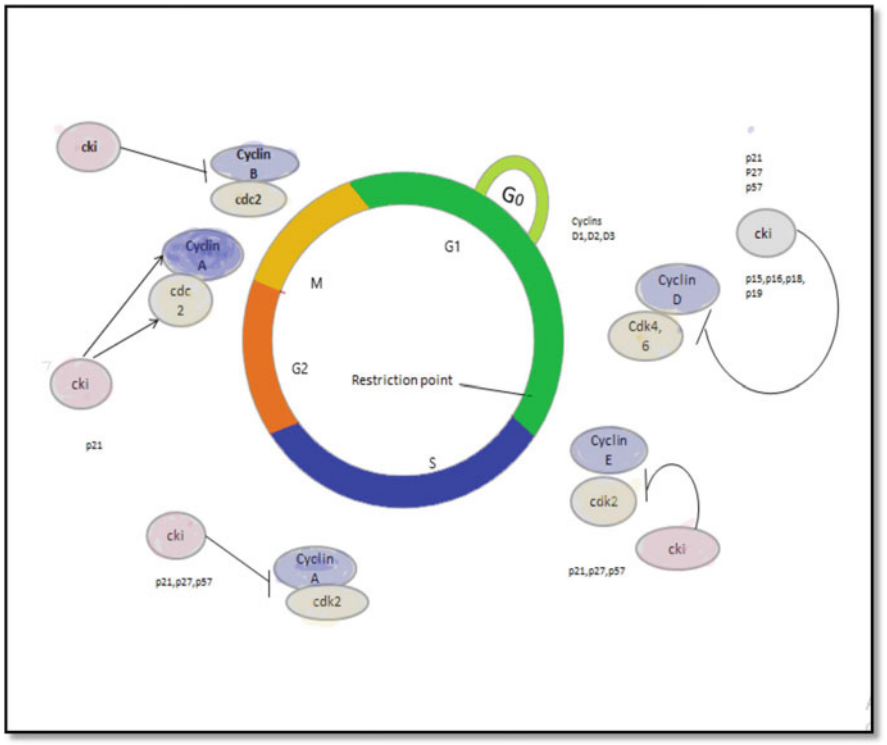

Fig. 6.4 The mammalian cell cycle includes passing through specific checkpoints in an organised manner for proper progression. By mitogen-induced CAK recruitment, the cyclin D1-CDk4 complex is brought into full holoenzyme activity. The PRB protein is phosphorylated by the cyclin D1-CDK4 complex, which causes cyclin E-Cdk2 to phosphorylate it later and release free E2F. Genes involved in the activation of S phase entrance are induced by the phosphorylation of pRB and the relaxation of downregulation by pRB

maintained by so-called pocket proteins and also the retinoblastoma gene product (pRb) that sequester the E2F family of transcription factors (Huun et al. 2017). Rest cells, on the other hand, when they pass the cell cycle, produce cyclin D1 in retaliation to adhesion cues and particular mitogen. After the formation of the activation complex with CDK4/CDK6, the newly generated cyclin D1 initiates phosphorylation of pRb. Transcription inhibition of E2F by pRb is abolished by phosphorylation of the cyclin D1: CDK4/6 complex. Cyclin E, a protein that binds to CDK2 and phosphorylates pRb and other G1/S checkpoint mediators. This process establishes a practical feedback loop in which cells irreversibly pass through the G1-S transition (also known as the "restriction point") and carry on the cell cycle without the use of mitogen (Deng et al. 2018). In the late S phase, cyclin A2 activates CDK2 and can switch from S phase to G2 phase. Finally, type A and type B cyclins stimulate CDK1 to accelerate the initiation and progression of mitotic processes (Fig. 6.4) (Goel et al. 2017).

Pan-CDK inhibitors were at first found to be ineffective in suppressing cancer cells and were related with serious side effects. Nonetheless, in later years, the success of tolerable, potent and selective CDK inhibitors has rekindled interest in this class of selected drugs. Long-term therapy with CDK4/6 inhibitors suppresses cell cycle genes and at the same time stimulates further genes responsible in various functions. In fact, inhibition of CDK4/6 is associated with stimulation of cell proliferation genes which are inhibited by endocrine therapy (Pernas et al. 2018), Strengthen the discussion for merging the two medicines. Palbociclib (PD0332991), Ribociclib (LEE011), and abemaciclib (LY2835219) are triplet highly selective inhibitors of CDK4 and CDK6 that bind to ATP cleft with low toxicity.

Dual function of $P27^{Kip1}$. In the context of a building factor, the cyclin D1 gene product contacts the regulatory element partner (Cdk4). An enzyme called a Cdk activating kinase (CAK), which itself is made up of multiple subunits, phosphorylates the cyclin D1-Cdk4 holoenzyme. The tumour suppressor Prb can then be upregulated by activated cyclin D1-Cdk4. Additionally phosphorylating pRB is Cyclin E-Cdk2. There is debate about the contribution of the p21 CKI family, represented by p27kip1, to the regulation of the cyclin D1-Cdk complex's activity. In some cases, p27kip1 is believed to reside in the complex's activity (Kim et al. 2008). In other situations, p27kip1 does not participate in the complex's assembly-factor activity. Cyclin D1 induction may facilitate S phase entrance via inoculating p27kip1 from an antagonistic complex with cyclin E-Cdk2 if p27kip1 inhibits cyclin E-Cdk2 but not cyclin D-Cdk4 (Wood et al. 2019). These results imply that p27kip1 activity may be influenced by stoichiometry or cell type (Fig. 6.5).

6.5.1 Palbociclib

Palbociclib (PD0332991, IBRANCE®, Pfizer) is a potent orally vigorous CDK4/6 inhibitor that binds to ATP fissures. Palbociclib was sensitive to ER-positive BC cells in an in vitro study operating a panel of BC cell lines, significantly reduced cell cycle progression due to G1 arrest, and prevented pRb hyperphosphorylation. Overall, susceptibility to the effects of palbociclib on cell cycle and growth inhibition was associated with increased Rb and cyclin D1 and decreased p16 (Kwapisz 2017). Non-luminal/basal BC cells showed the lowest activity, except for those with human epidermal growth factor receptor 2 (HER-2) amplification. In ER-positive and HER-2-amplified cell lines, palbociclib was synergistic with anti-estrogen tamoxifen and anti-HER-2 treatment trastuzumab, respectively. Palbociclib may also improve tamoxifen sensitivity in BC cell lines that have developed resistance to the drug (Malorni et al. 2018) and induce cellular senescence in hormone therapy-resistant cell lines. While most preclinical palbociclib studies focus on HR-positive BC, a few preclinical studies of HER-2-positive or triple-negative BC (TNBC) have shown promise. Palbociclib was more sensitive and additive in HER-2-positive BC models and primary human explants when used in combination with adtrastuzumab emtansine (TDM1). CDK4/6 and cyclin D complex formation is aided by external

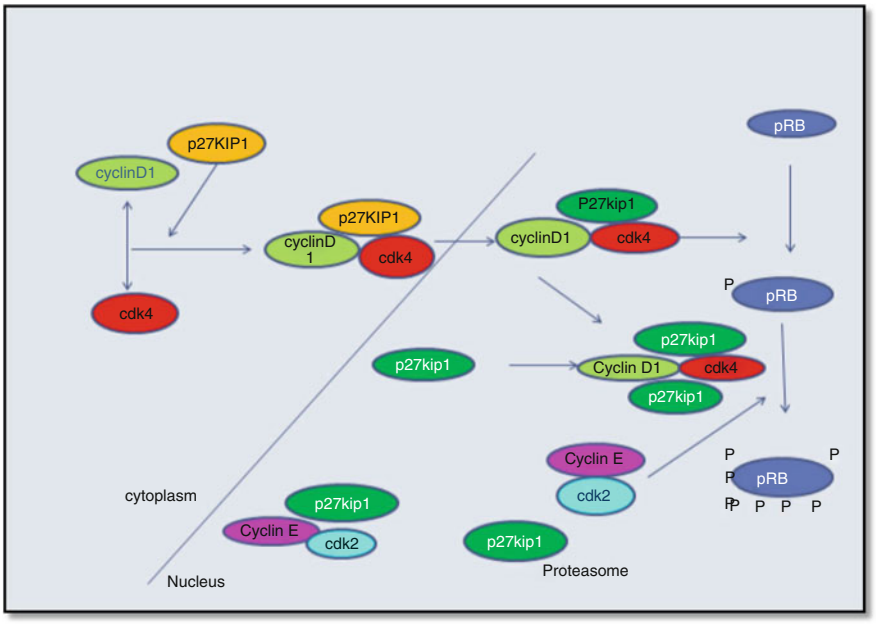

Fig. 6.5 Role of different cyclin/CDK complexes in the progression of cell cycle

mitogenic signals. The release of the E2F transcription factor, the transition from G1 to S phase, and the hyperphosphorylation of RB1 are all made possible by the CDK4/6-cyclin D complex, which promotes cell development (Zhang et al. 2020). Cell growth is inhibited by CDK4/6 inhibitors like palbociclib, Ribociclib, or abemaciclib because they prevent the phosphorylation of RB1 while it is still linked to the E2F transcription factor (Fig. 6.6).

6.5.2 Ribociclib

Ribociclib (LEE011; KISQALI; Novartis Pharmaceuticals Corp.) is an oral small molecule CDK4 and CDK6 inhibitor that completely dephosphorylates Rb, sequesters E2F transcription factors, and arrests Rb-positive cells' progression through the G1 cell cycle. In four ER-positive xenograft models, Ribociclib (Hortobagyi 2018) alone or in combination with letrozole or fulvestrant reduced tumour growth in vivo. Ribociclib and BYL719 (a PI3K inhibitor; alpericib) together improved tumour antigen presentation, cell cycle arrest, DNA damage, replication stress, and immunogenic cell death in the TNBC model. Ribociclib and BYL719 improved innate and adaptive immune system activation and cytotoxicity in immunocompetent mice while lowering the number of immunosuppressive monocytic bone marrow suppressor cells (MDSCs) in the tumour environment (Kwapisz 2017).

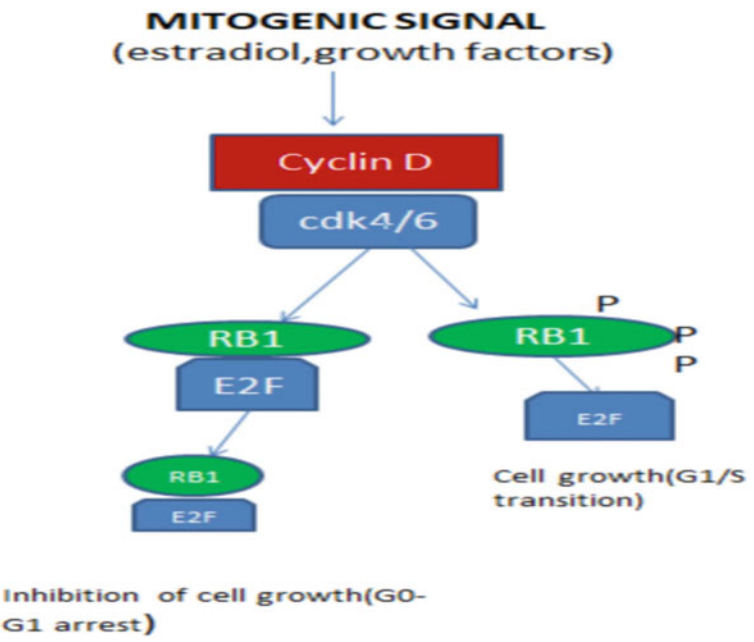

Fig. 6.6 Diagrammatic representation of the function of CDK4/6 inhibitors in cancer cells

6.5.3 Abemaciclib

Eli Lilly and Company's abemaciclib (LY2835219; VERZENIOTM) binds to ATP clefts and creates hydrogen bonds with the kinase's conserved catalytic residue (Lys43). It does not bind more selectively than Ribociclib or palbociclib, in this case. Abemaciclib prevents Rb from being phosphorylated along with CDK4 and CDK6, which causes Rb-competent cells to enter a G1 arrest and limit their ability to proliferate. In preclinical animals, Abemaciclib has a higher affinity for CDK4 than palbociclib or Ribociclib, which might account for the different toxicity profile. In vivo, ER-positive, HER-2-positive, and biomarker-selected TNBC xenografts demonstrated tumour growth suppression comparable to abemaciclib (Kwapisz 2017). In HER-2-positive BC models, the cyclin-D1-CDK4 pathway fosters resistance to anti-HER-2 therapy, and by boosting resistant tumour cells' dependence on EGFR-kinases, it resensitise resistance to anti-HER-2 therapy (Ahmed et al. 2015). Abemaciclib has been shown in preclinical research to pass the blood-brain barrier in a rodent model (Wander et al. 2022). In MDRMCFER-positive BC cells, it has been demonstrated that abemaciclib increases the intracellular accumulation of chemotherapeutic drugs as a result of decreased ABCB1/ABCG2 transport activity. It was discovered that abemaciclib capacity to reverse MDR is unrelated to CDK4/6 inhibition or Rb pathway phosphorylation blocking (Wander et al. 2022).

6.6 Summary

The discovery of four unique molecular subtypes in BC has brought about a new period in BC study and a pattern shift in treatment. Despite the fact that BC is still a horrifying diagnosis for all females, coordinated treatments help females survive longer with the disease, avoiding cytotoxicity and harsh treatments that often lead to comorbidities. In addition, each subtype has its own imaging characteristics, and importance of mammography (common method of breast imaging) in early observation stands important. Studies show that tumour size, endogenous subtypes and LN status are three key characteristics that forecast the result of early-stage BC. Recognition of the four unique molecular subtypes of BC (Luminal-A, Luminal-B, HER-2-rich, basal like) is beginning to elucidate BC heterogeneity and is more targeted to improve prognosis for all. Females diagnosed with BC will head to the progress of selected therapies. CDK4/6 inhibitors have emphatically changed the therapy climate for people suffering from HR-positive metastatic BC. Contrasted to endocrine therapy alone, all three Food and Drug Administration-approved drugs (palbociclib, Ribociclib, and abemaciclib) are related with further developed results and adequate harmfulness. If ongoing studies show clinical utility, CDK4/6 inhibitors may play a part in neoadjuvant or adjuvant situations in the near future. Unfortunately, resistance has evolved over time and new techniques are now being sought to hold up or control resistance. Studies are presently planned and of great importance to recognise victims/sufferers who can be successfully cured using endocrine therapy alone.

6.7 Further Readings

The authors can look for the following articles for further understanding of the given topic

(i) https://www.sciencedirect.com/science/article/pii/S1097276520307231
(ii) https://breast-cancer-research.biomedcentral.com/articles/10.1186/s13058-015-0661-5
(iii) https://www.mdpi.com/2227-9059/10/2/366

For more insights about the topic, we would suggest detailed findings from the books of (Mir MA, 2022) https://doi.org/10.1016/C2021-0-02565-7, https://doi.org/10.1016/C2014-0-02898-5 (Mir MA, 2021) https://doi.org/10.52305/WXJL6770, from cancer.net website, https://www.cancer.net/cancer-types/breast-cancer/types-treatment

For diagrammatic illustrations, descriptive tables, (Lazzeroni, 2012) http://www.eurekaselect.com/article/49928. The readers can also look for the following visual presentations for a better understanding of the topic:

(i) https://youtu.be/R_Y_du4Z3Zo
(ii) https://youtu.be/qKUPoovs92I
(iii) https://youtu.be/YA67P2k2d6A
(iv) https://youtu.be/poQEkyVhGMo

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