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The mevalonate pathway in breast cancer biology

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ABSTRACT

Breast cancer affects one in eight women during their lifetime. Although diagnostic and therapeutic options have improved, recurrence, metastasis, and therapeutic resistance remain clinical challenges, which affect life quality and prognosis. The mevalonate pathway is an essential part of cellular homeostasis by providing a number of essential isoprenoid products including cholesterol. However, the disturbance of this pathway paralleled by increased bioavailability of its products and their direct involvement in several steps of tumorigenesis has highlighted the mevalonate pathway as a promising hub in cancer treatment. In this review, we will specifically discuss how the mevalonate pathway affects breast cancer biology in terms of supporting and modulating soluble and cellular factors and distinct steps of tumorigenesis. We will further summarize antitumor effects of the mevalonate pathway-inhibiting drugs, statins and amino-bisphosphonates, in breast cancer and discuss how they are used for future precision therapy.

1. Introduction

Breast cancer (BrCa) affects one in eight women during the course of their lifetime and approximately 400,000 new cases are diagnosed in Europe each year [1,2]. Improved diagnostic and therapeutic tools have strongly increased the probability of affected patients to survive within the last three decades [1]. Current therapies for BrCa include surgery, chemotherapy, radiation, endocrine therapy as well as epidermal growth factor 2 (*ERBB2* or *HER2*)-targeted treatments [3]. Clinical studies on the inclusion of novel immunotherapies and targeted therapies into established concepts are underway [4]. However, long-term treatment of BrCa is still subject to several challenges. Recurrence of the disease by local regrowth of tumors or by metastases within distant organs represents a significant burden [1]. As the overall survival of recovered patients with primary BrCa continuously increases, the occurrence of metastases years after initially successful treatment becomes increasingly relevant. Secondly, BrCa is characterized by extensive molecular and genomic inter- and intratumoral heterogeneity that, together with the unneglectable contribution of the local tumor microenvironment (TME), impedes therapeutic intervention [5,6]. Thirdly, treatment approaches for the aggressive triple-negative BrCa (TNBC) subtype are still limited as these tumors are not sensitive to endocrine therapies such as tamoxifen or aromatase inhibitors (AI) [7]. Finally, a number of mechanisms contribute to acquired or *de novo* endocrine resistance, which blunts the initial efficacy of antihormonal treatments [8]. Given these challenges, novel therapeutic options to expand the current armament are highly desired. As a central part of cellular homeostasis and metabolism, the mevalonate pathway has been repeatedly in and out of the focus as a potential anti-tumor target in almost all types of malignancies, including BrCa for the last two decades [9]. This has led

Abbreviations: 27-hydroxycholesterol, (27-HC); 3-hydroxy-3-methylglutaryl-CoA reductase, (HMGCR); acetyl-coenzyme A, (acetyl-CoA); adenosine triphosphate, (ATP); amino-bisphosphonates, (N-BP); aromatase inhibitors, (AI); ATP citrate lyase, (ACLY); breast cancer, (BrCa); epithelial-to-mesenchymal transition, (EMT); estrogen receptor, (ER); farnesyl diphosphate synthase, (FDPS); farnesyl pyrophosphate, (FPP); geranylgeranyl pyrophosphate, (GGPP); guanosine triphosphate, (GTP); human epidermal growth factor receptor 2, (HER2); interferon γ, (IFN-γ); low density lipoprotein, (LDL); low density lipoprotein receptor, (LDLR); mammalian target of rapamycin, (mTOR); mitogen activated protein kinases, (MAPK); matrix metalloproteinases, (MMP); nuclear factor 'kappa-light-chain-enhancer' of activated B-cells, (NFκB); natural killer cells, (NK cells); programmed death-ligand 1, (PD-L1); regulatory T Cells, (Tregs); sterol regulatory element binding protein, (SREBP); tumor-associated macrophages, (TAM); tumor microenvironment, (TME); triple-negative breast cancer, (TNBC); Yes-associated protein, (YAP); transcriptional co-activator with PDZ-binding motif, (TAZ).

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to an accumulation of data, which are sometimes difficult to interpret. With an increasing understanding of this complex pathway, we review on the emerging pleiotropic mechanisms by which the mevalonate pathway affects different steps of BrCa tumorigenesis and how these may be utilized to improve clinical management of patients with BrCa.

2. Role and regulation of the mevalonate pathway

2.1. Providing essential products and modulating homeostasis

The mevalonate pathway (Fig. 1) is a pivotal part of cellular physiology by providing isoprenoid precursors as building blocks for the synthesis of several essential products [10,11]. Here, acetyl-coenzyme A (acetyl-CoA) is an indispensable substrate that can be provided from glycolysis and fatty acid oxidation, or by glutamine and acetate consumption, all of which can be increased in cancer [12]. Furthermore, acetyl-CoA is provided by metabolization of citrate from the tricarboxylic acid cycle via the ATP citrate lyase (ACLY) [13] [–] [15]. Two key enzymes of the mevalonate pathway are the 3-hydroxy-3-methylglutaryl-CoA reductase (HMGCR) that is responsible for mevalonate production [16] and the farnesyl diphosphate synthase (FDPS) which is critical for the production of farnesyl pyrophosphate (FPP) and allows for subsequent geranylgeranyl pyrophosphate (GGPP) production [15,17]. FPP and GGPP are activated substrates for specific posttranslational modifications called farnesylation and geranylgeranylation. Both mechanisms are referred to as “protein prenylation”, a process that ensures membrane anchoring and trafficking of a countless number of proteins [16,18,19]. Moreover, FPP is metabolized to cholesterol via squalene production [20]. Cholesterol is critical for membrane synthesis and intramembranous signal transduction, protein trafficking and cellular polarization as well as for the production of steroids, vitamin D, and bile acids [11,21] [–] [23]. The cholesterol pool also drives sex hormone production and therefor allows for their effects on several organ systems including control of mammary gland development during puberty, estrous cycles, and pregnancy [24]. Whereas ubiquinone is involved in mitochondrial electron transport and has antioxidantic effects, dolichol plays an important role in the glycosylation of proteins [16,25]. A number of additional contributions apply to immunity where the mevalonate pathway mediates trained immunity and supports survival and function of effector and regulatory T cells, macrophages, and dendritic cells [11,13,15,26] [–] [28]. Mutations of specific enzymes or altered cholesterol metabolism are associated with inflammatory symptoms and the pathogenesis of osteoarthritis [29,30]. Additional organs and functions that are affected and controlled by the mevalonate pathway include the brain, emotional and cognitive mechanisms, fat metabolism, and the maturation of autophagosomes [16,31] [–] [34].

2.3. Regulating the mevalonate pathway

The whole cascade of the mevalonate pathway includes a number of enzymes, cofactors, and intermediate products, all of which are tightly regulated by feedback mechanisms. High intracellular or circulating levels of cholesterol are toxic and associated with unwanted side effects such as oxidative damage, impaired function of signaling proteins, and cardiovascular diseases [35] [–] [41]. Particular regulations are ensured by intermediate or end products of the mevalonate pathway that in turn inhibit the activity and accelerate protein degradation of several key enzymes by negative feedback mechanisms on transcriptional and translational level or by affecting specific cofactors [10,42] [–] [44]. A well-known restorative feedback loop comprises the activation of sterol regulatory element binding proteins (SREBP). These factors are activated when intramembranous sterol levels are reduced and, in turn,

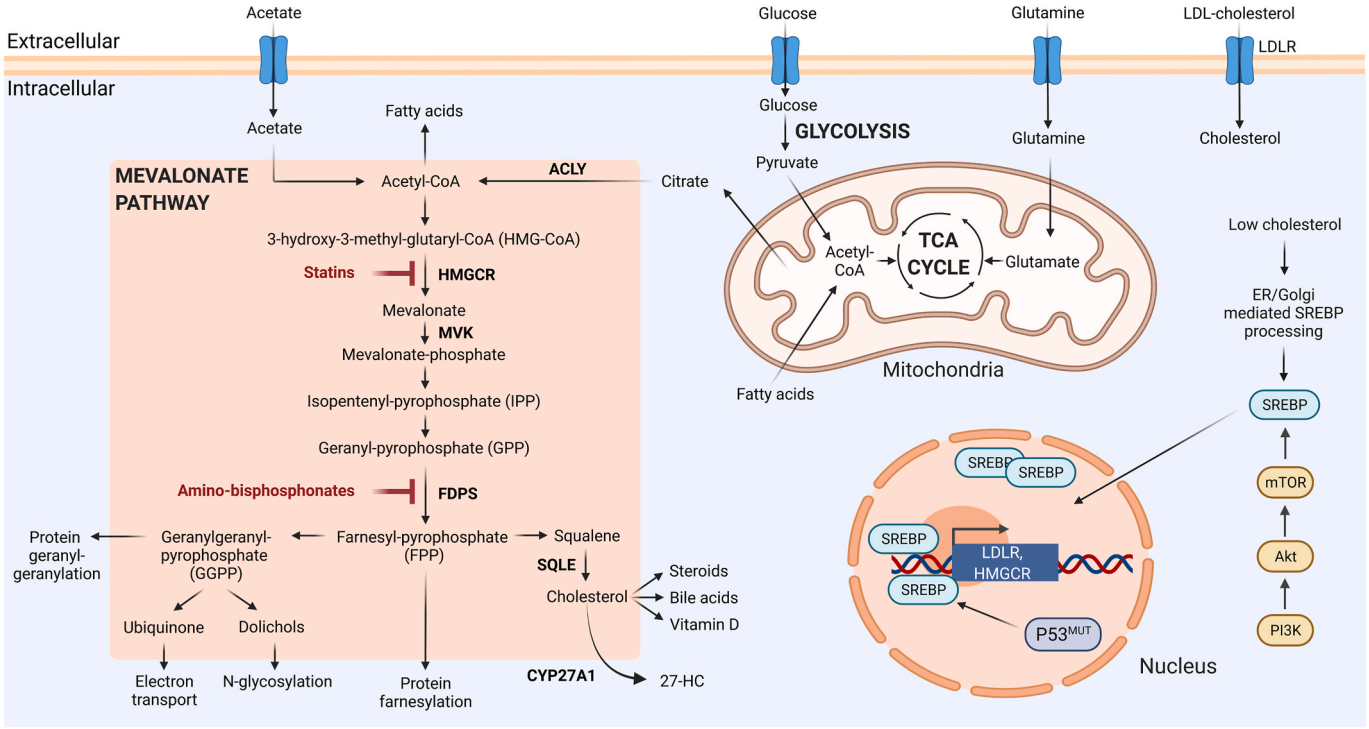

Fig. 1. Overview and regulation of the mevalonate pathway. The mevalonate pathway provides several essential products such as cholesterol by a series of enzymatic reactions starting with acetyl-coenzyme A (acetyl-CoA). Acetyl-CoA can be derived from glucose, glutamine, acetate, and fatty acid metabolism by the involvement of the tricarboxylic acid (TCA) cycle. Extracellular cholesterol is taken up by low-density lipoprotein receptor (LDLR). Upon decreasing levels of intracellular cholesterol, sterol regulatory element binding proteins (SREBP) are activated by endoplasmic reticulum (ER) and Golgi apparatus-mediated processing. SREBP activity itself is regulated by several cellular conditions including mammalian target of rapamycin (mTOR) signaling and the mutational status of p53. 27-hydroxycholesterol (27-HC); 3-hydroxy-3-methylglutaryl-CoA reductase (HMGCR); ATP citrate lyase (ACLY); farnesyl diphosphate synthase (FDPS); mevalonate kinase (MVK); phosphoinositide 3-kinase (PI3K); squalene epoxidase (SQLE): Created with Biorender.com.

activate the gene expression of the HMGCR and the low-density lipoprotein receptor (LDLR, Fig. 1). As a consequence, both the mevalonate pathway as well as LDLR-mediated endocytosis of extracellular LDL are fueled to restore the intracellular levels of cholesterol [9,36,41,45] [–] [47].

3. Dysregulation of the mevalonate pathway in breast cancer tumorigenesis

There is consensus that metabolic reprogramming is a key element in tumor initiation and progression and a well-established target in emerging therapeutic concepts [48] [–] [50]. The mevalonate pathway is involved in protein prenylation, cholesterol production, immunosurveillance, inflammation, and autophagy. All these aspects potentially interfere with diverse steps of tumorigenesis, are involved in tumor cell survival and in the function of the surrounding TME [50]. We will now summarize some specific contributions of the mevalonate pathway to BrCa (Fig. 2).

3.1. Cholesterol drives BrCa tumorigenesis

A number of genetic and non-genetic predispositions and risk factors have been identified for BrCa [51] [–] [53]. Interestingly, obesity and high levels of cholesterol are associated with an increased risk of developing BrCa and with reduced survival [54] [–] [59]. Moreover, cholesterol is a sex steroid precursor. In BrCa tissue estradiol levels can be massively upregulated by the overexpression of *CYP19A1* encoding for the aromatase enzyme [60]. In estrogen receptor (ER)-positive BrCa, tumor cell growth, proliferation, and survival are dependent on ER-signaling, explaining the success story of endocrine treatment concepts that have been introduced for this group of patients [60,61]. Given the involvement of cholesterol in sex hormone synthesis, many studies prompted to identify the role of this molecule in BrCa development and progression.

Tumor cells need higher cholesterol levels for proliferation, cell cycle, membrane synthesis, as well as the regulation of cell signaling, adhesion, and apoptosis by lipid rafts [22,23,56,62] [–] [64]. High levels of cholesterol as well as increased cellular production and uptake, high expression of the LDLR and decreased efflux of cholesterol accelerate tumor growth, migration, metastasis, cancer stemness, and angiogenesis and are associated with a shorter survival in preclinical models of BrCa and when assessing patient cohorts [65–73]. However, clinical studies on cholesterol and BrCa are controversial and need careful interpretation, especially as some studies show no or even an inverse association [57,74]. It seems critical to separate effects of different metabolic cholesterol types and to further assess their role after stratifying patients into clinical subtypes, for example according to the menopausal or the tumor hormone receptor status [52,65,74–76].

Mechanistically, cholesterol is undergoing metabolization into derivatives such as oxysterols that can be abundantly produced within the TME, where they markedly affect cellular players [77]. One of them, 27-hydroxycholesterol (27-HC), alters ERβ-signaling and fosters growth and metastasis of ER-positive BrCa cells by mechanisms that involve the mobilization of tumor-promoting immune cells, the induction of angiogenesis, and the inhibition of the tumor suppressor p53 [71, 78–82]. High expression levels of 27-HC and its corresponding enzyme CYP27A1, but low expression of its catabolizing enzyme, CYP7B1, are associated with poor survival in BrCa patients [56,78,79,83] [–] [85]. CYP27A1 is expressed in myeloid cells including macrophages where 27-HC production shifts their phenotype into an immune-suppressive one that inhibits T cell expansion and activation [86]. Intriguingly, reprogramming cholesterol and 27-HC production is also a strategy by which BrCa cells evade endocrine therapies such as AI [87] [–] [89]. Cholesterol and mevalonate also drive alterations in the metabolic activity of ER-positive and TNBC cells and induce resistance to tamoxifen and doxorubicin [72]. Additional cholesterol and 27-HC-driven mechanisms include the interaction with numerous other pathways and regulators that are implicated in tumorigenesis such as liver X receptors, growth factor receptors, nuclear factor 'kappa-light-chain-enhancer' of activated B-cells (NFκB) and Akt signaling, or oncogenic micro-RNAs [50,67,90,91]. Moreover, cholesterol is convertible into additional oncometabolites that drive BrCa proliferation and migration via the

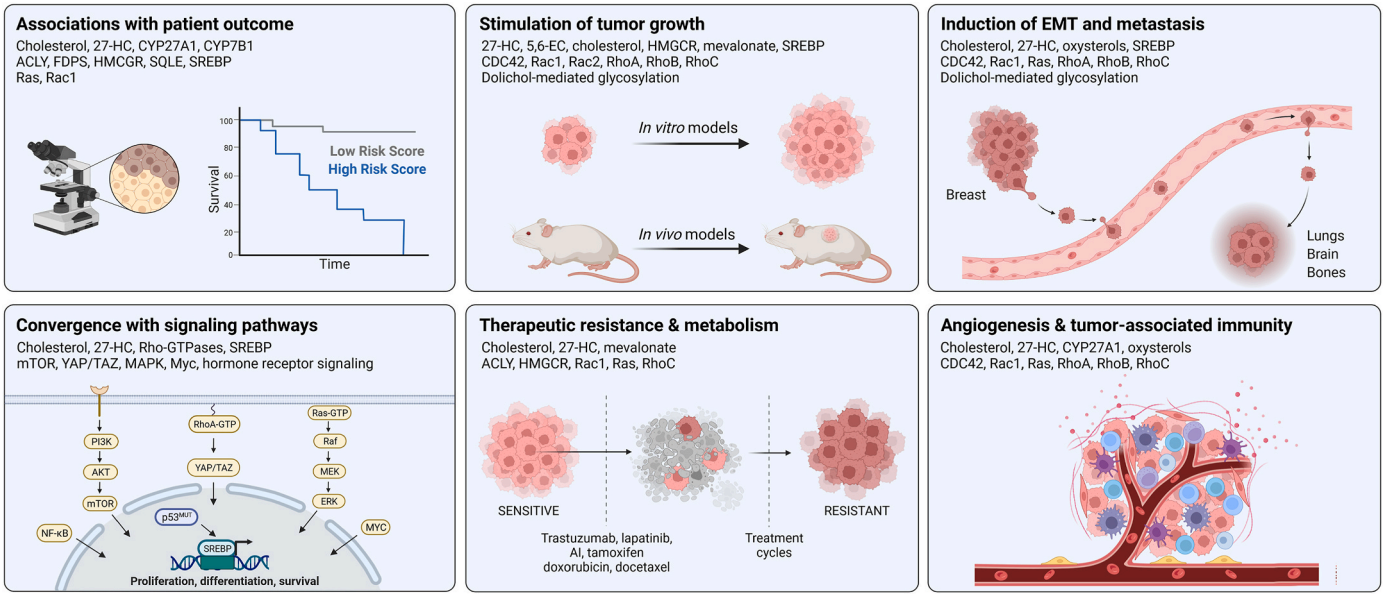

Fig. 2. The role of the mevalonate pathway in breast cancer. The mevalonate pathway affects several steps of breast cancer tumorigenesis including effects on primary tumor growth, epithelial-to-mesenchymal transition (EMT), metastasis, and the interconnection with additional signaling pathways. Furthermore, upregulation of the mevalonate pathway and its corresponding products is associated with therapeutic resistance and the modulation of the local tumor microenvironment. 27-hydroxycholesterol (27-HC); 3-hydroxy-3-methylglutaryl-CoA reductase (HMGCR); ATP citrate lyase (ACLY); cell division cycle 42 (CDC42); cholesterol-5,6-epoxide (5,6-EC); estrogen receptor (ER); farnesyl diphosphate synthase (FDPS); mammalian target of rapamycin (mTOR); nuclear factor 'kappa-light-chain-enhancer' of activated B-cells (NFκB); phosphoinositide 3-kinase (PI3K); squalene epoxidase (SQLE), sterol regulatory element binding protein (SREBP); Yes-associated protein (YAP) and transcriptional co-activator with PDZ-binding motif (TAZ). Created with BioRender.com.

glucocorticoid receptor [92,93]. Reducing cholesterol availability and absorption and 27-HC production as well as increasing its cellular efflux and activating LDLR degradation have shown promising benefits in preclinical models of primary and metastasizing BrCa [71,94–98]. These lines of evidence highlight the undisputed role and the great complexity of cholesterol in different stages of BrCa tumorigenesis.

3.2. The dysregulation of the mevalonate pathway and interconnected signaling partners in BrCa tumorigenesis

Importantly, cholesterol is not the only mevalonate pathway-derived protumorigenic factor. Indeed, mevalonate and N-glycosylation are associated with BrCa tumor growth and metastasis [99] [–] [101]. It is further worth emphasizing that not only intermediate or final products of the mevalonate pathway play distinct roles in cellular transformation. In addition, dysregulated enzymes and transcription factors of the pathway equally contribute to several steps of tumorigenesis by perturbing the fine-tuned availability of these products and by interacting with additional signaling pathways such as p53, mammalian target of rapamycin (mTOR), Yes-associated protein (YAP) and transcriptional co-activator with PDZ-binding motif (TAZ) proto-oncogenes. In BrCa, ectopic HMGCR expression accelerates the growth of ER-positive BrCa cells proving the oncogenic potential of a mevalonate pathway disruption [102]. An increased dependence on the mevalonate pathway is also observed upon BrCa stem cell differentiation and in tumor cells that develop resistance to tamoxifen and anti-HER2-targeted therapies such as lapatinib and trastuzumab [103] [–] [105]. In patients, high protein expression and activation levels of the mevalonate pathway enzymes HMGCR, FDPS, and squalene epoxidase are associated with worse clinical outcome [73,106] [–] [108]. Similarly, increased SREBP1/2 expression reduces the metastasis-free survival and prognosis in patients with BrCa and preclinical models revealed a role for SREBP in osteolytic bone metastases [109,110]. High expression of ACLY is associated with worse prognosis and mediates docetaxel resistance [111]. Cancer subtype- and patient subgroup-specific differences mirror the role of additional confounders that affect the clinical consequence of an enzymatic dysregulation of the mevalonate pathway. For example, HMGCR protein expression in clinical BrCa samples can be associated with favorable parameters such as ERα-positivity, smaller tumor volume, tamoxifen response, and decreased proliferation [112] [–] [114] and correlates with survival benefits in ER-positive but not ER-negative patients [115]. However, other studies prove a connection between upregulated HMGCR expression and high proliferation index, ER negativity and worse prognosis and verify the oncogenic role of the HMGCR in experimental BrCa [102,107,116,117]. Importantly, the poor specificity of some HMGCR antibodies is likely to be responsible for such discrepancies [102,117].

Mechanistic investigations revealed that the tumor suppressor p53 inhibits the mevalonate pathway by interfering with SREBP maturation, cholesterol export, and gene expression of enzymes involved in sterol production [107,118]. *Vice versa*, gain-of-function mutations of p53 accelerate tumorigenesis by activating the mevalonate pathway in BrCa, a mechanism that can be reversed by targeting mutated p53 [107,119]. Additionally, SREBP expression, maturation, and activity is controlled by the PI3-kinase/Akt/mTOR axis which fuels *de novo* lipid synthesis in BrCa cells by upregulating SREBP targets [50,120] [–] [122]. This is reflected by high activity of SREBP-regulated target genes in primary BrCa tissues with a strong engagement of mTOR activity [121]. Genetic inactivation of *SREBF1* and *SREBF2* in human BrCa cell lines activates endoplasmic reticulum stress, unfolded protein response, and apoptosis [123]. Moreover, mevalonate pathway upregulation and subsequent geranylgeranylation of Rho-GTPases by a concerted action of mutant p53 and SREBP activity drives the activation of YAP/TAZ proto-oncogenes in TNBC cell lines [119]. SREBP activity is also modulated by acidification, inflammation, and ER stress in colorectal and hepatocellular cancer cells and similar regulations are likely to occur in BrCa, too [77]. Collectively, aberrant activity of the mevalonate pathway fuels BrCa in an intensive dialogue with additional tumor-supporting signaling pathways.

3.3. The role of prenylation in BrCa

The activity, membrane attachment, and subcellular trafficking of a countless number of signaling proteins depends on a posttranslational lipid-modification referred to as protein prenylation. Here, FPP is used for protein farnesylation, whereas GGPP is a specific substrate for geranylgeranylation [124,125]. In BrCa cells, geranylgeranylation seems to be critical for tumor cell survival as GGPP supplementation often fully reverses antitumor effects elicited by inhibitors of the mevalonate pathway [103,126,127]. A major family of signaling proteins that undergoes prenylation are Rho-GTPases [19]. In physiological homeostasis, Rho-GTPases hold essential functions in cellular adhesion, differentiation, motility, cell cycle, gene expression, cytoskeletal remodeling, and survival [128] [–] [130]. The pleiotropic functions of Rho-GTPases in tumorigenesis are undisputed [128,131] [–] [135]. In reciprocal cooperation with additional regulators like Akt, signal transducers and activators of transcription (STATs) or Myc, classical Rho-GTPases such as members of the Ras superfamily in are involved in BrCa tumor cell growth, motility, invasion, stemness and self-renewal, mutant p53 stabilization, angiogenesis, and drug resistance [102,103,108,119,130,136–143]. Recently, Rac1 has been shown to be upregulated in chemoresistant BrCa cells and to drive the non-oxidative pentose phosphate pathway, which results in enhanced nucleotide production and protection against DNA-damaging chemotherapeutics [144]. High expression and activity of Ras or Rac1 as well as related signaling pathways including mitogen-activated protein kinases (MAPK) are associated with worse clinical outcome and local recurrence in patients with BrCa [140,144] [–] [146]. Importantly, some Rho-GTPases present with both pro-and antitumoral functions depending on specific circumstances. For example, RhoA activation by Raf-1 kinase inhibitor protein suppresses BrCa invasion and metastasis and facilitates a reduced intratumoral accumulation of macrophages [147]. RhoB is a tumor suppressor in early BrCa growth but promotes tumor growth once neoangiogenesis becomes an integral part of tumor progression [148]. Given the generally broad protumorigenic roles of Rho-GTPases in BrCa and encouraging preclinical investigations, clinical studies aimed to prove the efficacy of specific inhibitors of farnesyl and geranylgeranyl transferases, enzymes that facilitate protein prenylation [125,149]. However, the outcome of these studies was mostly discouraging in several malignancies including BrCa [12,125]. The underlying reasons that have been speculated include alternative prenylation of Ras proteins, unsuitable tumor stages in which the inhibitors have been used and toxicity concerns [9,125]. Novel and optimized approaches to target prenylated key players of BrCa tumorigenesis, including Rho-GTPases, are to be expected in the future.

4. The antitumor effects of statins and amino-bisphosphonates in BrCa

In this review, we focus on the antitumor effects of statins and N-BP (Fig. 3) as these agents are clinically approved: Statins as a gold-standard to treat high cholesterol levels in patients prone to an increased risk of developing cardiovascular diseases and N-BP for the treatment of osteoporosis and bone metastases secondary to osteotropic malignancies such as BrCa [41,150]. Statins lower serum cholesterol by blocking the HMGCR, depriving intracellular cholesterol levels and by stimulating a subsequent increase of LDLR expression via the SREBP-driven feedback loop [41]. N-BP inhibit the FDPS and interfere with the prenylation of Rho-GTPases, whose activity is crucial for the unrestricted function of bone-resorbing osteoclasts [151]. As N-BP show strong affinity to hydroxyapatite in bone tissue they are ideally suited as a therapy in diseases that are associated with increased osteoclastic bone

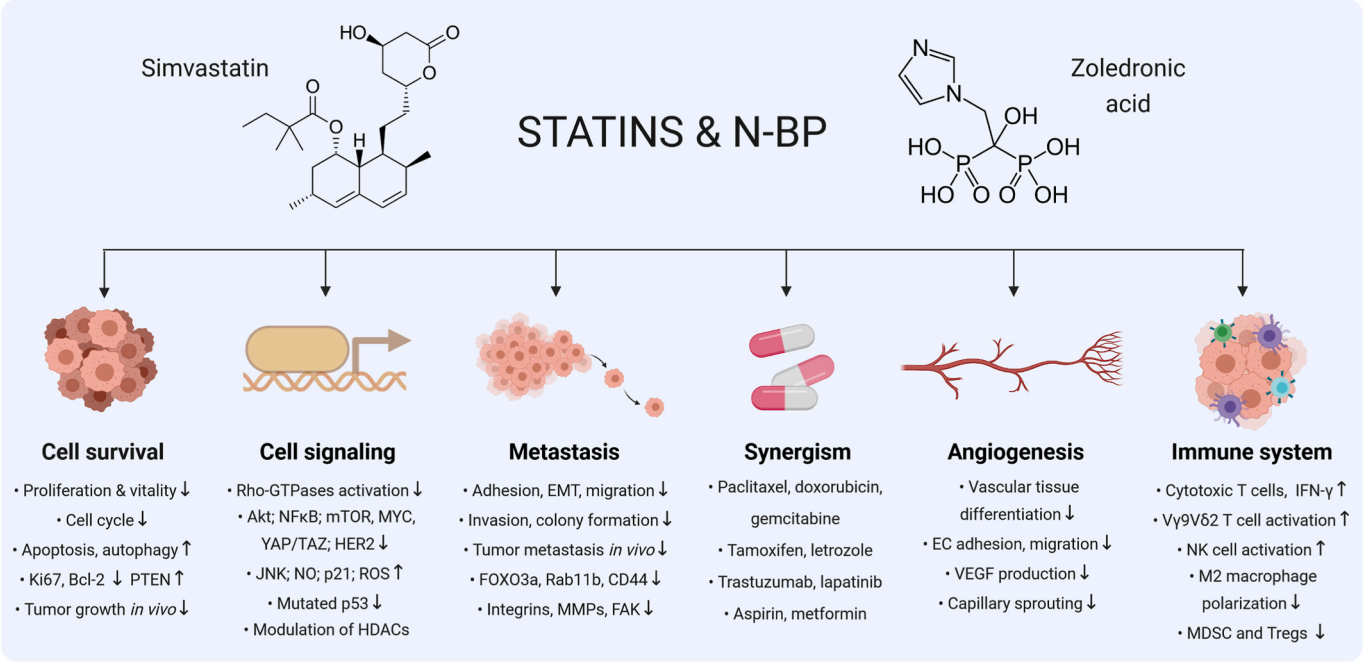

Fig. 3. Antitumor effects of statins and amino-bisphosphonates (N-BP) in breast cancer. The figure represents six major categories including some underlying mechanisms and the exemplary chemical structures of simvastatin and zoledronic acid. Ak strain transforming (Akt); B-cell lymphoma 2 (Bcl-2); c-Jun N-terminal kinase (JNK); cluster of differentiation 44 (CD44); endothelial cell (EC); epithelial-to-mesenchymal transition (EMT); focal adhesion kinase (FAK); Forkhead box O3 (FOXO3a); histone deacetylases (HDACs); human epidermal growth factor receptor 2 (HER2); interferon (IFN)-γ; mammalian target of rapamycin (mTOR); matrix metalloproteinases (MMPs); myeloid-derived suppressor cells (MDSC); natural killer cell (NK cell); nuclear factor 'kappa-light-chain-enhancer' of activated B-cells (NFκB); nitric oxide (NO); phosphatase and tensin homolog (PTEN); Ras-related protein Rab-11B (Rab11b); reactive oxygen species (ROS); regulatory T cells (Tregs); tumor-associated macrophages (TAM); V gamma 9/V delta 2 T cells (Vγ9Vδ2 T cells); vascular endothelial growth factor (VEGF); Yes-associated protein 1 (YAP) and transcriptional co-activator with PDZ-binding motif (TAZ). Created with BioRender.com.

resorption and subsequent skeletal-related events such as fractures or hypercalcemia [152] [–] [158]. Moreover, N-BP are recommended in patients with BrCa who are prescribed with endocrine therapy and at high risk of developing bone loss [159].

4.1. *Affecting tumor cell survival*

Statins and N-BP decrease vitality, proliferation, and cell cycle progression of several BrCa cell lines and simultaneously induce apoptosis and autophagy *in vitro* and in animal models of primary and metastasizing BrCa [160,161,170] [–] [162,177] [–] [169]. The underlying mechanisms include several modulations of cellular factors such as cyclins, p21, p27, caspases, anti-apoptotic proteins, TNF-related apoptosis-inducing ligand (TRAIL), Her2 protein expression, or nitric oxide [127,165,167,173,178] [–] [180]. Of importance, the susceptibility of BrCa cells strongly varies depending on their distinct molecular and genetic profiles and is further dependent on the nature of the statin (lipophilic vs. hydrophilic) or the type of the N-BP. In preclinical models of BrCa, lipophilic statins such as atorvastatin and simvastatin were superior over hydrophilic rosuvastatin and pravastatin [127,168]. This can be attributed to varieties in HMGCR affinity and the differences of membrane crossing between lipophilic and hydrophilic statins [168]. Among N-BP, zoledronic acid has shown superiority over other N-BP tested [172,181,182].

4.2. *Modulating tumor cell signaling*

Statins and N-BP target signaling pathways and mediators that facilitate distinct protumorigenic effects in primary and metastasizing BrCa such as Akt, Erk, JNK, YAP/TAZ, mTOR, chemokines, prostaglandins, cyclooxygenase-2, as well as Her2-and NFκB-signaling [119, 161,168,177–179,183–186]. Moreover, statins stimulate the degradation of mutated p53 but activate wildtype p53 functions in BrCa cells. Mechanistically, the reduction of cellular mevalonate-5-phosphate specifically inhibits the interaction of mutated p53 with its chaperone DNAJA1 [187]. Mutant p53 stabilization depends on RhoA geranylgeranylation and on the interaction with heat shock protein 90 which is disrupted by statin-mediated prenylation inhibition [136]. Of note, lovastatin activates liver kinase B1 and p38 kinase leading to an activation of wildtype p53 that in turn inhibits survivin and activates cell death in MCF-7 BrCa cells [188].

The underlying mechanisms that are responsible for the numerous antitumor effects of statins and N-BP on cancer cell signaling and, consequently, on the survival fate, remain incompletely understood. A lot of effects which have been described can be rescued by supplementing BrCa cells with mevalonate, FPP or GGPP which allows for recovering prenylation as well as the production of downstream molecules including dolichol or cholesterol [126,127,162,183,187]. Hence, one obvious mechanism is the reduction of the intracellular pool of isoprenoids as building blocks for the synthesis of several pivotal products that, among others, facilitate membrane attachment and activity of Rho-GTPases [161]. By affecting prenylation, atorvastatin, cerivastatin, and N-BP reduce the membrane-bound fraction of Ras and RhoA in TNBC cells and lead to the accumulation of unprenylated and inactivated Rho-GTPases in BrCa tumors [168,173,183,189] [–] [191]. As Rho-GTPases affect numerous signaling proteins including NFκB, mevalonate pathway inhibitors are likely to affect cancer cell signaling by disturbing Rho-GTPase localization, activation, and downstream pathways [192]. Moreover, mevalonate pathway inhibitors reduce cholesterol production which affects cell membrane rigidity and fluidity and thereby the localization of membrane-associated molecules. For example, by lowering membrane cholesterol, lovastatin treatment leads to internalization and degradation of ErbB2 [193]. Another mechanism is the impaired N-glycosylation of several membrane-associated

glycoproteins with distinct roles in cancer such as induction of EMT [101]. Furthermore, statins increase the expression of the tumor-suppressor PTEN in BrCa xenograft models by preventing promoter binding by NFκB [178]. In addition, statins modulate the epigenome by regulating DNA methyltransferases and histone deacetylases in BrCa cells [194]. The underlying mechanisms include a disruption of the crosstalk between Ras and PI3/Akt/mTOR signaling as well as the modulation of metabolic reactions that provide NADPH [194]. Transcriptome analysis revealed that statin effects involve on- and off-target alterations of gene transcription at promoter and transcription factor level by which several pathways are affected [195]. Hence, a multifaceted spectrum of responsible mechanisms beyond inhibited protein prenylation account for the pleiotropic effects of mevalonate pathway inhibitors in cancer cells and further investigations are needed to fully elucidate them.

4.3. Interfering with steps of the metastatic process

Patients with BrCa mostly present with metastases to lungs, brain, liver, and bones. In respective mouse models, statins and zoledronic acid prevent metastasis formation and proliferation [101,108,160,169,174]. Among other factors, these effects were mediated by regulating the tumor suppressor FOXO3a, which downregulation is associated with poor survival in affected patients [160]. Atorvastatin did not reduce tumor burden or proliferation of primary BrCa cells growing in murine mammary fat pads, but significantly prevented secondary tumor outgrowth within the lungs [169]. A recent study demonstrated that simvastatin and pitavastatin prevent BrCa brain metastases and improve survival by targeting the small Rho-GTPase Rab11b [196]. Moreover, simvastatin reduced the growth of osteolytic bone metastases derived from MDA-MB-231 cells by downregulating the cancer stem cell marker CD44 [197]. In a concerted action with their hydroxyapatite-binding potential and inhibitory effect on osteoclasts, N-BP reduce cancer cell adhesion to bone, disrupt the release and signaling of protumorigenic factors stored within the bone matrix, and suppress tumor burden and incidence of bone metastasis in BrCa mouse models [152,174,198–203].

A prerequisite for metastasis is epithelial-to-mesenchymal transition (EMT). Here, several EMT-related genes including vimentin and E-cadherin are downregulated by simvastatin, fluvastatin, and atorvastatin [204]. Furthermore, fluvastatin reduces dolichol-dependent glycosylation that is an essential part of the EMT program [101]. Also BrCa cell adhesion, migration, and invasion are perturbed by statins and N-BP, for example by inhibiting Rho-GTPases, downregulation of integrins, matrix metalloproteinases (MMP), and the focal adhesion kinase [152,171,181,189,205,206].

4.4. Synergizing with cytotoxic drugs and overcoming resistance

Statins and N-BP synergize and potentiate individual antitumor effects when combined with each other or with chemo-, radio- and endocrine therapy, including doxorubicin, paclitaxel, gemcitabine, lapatinib, tamoxifen, and letrozole [108,127,173,193,204,207–216]. In TNBC cells, simvastatin synergizes with the histone deacetylase inhibitor vorinostat both *in vitro* and in mouse models [217]. Interestingly, fluvastatin efficacy is potentiated by activators of the AMP-activated protein kinase such as aspirin and metformin [218]. Simvastatin and zoledronic acid also overcome lapatinib- and trastuzumab-resistance in BrCa cells, in part by affecting survivin [105]. These findings indicate mutual drug sensitizations between mevalonate pathway inhibitors and conventional treatments. Such combinations can aid in reducing individual concentrations and in overcoming both resistance mechanisms and the limitation of clinically achievable levels, which are often in contradiction to those used in preclinical studies.

4.5. Altering the tumor microenvironment and immune system

Statins and N-BP exert several immune-modulating effects in models of BrCa and in patients, highlighting their complex potential in reprogramming resident cells of the TME. First, both classes of drugs stimulate the infiltration of the tumor by effector T cells, reduce the recruitment of immunosuppressive tumor-associated macrophages (TAM), and reverse their tumor-promoting M2 into the tumor-suppressive M1 phenotype [170,171,219]. By reducing TAM recruitment and MMP9 production, zoledronic acid reduces the intratumoral infiltration of myeloid-derived suppressor cells [171]. In experimental BrCa, zoledronic acid potentiated the antitumor effect of a programmed cell death protein (PD)-1 antibody by increasing the recruitment of cytotoxic T cells and the systemic production of antitumoral interferon (IFN)-γ [220]. Chemokine production by BrCa cells also triggers expansion and immunosuppressive activity of regulatory T cells (Tregs), which in turn stimulate the migratory potential of tumor cells. This reciprocal interaction is attenuated by zoledronic acid in preclinical and clinical settings [221] [–] [223]. Notably, N-BP and especially tumor cells with inhibited FDPS and accumulation of mevalonate pathway intermediates due to its higher activity recruit and activate a specific subset of blood T cells named Vγ9Vδ2 T cells [152,153,224]. Activated Vγ9Vδ2 T cells, directly or indirectly via natural killer (NK) cell and IFN-γ stimulation, mediate cytotoxicity against N-BP-treated BrCa cells and macrophages independently of their polarization profile [224] [–] [230]. NK cells are also activated directly by statins and interleukin-2 by support of specific dendritic cells [231].

Another integral part of the tumor microenvironment that preserves continuous tumor growth is local blood and nutrient supply by *de novo* angiogenesis. Especially N-BP impair angiogenesis in models of BrCa by mechanisms that include downregulation of vascular endothelial growth factor, suppression of MMP produced by TAM, impaired vascular tissue differentiation and reduced capillary sprouting, mechanism that can be partially recapitulated in treated patients, too [126,152,171,182,186,201,232,233]. Additionally, phenotype, expansion, activity, and recruitment of several other cellular players involved in tumorigenesis are affected by statins and N-BP including hematopoietic stem cells, monocytes, macrophages, osteoblasts, and endothelial cells [170,171,234] [–] [238].

4.6. Results of clinical studies

Several clinical studies have assessed the impact of statins and N-BP on BrCa. Of note, interpretation and comparability of these studies is difficult as different study designs and varying outcome parameters are used and randomized controlled trials in this setting remain rare (presented in Tables 1 and 2 and reviewed elsewhere [239] [–] [241]). A meta-analysis from 2012 including thirteen cohort and eleven case-control studies reported no impact of long-term statin use on the risk of BrCa (RR = 1.03; 95% CI = 0.96–1.11) [242]. A Danish prospective cohort study including 18,769 patients with stage I-III invasive BrCa demonstrated a reduced 10-year risk of recurrence (HR 0.73; 95% CI 0.60 to 0.89) exclusively by lipophilic, but not by hydrophilic statin prescription [243]. Of note, in a retrospective study in patients with inflammatory BrCa, a reduction of the recurrence risk (HR 0.63; 95% CI 0.42 to 0.96; $p < 0.001$) and longer progression-free survival (4.9 years vs. 1.8 years; $p = 0.04$) were seen by hydrophilic, but not lipophilic statins [244]. In two additional studies including patients with stage I to III BrCa, an increase of BrCa-specific survival was only seen in the TNBC subgroup or in case of tumors expressing low or weak HMGCR levels [116,245]. Further evidence of clinical efficacy of pre- and post-diagnostic statin use was reported in additional prospective and retrospective studies [246] [–] [252]. There is also evidence that

Table 1
Selected clinical trials and findings using statins in patients with BrCa.

Cancer type	n	Timing/Doses	Medium follow-up/ duration	Selected findings	References
Prospective trials					
Stage I-III BrCa	1945	Statin use of >100 days after diagnosis	5 years	**Risk of recurrence**: HR (95% CI): 0.67 (0.39–1.13) for use >100 days; p linear trend = 0.02 for longer use	[249]
Stage I-III BrCa	18,769	Statin use after diagnosis	6.8 years	**10-year risk of recurrence**: HR (95% CI): 0.73 (0.60–0.89) by L-statins	[243]
Stage I-III BrCa	910	Statin use before or after diagnosis	5.4 years	Tendency of reduced **BCSS** in patients with negative/week HMGCR expression (Adjusted HR 0.37, 95% CI 0.11–1.24, P = 0.11)	[116]
Retrospective trials					
Stage II-III invasive BrCa	703	Statin use of >6 month after diagnosis	55 months	**Risk of recurrence**: HR (95% CI): 0.40 (0.24–0.67); p < 0.001. **Median DFS**: 112.0 vs. 90.0 months; p = 0.001	[247]
Stage III inflammatory BrCa	723	Statin use at diagnosis	2.9 years	**Risk of recurrence**: HR (95% CI): 0.63 (0.42–0.96); p < 0.001. **Median PFS**: 4.9 years (H-statins) vs.1.8 years (no statins); p = 0.04	[244]
Stage I-II BrCa	4216	Statin use after diagnosis	6.3 years	**Risk of recurrence**: HR (95% CI): 0.76 (0.54–1.05) for L-statins	[246]
Stage I-IV BrCa	31,236	Statin use before, at, or after diagnosis	3.3 years	**RBCD:** HR (95% CI): 0.46 (0.38–0.55) in post-diagnostic and 0.54 (0.44–0.67) in pre-diagnostic users	[252]
Stage I-IV BrCa	20,559	Statin use before or after diagnosis	61.6 months	**Risk of BrCa death:** HR (95% CI): 0.83 (0.75–0.93; P = 0.001) in post-diagnostic and 0.77 (0.63–0.95; P = 0.014) in pre-diagnostic users	[251]
Stage I-III TNBC	23,192	Statin use within 1 year after diagnosis	4.4 years	**BCSS:** HR (95% CI): 0.42 (0.20–0.88); P = 0.022. **OS:** HR (95% CI): 0.70 (0.50–0.99); P = 0.046	[245]
Selected window-of-opportunity (neoadjuvant) trials					
Stage 0 or I invasive BrCa	45	20 mg/day and 80 mg/day fluvastatin	3–6 weeks before surgery	Decrease of Ki67 in high-grade tumors by 7.2% (p = 0.008) Increase of CC3 in high-grade tumor (60% vs. 13%; p = 0.015)	[255]
Stage I-III BrCa	50	80 mg/day atorvastatin	2 weeks before surgery	Posttreatment increase of HMGCR expression (p = 0.0005) Decrease of Ki67 in HMGCR-positive tumors by 24% (p = 0.02)	[253]
Primary invasive BrCa	50	80 mg/day atorvastatin	2 weeks before surgery	Decrease of nuclear cyclin D1 gene expression (p = 0.008) Increase of p27 expression in tumor cells (p = 0.03)	[254]
Primary invasive BrCa	42	80 mg/day atorvastatin	2 weeks before surgery	Decrease of CYP27A1 mRNA expression (p = 0.09) Increase of CYP27A1 protein expression (p = 0.033)	[85]

3-hydroxy-3-methylglutaryl-CoA reductase (HMGCR); breast cancer specific survival (BCSS); BrCa (breast cancer); cleaved caspase-3 (CC3); disease-free survival (DFS); HR (Hazard ratio); n (number of patients enrolled); overall survival (OS); progression-free survival (PFS); Risk of Breast Cancer Death (RBCD); triple-negative breast cancer (TNBC).

Table 2
Selected clinical trials and findings using N-BP in patients with BrCa.

Cancer type	n	Timing/Doses	Medium follow-up/	Selected findings on patient outcome	References
Prospective trials					
Stage I to II ER + BrCa	1803 premenopausal	4 mg q 6 months ZOL + goserelin + endocrine therapy for 3 years	47.8 months 94.4 months	**Risk of disease progression:** HR (95% CI): 0.64 (0.46–0.91); P = 0.01. **Risk of disease progression:** HR (95% CI): 0.77 (0.60–0.99); P = 0.042. **Risk of death:** HR (95% CI): 0.66 (0.43–1.02); P = 0.064	[280] [282]
Invasive BrCa	154,768 postmenopausal	Use of BP before and at diagnosis	7.8 years	**BrCa risk:** HR (95% CI): 0.68 (0.52–0.88); P<0.01	[290]
Stage I to III ER + BrCa	602 postmenopausal	4 mg q 6 months ZOL (immediate vs. delayed) + 2.5 mg/day letrozole	61 months	**Rate of disease progression:** 9.8 (95% CI 6.0–10.3) immediate vs. 10.5 (95% CI 6.6–14.4) delayed ZOL P = 0.628	[278]
Stage II to III Er+ and ER- BrCa	3360 pre- and postmenopausal	4 mg q 1–6 months ZOL + adjuvant endocrine and/or chemotherapy	59 months 117 months	**DFS:** HR (95% CI): 0.75 (0.59–0.96); P = 0.02 in women >5 years postmenopausal. **OS:** HR (95% CI): 0.74 (0.55–0.98); P = 0.04 in women >5 years postmenopausal. **DFS:** HR (95% CI): 0.82 (0.67–1.00) in women >5 years postmenopausal **Incidence of bone metastases as first DFS recurrence:** HR (95% CI): 0.76 (0.63 to 0–92); P = 0.005	[284] [285]
Stage II to III Er+ and ER- BrCa	205 pre-and postmenopausal	4 mg q 4 weeks ZOL + neoadjuvant CT	6 months until surgery	**RITS:** 27.4 mm (CT) vs. 15.5 mm (CT + ZOL); P = 0.006	[283]
Stage I to III ER + BrCa	1065 postmenopausal	4 mg q 6 months ZOL (immediate vs. delayed) + 2.5 mg/day letrozole	60 months	**DFS** for immediate vs. delayed ZOL: HR (95% CI): 0.66 (0.44–0.97); P = 0.0375. **DFS** for delayed vs. no ZOL: HR = 0.46; P = 0.0333	[281]
Retrospective trials					
Invasive BrCa	5992 pre-and postmenopausal	Use of BP before diagnosis	NR	**BrCa risk:** HR (95% CI): 0.67 (0.51–0.89) in current users; P-trend = 0.01 for increased duration of use	[291]
Stage I to IV HR + BrCa	3731 postmenopausal	Alendronate or risedronate after diagnosis	70 months	**OS:** OR (95% CI): 0.63 (0.41–0.96); P = 0.03. **BCSS:** OR (95% CI): 0.28 (0.09–0.91); P = 0.035	[292]

Breast cancer (BrCa); chemotherapy (CT); disease-free survival (DFS); hazard ratio (HR); number of patients enrolled (n); not reported (NR); odds ratio (OR); residual invasive tumor size (RITS); zoledronic acid (ZOL).

combining statins with angiotensin-converting enzyme inhibitors may be beneficial for the outcome of patients with stage II/III BrCa [247]. A recent meta-analysis on statins, including seventeen cohort studies with 168,000 patients, described a significant decline of recurrence (HR = 0.72; p<0.001) and disease-specific mortality rates (HR = 0.80; p<0.001). Benefits were observed independently of the type of statin used [248]. In window-of-opportunity trials, high doses of atorvastatin (80 mg/day) or fluvastatin (80 mg/day or 20 mg/day) were administered for few weeks prior to surgery in patients with newly diagnosed BrCa. Here, statin treatment increased apoptosis markers as well as HMGCR and tumor suppressor p27 protein expression, while reducing the expression levels of Ki67, cyclin D1, and CYP27A1 [85,253–255]. However, in several other clinical studies, no clinical improvement was observed in patients receiving statins in BrCa. While these results may have resulted from differences in the study setup, they could also be seen as an indicator that the beneficial effects of statins may be limited to selected disease conditions, or depend on the chosen therapeutic regimen [116,242,256] [–] [259]. The controversial relationship between cancer and the use of statins may be explained by the discrepancy of statin concentrations that are needed to achieve reasonable effects in preclinical models and measurable serum and intratumoral levels in patients [260]. Atorvastatin accumulates in BrCa tissue; however, it is still unclear, whether all statins have a similar potential and if yes, in which BrCa subtypes with varying biochemical and histopathological features [261]. In addition, some BrCa types with a stronger level of mevalonate pathway addiction might be more sensitive to statins. Future studies, especially aimed at identifying specific predictive markers of drug efficacy, need to further evaluate the group of patients that will mostly benefit from a treatment with statins. Circumvention of intrinsic resistance mechanisms to statins would further offer a strategy to potentiate their clinical efficacy [262]. In BrCa cell lines and clinical samples, both high basal expression of several mevalonate pathway genes including SREBP as well as the induction of a restorative feedback loop via the SREBP-HMGCR-axis by statin treatment mediates resistance [116,117,218,261,263,264]. This resistance is reversible by pharmacological and genetic targeting of SREBP maturation and HMGCR expression [263,265] [–] [267]. Statin-sensitive BrCa cell lines appear defective of this feedback, but acquire statin resistance after long-term simvastatin exposure via HMGCR induction [263]. Moreover, statin-sensitivity is associated with a basal-like, ERα-negative subtype, alterations of E-cadherin expression and the *Myc* oncogene, p53 mutational status, induction of an EMT programme, as well as elevated levels of lipid rafts which reinforces the idea of BrCa subtype-specific statin benefits [98,101,169,255,264,268] [–] [271].

Given their inhibitory potential on bone resorption and strong preclinical data, a number of large clinical trials have been conducted to assess the clinical impact of adjuvant bisphosphonates in BrCa (summarized in Ref. [272]). An initial study published by Diel et al. more than 20 years ago demonstrated that, in addition to significantly decreasing the occurrence of bone metastases, oral treatment with the non-nitrogen bisphosphonate clodronate also led to a reduction of visceral metastases (p = 0.003) [273]. When given in a neoadjuvant setting, ibandronate and zoledronic acid have the capability of reducing the number of disseminated tumor cells in the bone marrow [274] [–] [276]. Although not always primarily designed for this purpose, a set of large randomized control trials assessed the impact of zoledronic acid on disease outcome and survival rates in BrCa [277] [–] [279]. While demonstrating that zoledronic acid prevents endocrine therapy-induced bone loss, findings of the ABCSG-12 and ZO-FAST studies proofed an additional long-term reduction in the risk of disease progression and recurrence in patients with early BrCa undergoing endocrine treatment [279] [–] [282]. Adding zoledronic acid to neoadjuvant chemotherapy significantly reduced the residual invasive tumor size within 6 months until surgery (27.4 mm vs. 15.5 mm; p = 0.006) [283]. Of note, a reduction of disease- and recurrence-free survival was only seen in postmenopausal patients treated with the combinatory approach [283,

284]. This positive effect in postmenopausal women persisted over a follow-up period of 10 years and was accompanied by a significantly reduced incidence of disease recurrence (HR (95% CI): 0.76 (0.63 to 0–92); P = 0.005) [285]. A meta-analysis confirmed the beneficial effects of bisphosphonates on BrCa survival and bone recurrence. However, this effect was also limited to postmenopausal patients [286,287]. The relevance of these findings is underpinned by the observation that effects of zoledronic acid on bone-metastatic growth of BrCa cells was limited to ovariectomized mice mimicking postmenopausal conditions [288].

The positive effect of bisphosphonates in postmenopausal women may, in part, be simply explained by the resulting suppression of bone turnover, thus, creating a more hostile environment for cancer cells. However, there is evidence for additional effects. Estrogens counteract the immunomodulatory functions of zoledronic acid by driving Tregs expansion, stimulating the PD-1/PD-L1 axis and impairing NK cell cytotoxicity [289]. There is additional data to suggest that bisphosphonates reduce the risk of developing BrCa. A prospective study involving almost 155,000 postmenopausal women showed a 30% reduced risk of developing BrCa (HR 0.68; 95% CI 0.52 to 0.88; p = 0.02) in patients taking oral bisphosphonates and this was later confirmed in a population-based case–control study [290,291].

While the benefit of adjuvant bisphosphonate in postmenopausal women receiving endocrine treatment for BrCa is well established, and the recommendation for their use has now been implemented in national and international guidelines, not all studies with bisphosphonates have yielded favorable outcomes. As such their use in premenopausal women or in a neoadjuvant setting is not generally recommended and should be conducted within appropriate clinical trials where possible.

5. Outlook

The relevance of the mevalonate pathway as a metabolic contributor in BrCa tumorigenesis has been clearly established. The pathway supports tumor cell growth, cell signaling, metastasis, and a spectrum of resistance mechanisms against established endocrine and targeted therapies. Depriving cancer cells from tumor-promoting derivatives and target molecules of the mevalonate pathway such as cholesterol and prenylated proteins has become an approach to restrain tumor growth with clinical relevance. Statins and N-BP mediate a plethora of multifaceted antitumor effects apart from simply inducing cell death that involve the modulation of the local signature of cellular and soluble components within the TME. However, several not fully resolved questions still need to be addressed: Which underlying mechanisms specifically predispose BrCa cells to an increased addiction to the mevalonate pathway? What is the profound role of mevalonate pathway products in distinct stages of BrCa and how do they interconnect with alterations of other metabolic pathways? How and when should the pathway precisely be targeted to achieve inhibitory effects on cancer cells while supporting antitumoral immune functions? What are the optimal treatment regimens that exploit spatio-temporal dynamics of drug distribution and actions on cancer cells? Which combination therapies are a useful tool to reduce drug concentrations and to overcome potential resistance mechanisms including those related to conventional therapies? And finally, which biomarkers of statin and N-BP efficacy allow for identifying patients that would mostly benefit from these therapies? As statins and N-BP are commonly used in a broad range of patients with a comparably low spectrum of side effects, unravelling these questions is of utmost importance to fully utilize their potential in tailored approaches in clinical BrCa management.

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