

Estrogen receptors as the novel therapeutic biomarker in non-small cell lung cancer

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Abstract

Although a wide range of studies have addressed the relationship between estrogen receptor (ER) expression and prognosis in non-small cell lung cancer (NSCLC), that relationship remains controversial. This is in large part because there is no consensus on the rate of ER expression in NSCLC or on the intracellular distribution of ER expression. This suggests that establishing the relationship between ER expression and prognosis will require standardization of the antibodies used as well as the definition of a positive response. For example, it is supposed from previous studies that ERs in the cytoplasm and nucleus have different relationships to prognosis than ERs in the cytoplasm. Moreover, ER signaling in NSCLC is known to be affected by aromatase, progesterone receptor and epidermal growth factor receptor mutation. However, there has been little functional analysis these mutants and subtypes. This review will focus on what is known about the role of ERs in NSCLC and whether ER can be a useful prognostic marker or therapeutic target in NSCLC.

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Key words: Estrogen receptor; Non-small cell lung cancer; Epidermal growth factor receptor; Fulvestrant; Combined therapy

Core tip: Although there were many studies regarding

the role of estrogen receptor (ER) in non-small cell lung cancer (NSCLC), the rate of ER expression or the intracellular distribution of ER remains controversial. This suggests that establishing the relationship between ER expression and prognosis will require standardization of the antibodies used as well as the definition of a positive response. Furthermore, there has been little functional analysis for ER variants. This review will focus on what is known about the role of ERs in NSCLC and whether ER can be a useful prognostic marker or therapeutic target in NSCLC.

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INTRODUCTION

The estrogen receptor (ER) is one of the main targets of breast cancer therapy, and hormone therapy is generally administered to ER-positive breast cancer patients. There are two known ER subtypes, α and β . ER- α is the conventional receptor and is a useful prognostic marker in breast cancer. On the other hand, ER- β is a recently identified ER subtype, widely expressed in various organs including mammary gland and uterus. ER has also been detected in lung cancer cells. The first report of ER expression in lung cancer appeared in 1982^[1]. At that time, ERs were detected using radioimmunoassays, and the detection rate was relatively low. The first use of immunohistochemical staining to detect the ER in lung cancer tissue was reported by Canver *et al*^[2] in 1994. Since then, several different anti-ER antibodies have been employed to detect the receptor, and it has become apparent that there are differences in the detection rates and localization of the antigen, depending upon which antibody is used or the definition of a positive result^[3-30]. Further-

Table 1 Previous studies involving immunohistochemical detection of estrogen receptor- α in non-small cell lung cancer

Ref.	Antibody clone	Location	Detection rates
Canver <i>et al</i> ^[2]	NS	Nucleus	97%
Ollayos <i>et al</i> ^[3]	NS	Nucleus	7%
Su <i>et al</i> ^[4]	NS	Nucleus	6%
Di Nunno <i>et al</i> ^[5]	1D5	None	0
Omoto <i>et al</i> ^[6]	1D5	None	0
Dabbs <i>et al</i> ^[7]	1D5/6F11	None/nucleus	0/67%
Radzikowska <i>et al</i> ^[8]	1D5/6F11	Nucleus	3%/3%
Kawai <i>et al</i> ^[9]	HC-20	Cytoplasm	73%
Schwartz <i>et al</i> ^[10]	1D5/6F11	None	0/0
Wu <i>et al</i> ^[11]	NS	Cytoplasm	3%
Schwartz <i>et al</i> ^[12]	HC-20	Cytoplasm	66%
Márquez-Garbán <i>et al</i> ^[13]	HC-20	Nucleus/cytoplasm	45%/75%
Skov <i>et al</i> ^[14]	1D5	Nucleus/cytoplasm	3%/55%
Niikawa <i>et al</i> ^[15]	6F11	Nucleus	54%
Nose <i>et al</i> ^[16]	HC-20	Cytoplasm	84%
Raso <i>et al</i> ^[17]	6F11	Nucleus	36%
	HC-20	Nucleus/cytoplasm	5%/42%
	1D5	Nucleus/cytoplasm	34%/18%
Abe <i>et al</i> ^[18]	6F11	Nucleus	1%
Gomez-Fernandez <i>et al</i> ^[19]	1D5/6F11/SP-1	Nucleus	8%/14%/27%
Mauro <i>et al</i> ^[20]	6F11+HC-20	Nucleus/cytoplasm	38%/71%
Stabile <i>et al</i> ^[21]	HC-20	Nucleus/cytoplasm	39%/54%
Sun <i>et al</i> ^[22]	HC-20	Cytoplasm	36%
Rades <i>et al</i> ^[23]	1D5	NS	19%
Shimizu <i>et al</i> ^[24]	HC-20	Cytoplasm	47%
Rouquette <i>et al</i> ^[25]	1D5	Nucleus	9%
	F10	Nucleus	8%

NS: Indicates not specified.

more, Stabile *et al*^[31] demonstrated that both NSCLC and normal lung express ERs and show biological responses to estrogen. Consequently, the role of ER in lung cancer remains controversial.

It is now known that ER affects other signals, such as that mediated *via* epidermal growth factor receptor (EGFR)^[32]. Based on this finding, a clinical trial of the target plus hormone therapy is now ongoing^[33]. However, many questions remain unanswered. This is in part because the reasons for differences in the ER detection rate and the apparently different functions of ERs at different sites remain unclear. This review will focus on previous findings to assess the potential utility of ER as a prognostic factor and as the basis for novel therapeutic strategies for NSCLC, as well as the challenges that will need to be overcome in the future.

IMMUNOHISTOCHEMICAL DETECTION OF ER IN NSCLC

In breast cancer cells, the intracellular localization of ER- α is generally performed using clone 1D5 antibody, the epitope for which is in the N-terminus of ER- α . Using this antibody, ER- α is detected in the nucleus. Nuclear ER- α has also been detected using clone 6F11 antibody, which was raised against the full-length form of the receptor molecule^[7,8,15,17,20,25]. On the other hand, the rate of ER- α detection in NSCLC using clone 1D5 is very low, from 0%-7%^[5-8,10,17,19,23,25]. Moreover, ER- α is report-

edly located not only in the nucleus, but also in the cytoplasm and in the plasma membrane^[9,11-14,16,17,20-22,24]. Cytoplasmic and plasma membrane ER- α is mainly detected using clone HC-20 antibody, the epitope for which is in the C-terminus. The detection rate with this antibody is 70%-80%, much higher than with clone 1D5^[5-14,16,17,19-25]; indeed, we confirmed that ER- α detected using clone HC-20 is nearly always missed by clone 1D5. This suggests that ER- α detected by clone HC-20 may have an N-terminal deletion mutation that prevents its translocation to the nucleus^[9,31].

The reports published to date on the immunohistochemical detection of ER- α expression in NSCLC are listed in Table 1. It is noteworthy that the positivity rates vary depending on the definition of "positive" used and on the antibody. To establish ER- α as a prognostic marker in NSCLC, it will necessary to standardize the definition of "positive" based on the use of a particular antibody.

ER- β was first identified in 1996^[34], and the first report of ER- β expression in NSCLC was from Omoto *et al*^[6] in 2001. They observed that ER- β is expressed in lung carcinomas as well as in normal lung tissue. They also showed that adenocarcinomas expressed significantly more ER- β than squamous cell carcinomas. Unlike ER- α , strong expression of ER- β is observed in the cytoplasm as well as the nucleus of NSCLC cells. The reports published to date on immunohistochemical detection of ER- β expression in NSCLC are listed in Table 2. Three

Table 2 Previous studies involving immunohistochemical detection of estrogen receptor- α in non-small cell lung cancer

Ref.	Antibody clone	Location	Detection rates
Omoto <i>et al</i> ^[6]	NS	Nucleus	67%
Kawai <i>et al</i> ^[9]	H-150	Nucleus	51%
Schwartz <i>et al</i> ^[10]	PPG5/10	Nucleus	61%
Wu <i>et al</i> ^[11]	NS	Nucleus	46%
Márquez-Garbán <i>et al</i> ^[13]	Polyclonal	Nucleus	52%
		Cytoplasm	69%
Skov <i>et al</i> ^[14]	PPG5/10	Nucleus	84%
Niikawa <i>et al</i> ^[15]	MS-ER β 13-PX1	Nucleus	90%
Ali <i>et al</i> ^[26]	PPG5/10	Nucleus	75%
Nose <i>et al</i> ^[16]	H-150	Nucleus	74%
Raso <i>et al</i> ^[17]	H-150	Nucleus	56%
		Cytoplasm	98%
	14C8	Nucleus	42%
		Cytoplasm	19%
Abe <i>et al</i> ^[18]	14C8	Nucleus	71%
Mauro <i>et al</i> ^[20]	NS	Nucleus	40%
		Cytoplasm	64%
Navaratnam <i>et al</i> ^[27]	14C8	Nucleus	49%
Rouquette <i>et al</i> ^[25]	Polyclonal	Nucleus	38%
Karlsson <i>et al</i> ^[28]	14C8	Nucleus	86%
Liu <i>et al</i> ^[29]	PPG5/10	Nucleus	45%
		Cytoplasm	59%

NS: Indicates not specified.

antibody clones were mainly used in those studies. The epitopes for clones H-150 and 14C8 are in the N-terminus of ER- β , and their detection rates in the nucleus are 51%-74% and 42%-71%, respectively^[9,16-18,27,28]. The epitope for the third clone, PPG5/10, is in the C-terminus, and the detection rate in the nucleus is 61%-84%^[10,14,26,29]. In recent years, expression of ER- β in NSCLC has been the focus of study more frequently than ER- α , including immunohistochemical analysis of ER- β variants^[29]. However, further study will be needed to determine which ER- β variant has the most impact in NSCLC. In immunohistochemical study, it should be made clear which ER expression (*i.e.*, type or location) is more responsible for the NSCLC progression. In addition, it should be also evaluated which antibody is reliable for detecting ER as the biomarker for NSCLC therapy.

On the other hand, there were some new studies on RNA expression of ERs in NSCLC^[35,36]. Brueckl *et al*^[35] reported that ER- α high expression was of significant positive prognostic value and patients with ER- α high tumors did not have any benefit from adjuvant chemotherapy. Atmaca *et al*^[36] demonstrated that ER- α mRNA expression was an independent prognostic factor in metastatic NSCLC. These studies were interesting because of different approach from immunohistochemistry, however, there were small size and needed to be more studied in the future.

ER AS A PROGNOSTIC MARKER IN NSCLC

It is well known that ER- α expression is a useful prog-

Table 3 Previous studies of estrogen receptors as prognostic markers in non-small cell lung cancer

Ref.	ER subtype	Methods	Location	Prognosis
Kawai <i>et al</i> ^[9]	α	IHC	Cytoplasm	Worse
	β	IHC	Nucleus	Better
Wu <i>et al</i> ^[11]	β	IHC	Nucleus	Better
Schwartz <i>et al</i> ^[10]	β	IHC	Nucleus	Better (male)
Skov <i>et al</i> ^[14]	β	IHC	Nucleus	Better (male)
Nose <i>et al</i> ^[16]	α	IHC	Cytoplasm	Worse
Abe <i>et al</i> ^[18]	β	IHC	Nucleus	Better
Mauro <i>et al</i> ^[20]	β	IHC	Nucleus	Better
Olivo-Marston <i>et al</i> ^[30]	α	RT-PCR	NS	Worse
Stabile <i>et al</i> ^[21]	β	IHC	Cytoplasm	Worse
Rouquette <i>et al</i> ^[25]	α	IHC	Nucleus	Better
Rades <i>et al</i> ^[23]	α	IHC	NS	Worse
Karlsson <i>et al</i> ^[28]	β	IHC	Nucleus	Better (ADCA)
Liu <i>et al</i> ^[29]	β 2,5	IHC	Cytoplasm	Better

ER: Estrogen receptors; NS: Indicates not specified; ADCA: Adenocarcinoma; IHC: Immunohistochemistry; RT-PCR: Reverse transcription polymerase chain reaction.

nostic marker in breast cancer^[37,38]. In 2005, we first proposed that ERs could potentially serve as prognostic factors in NSCLC^[9]. In that study, we observed that cytoplasmic ER- α was predictive of a survival rate in NSCLC. The reports published to date on the relationship between ER expression and prognosis in NSCLC are listed in Table 3. Unlike in breast cancer, expression of ER- α in NSCLC cells is mainly observed in the cytoplasm, and its detection is associated with a poorer prognosis. Among those studies, only one reported that ER- α is predictive of a better prognosis in NSCLC^[25]. In that paper, unlike the others, ER- α was detected in the nucleus. Recently, Mauro *et al*^[20] reported that nuclear immunostaining for ER- α expression declines with age. However, it is unclear whether the age-related reduction in nuclear ER- α is associated with prognosis in NSCLC. The cytoplasmic ER- α in NSCLC is a variant type and may be associated with non-genomic signaling. However, it is still unclear whether or not cytoplasmic ER- α affects wild type nuclear ER- α . Thus, many questions remain unanswered about the role of ER- α in NSCLC.

In the time since we first reported that ER- β expression was an independent factor associated with a better prognosis of NSCLC^[9], there have been several other studies on the relation between ER- β and prognosis in NSCLC (Table 3). Most found that nuclear ER- β was predictive of a better prognosis in NSCLC. When nuclear ER- β is high in NSCLC, nuclear ER- α is low; *i.e.*, wild type ER- α is low. It is therefore thought that ER- β dominates estrogen signaling in NSCLC. On the contrary, a study by Stabile *et al*^[21] found that cytoplasmic ER- β is associated with a poorer prognosis. Interestingly, both ER- α and ER- β are associated with a poor prognosis in NSCLC when they are detected in the cytoplasm. This might be indicative of the non-genomic actions of ER variants.

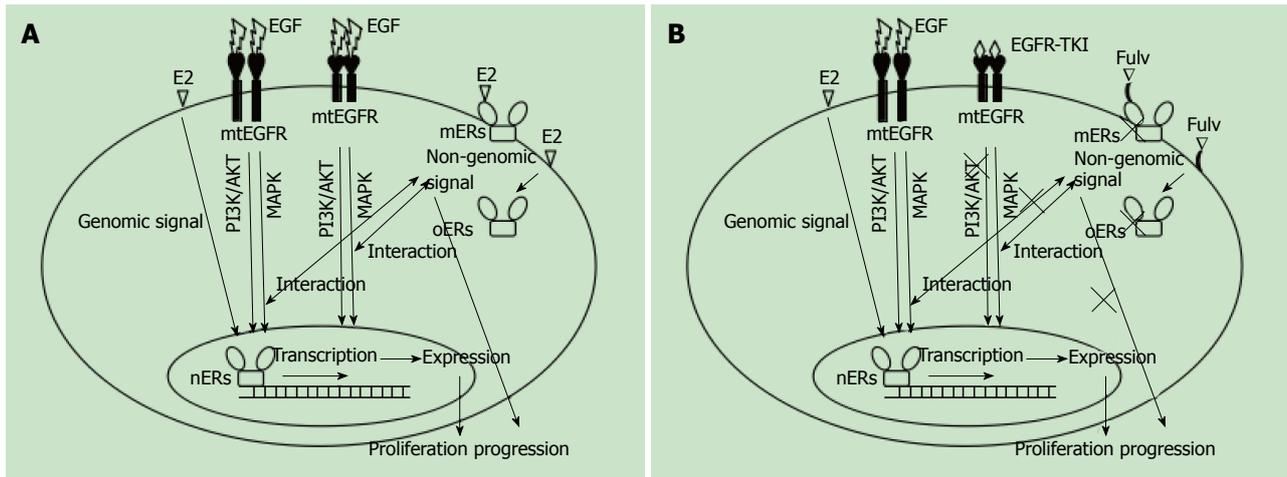


Figure 1 Intracellular estrogen receptor and epidermal growth factor receptor signaling pathway in non-small cell lung cancer. A: Mechanisms of ER and EGFR signaling in NSCLC. E2 (17 β -estradiol)-bound ER acts in part as a transcription factor in the nucleus. Once the ER binds to the DNA in the estrogen response element of a gene, it generally recruits co-activator complexes to modulate gene transcription (genomic signal). In addition, E2-bound ER also acts in the cytoplasm (non-genomic signal) by interacting with downstream mediators of EGFR signaling, such as MAPK and PI3K/AKT. EGFR is a cell membrane receptor tyrosine kinase that transmits a signal when it binds EGF; B: Mechanisms of combination therapy for NSCLC. The estrogen antagonist fulv binds to ERs and blocks estrogen signaling. EGFR-TKIs, such as gefitinib or erlotinib, bind to mtEGFR and inhibit EGFR signaling. Both treatments block the interaction between ER and EGFR signaling. EGFR: Epidermal growth factor receptor; ER: Estrogen receptor; TKI: Tyrosine kinase inhibitor.

THE ROLE OF ER VARIANTS IN CANCER CELLS

The role of ER variants in cancer cells has attracted much interest^[39-43]. It now appears that the oncogenic potential of ER variants derives from their ability to suppress the action of the normal hormone receptor, thereby acting as a dominant negative oncogene, or from their ability to activate hormone-responsive genes in a hormone-independent manner^[44]. ER has two functional domains: AF-1, which associates with a hormone-independent signaling pathway, and AF-2, which associates with a hormone-dependent pathway. Consequently, the oncogenic activity of an ER variant likely depends on specific site of its mutation.

In breast cancer, ER variants are often co-expressed with the wild type receptor, which can affect disease sensitivity to hormone therapy^[40,42]. For example, expression of the variant ER- α 36 affects estrogen signaling and is associated with tamoxifen resistance in breast cancer^[45]. In addition, the localization of ER variants in breast cancer cells reportedly differs from that of wild type ER^[42,46].

There has been very little study of ER- α variants in NSCLC, although they appear to be present, given the observed antibody-dependent variation in the ER positivity rate and intracellular localization. There have also been reports that the ER- β 1, 2 and 5 variants have distinct distributions within NSCLC cells and distinct effects on prognosis^[29]. However, there has been no analysis of the relationship between wild type ER- β and its variants, or their influence on estrogen signaling.

INTERACTION OF ASSOCIATED FACTORS WITH ER IN NSCLC

EGFR is a receptor tyrosine kinase involved in path-

ways leading to DNA synthesis and cell proliferation^[47]. Evidence suggests that ER interacts with one or more of the downstream mediators of EGFR signaling in NSCLC^[32,48-51], and that mutation of EGFR makes it susceptible to EGFR-tyrosine kinase inhibitor (EGFR-TKI), and thus a therapeutic target^[52,53]. The scheme of the interaction of between ER and EGFR signaling in NSCLC is shown in Figure 1A. It is well known that cancers usually become resistant to EGFR-TKI^[54], which raises the possibility that this drug resistance is related to the interaction between the EGFR and ER signals. For example, Stabile *et al.*^[32] showed that ER signaling is activated by EGFR-TKI in lung cancer cells, while EGFR signaling is activated by anti-estrogen drugs.

Other ER-related mediators include progesterone receptor (PR), androgen receptor (AR) and aromatase. The functional importance of PR and AR in NSCLC remains unknown because expression levels are very low. Aromatase catalyzes the synthesis of estrogen in adipose tissue, and is associated with endogenous estrogen expression in NSCLC^[15]. In addition, BRCA1 is a regulator of ER signaling in breast cancer^[55-57], and was also recently detected in NSCLC^[58-60]. Rosell *et al.*^[61] suggested that expression of BRCA1 and an EGFR variant carrying a T790M mutation (known as the EGFR-TKI resistant gene) is predictive of outcome and could provide the basis for alternative individualized treatment to patients with NSCLC. Although it is not yet clear whether BRCA1 is associated with ER in NSCLC, such an association could be a critical determinant of ER signaling in NSCLC.

NOVEL THERAPEUTIC STRATEGIES TARGETING ER AND EGFR IN NSCLC

Clinical trials of lung cancer treatments targeting ER and EGFR are currently ongoing^[62]. In these trials, fulvestrant,

an ER antagonist, is used in nearly all tests. Fulvestrant acts on ER, blocking its signal, irrespective of whether the receptor is localized in the nucleus, cytoplasm or cell membrane (Figure 1B)^[63]. It is therefore thought that fulvestrant would be effective, even in tamoxifen-resistant breast cancers^[64]. However, fulvestrant is a selective ER- α antagonist, and in one report fulvestrant acted to stabilize, and thus enhance, ER- β signaling^[63]. In NSCLC, extranuclear ER- α is a variant type thought to be involved in non-genomic signaling^[31], whereas ER- β is localized in the nucleus, where it exerts genomic effects and associates with a better prognosis^[9,11,14,18,20]. It is possible that the genomic signal mediated by ER- β is enhanced by fulvestrant's blocking of the non-genomic signal of the ER- α variant. Further studies will be needed to resolve the mechanism underlying the therapeutic effects by fulvestrant in NSCLC.

Erlotinib and gefitinib are two tyrosine kinase inhibitors used in the treatment of lung cancer. Erlotinib is used far more to target EGFR and, notably, the effects of both these medications may vary depending upon the race and/or gender of the patient. The intratumoral concentration of gefitinib reaches levels 40 times higher than that in blood^[65]. In other words, gefitinib is well distributed to the target tissue. By contrast, intratumoral concentrations of erlotinib are generally lower than its blood concentration^[65,66]. Nonetheless, erlotinib's IC50 for EGFR is more than 10 times lower than that of gefitinib^[67]. That is, the effective anti-EGFR dose of erlotinib is substantially lower than that of gefitinib. Clinical findings show that both drugs produce an effective response against mutant EGFR, but are less effective against wild type EGFR. To establish a combination therapy targeting both ER and EGFR signaling, development of an antagonist effective against wild type EGFR will be necessary. For example, if the intratumoral concentration of erlotinib could be increased without raising its blood concentration, it may be possible to enhance its antitumor effects without worsening its side effects. With that aim, the use of erlotinib with the angiogenesis inhibitor bevacizumab is being considered^[68]. In addition, because EGFR forms a heterodimer with HER-2, the use of the HER-2 inhibitor trastuzumab may be an effective approach to treatment. It may also be useful to consider the interaction of EGFR and/or ER with the ALK fusion protein, which is expressed exclusively with the variant receptors.

CONCLUSION

The role of ER in NSCLC is gradually becoming clearer. However, ER is involved in a complicated network through its interaction with a variety of mediators. In conventional immunohistochemical studies, wild type ER and its variants are handled similarly, but this may not be the best approach to future development of new strategies for treating NSCLC. Instead, it will be important to establish novel treatments based on the specific ER types

dominant in the particular lung cancer being treated, and to select the most effective drugs in that context.

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