Non-Coding RNAs in Tamoxifen Resistance

Subjects: Medicine, General & Internal
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Despite the clinical efficacy of Tam, intrinsic or acquired resistance is an important obstacle limiting the success of ER + breast cancer patient treatment. It is a challenge that needs to be overcome to improve the prognosis of these patients. The main mechanisms of resistance to tamoxifen can be divided according to different causes: mechanisms that involve genetic mutations and lead to loss or gain of function of the receptor and mechanisms that modulate other protumorigenic pathways, including other receptors involved in estrogen's pathway of action.

Keywords: breast cancer ; estrogen receptor ; tamoxifen ; endocrine resistance ; ncRNA ; lncRNA ; microRNA

1. Introduction

Breast cancer is the most commonly diagnosed cancer and the leading cause of cancer mortality among women [1]. Breast tumors can be classified in clinical practice as hormone receptor and/or HER2 positive (HR+ and/or HER2+) vs negative (HR- and/or HER2-) by immunohistochemical detection or as luminal A, luminal B, HER2-enriched and basal-like according to transcriptome profiling using gene signatures such as PAM50 [2]. Hormone receptors include the estrogen receptor alpha (ERα), the main driver of breast cancer cell proliferation, and the progesterone receptor (PR), a gene regulated by ER, both acting as hormone-dependent transcription factors. HR+ tumors are positive for ER and/or progesterone receptor (PR). The HR+HER2- subtype is the most common, representing around 73% of all occurrences, and generally has a good prognosis. The HR+HER2+ subtype has a higher cell proliferation index and usually a more aggressive phenotype, constituting 11% of occurrences [3].

Breast cancer classification and the development of targeted therapies has considerably improved treatment options and patient prognosis [4]. The subtypes that are positive for the estrogen receptor usually respond to endocrine therapies targeting the estrogen receptor (ER) pathway, based on antiestrogens, which include selective ER modulators (SERMs) and selective ER downregulators (SERDs), or on aromatase inhibitors (AIs), which prevent endogenous production of estrogens [5]. One of the most commonly prescribed first-line SERM for hormone responsive subtypes is tamoxifen [6]. Tamoxifen (Tam) is a highly efficient SERM widely used for treatment of all stages of breast cancer in pre- and post-menopausal women. It binds ER and blocks its transcriptional activity. Tam use in the clinic has led to a drop in the recurrence rate by 50% at 5 years and 30% lower during the next 5 years [7]. However, approximately 50% of advanced ER-positive breast tumors are intrinsically resistant to tamoxifen and about 40% of patients receiving adjuvant tamoxifen eventually relapse [8].

The mechanisms that are involved in Tam resistance are complex and involve multiple signaling pathways [9][10]. Recently, roles for microRNAs and lncRNAs in controlling ER expression and/or tamoxifen action have been described, but the underlying mechanisms are still little explored. In this review, we will discuss the current state of knowledge on the roles of microRNAs and lncRNAs in the main mechanisms of tamoxifen resistance.

2. Estrogens and Estrogen Receptor Alpha

Estrogens are mitogenic hormones that play crucial roles in normal breast development, but also in carcinogenesis. They are predominantly synthesized in the ovaries of premenopausal women and to a lesser extent in peripheral tissues, including breast tissue. In postmenopausal women, estrogens are only produced in extragonadal peripheral tissues [11].

The estrogen receptor alpha (ERα) is one of the most significant biological markers for the diagnosis/prognosis of breast cancer and its accurate detection is important for therapeutic choice in BC patients. ERα is member of the nuclear receptor superfamily of ligand activated transcription factors [12][13]. There are two functionally distinct ERs: ERα and ERβ. The human ESR1 gene, which encodes ERα is located on chromosome 6 while the human ESR2 gene, coding for ERβ, is located on chromosome 14 [14][15]. These receptors have different and often opposite effects and the proliferative response caused by estrogens in breast epithelial cells is thought to be the result of a balance between ERα and ERβ

signaling. While ERα has a proliferative effect on breast cells, acting as a transcriptional activator of genes associated with cell survival and proliferation, the role of ERβ is usually antiproliferative and proapoptotic [16][17]. However, ERα is overexpressed in ER+ tumors while ERβ expression is reduced.

The ERα is a 66 kDa nuclear protein and its transcriptional activity is ligand-dependent. Estrogens bind to the receptor and change its conformation, inducing binding to specific target DNA sequences called estrogen response elements (EREs) [12][13]. On DNA, the estrogen-ERα complex interacts with coregulatory proteins, modulating the transcription of genes involved in cell cycle regulation, DNA replication, cell differentiation, cell survival, and angiogenesis [14][18]. The estrogen-ER complex can also act on non-nuclear pathways through the regulation of membrane receptors (for example, IGFR, FGFR, and HER2) and kinases (for example, mitogen activated protein kinases, receptor tyrosine kinases, PI3K, AKT, mTOR, Src, and CDK4/6) [14][18].

The ESR1 gene also encodes ER variants, such as ERα36 and ERα46 [19][20]. ERα36 has a novel noncoding exon as its first exon and also a unique 27 amino acid domain that replaces the last 138 amino acids in ERα66, and as a result lacks both transcription activation domains (AF-1 and AF-2) [21]. ERα46 is a truncated form that lacks the transactivation function domain 1 (AF1) and functions to inhibit the AF1 activity of the full length ERα66 [22].

3. Mechanisms of Tamoxifen Resistance

ER isoforms, without gene mutations, may also be associated with Tam resistance. Although tamoxifen is an antagonist of ERα66, it activates ERα36. This activation might play critical roles in intrinsic and acquired Tam resistance [23]. Additionally, the ER-α46 variant enhances sensitivity to estrogens in breast cancer cells [22].

Some of the cellular mechanisms related to Tam resistance involve alternative oncogenic signaling pathways that can provide tumors with estrogen-independent stimuli for proliferation and survival (**Figure 1**). An example is the activation of the ERBB2 pathway (Erb-B2 tyrosine receptor kinase 2 or HER2), known to reduce sensitivity to tamoxifen [24][25]. RBP2 (retinoblastoma-binding protein 2), also known as KDM5A (lysine demethylase 5A), physically interacts with ER, increases the stability of the EGFR and HER2 proteins, and promotes activation of the PI3K/AKT pathway, inducing tamoxifen resistance [26].

The phosphoinositide 3-kinase/Akt/mammalian target of the rapamycin (PI3K/Akt/mTOR) pathway is a cell signaling pathway that plays an important role in controlling cell cycle, survival, and cell growth [27]. The PI3K /AKT/mTOR pathway is dysregulated in many types of cancers. In breast cancer, it can lead to the resistance to endocrine therapy [28]. Indeed, inhibiting this pathway improved the effectiveness of tamoxifen in cultured cells [29].

Thus, defects in several signaling pathways can lead to resistance to Tam. The study of non-coding RNAs that interfere with either ER expression or with pathways involved in Tam resistance has added another layer of complexity to these mechanisms.

4. Non-Coding RNAs

Advances in sequencing technologies and computational approaches in the past few decades revealed that 75–85% of the genome is transcribed, although less than 3% of the human genome represents coding gene exons [30][31][32][33][34][35]. The remaining transcripts are non-coding RNAs (ncRNAs) and can be divided in subclasses. Ribosomal and transfer RNAs are the best known non-coding RNAs. However, in the past decade, increasing attention has been given to other classes of non-coding RNAs such as microRNAs, long non-coding RNAs, and circular RNAs, among others, notably for their roles in the regulation of gene expression and chromatin structure.

MicroRNAs (miRNAs/miRs) are small (approximately 18–25 nucleotide long) non-coding RNAs that, most of the time, interact with the 3′UTR of target mRNAs and post-transcriptionally regulate their expression by mRNA cleavage or by inhibition of translation [36]. Dysregulated miRNA expression is frequently associated with hallmarks in cancer development and resistance to therapies [37][38]. In breast cancer, several reports suggested that miRNAs might have an essential role in Tam resistance by the regulation of genes in previously described pathways [39][40][41][42][43].

Long non-coding RNAs (lncRNAs) are a class of non-coding transcripts that are over 200 nucleotide long [44][45]. LncRNAs have similarities with mRNAs in terms of length, transcription and splicing structure, yet lack protein-coding potential due to the absence of sizeable open reading frames, although some lncRNA may encode small functional peptides [44][46][47]. LncRNAs are located in intergenic, intronic or exonic loci, and can be imprinted. They may overlap with protein-coding genes in a sense or antisense direction [46][48][49][50][51].

There is growing evidence indicating that many lncRNAs are expressed in a temporal and tissue-specific manner and play a role in gene regulation through different mechanisms [45][49][50][51][52][53]. Accumulating evidence suggests that some lncRNAs may be key regulators of biological processes like imprinting [54][55], pluripotency [56][57][58][59] , cell differentiation [57][58], DNA damage response [51], cell apoptosis [53], inflammatory and immune responses [60]. Mutations, polymorphisms or altered expression patterns of lncRNAs have been associated with the progression and/or severity of several diseases, including breast cancer [51][61][62][63][64]. More recently, lncRNA deregulation has also been associated with Tam resistance in breast cancer cells [65].

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