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Estrogen Receptors Expression in Lung Cancer and Breast Cancer

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Abstract: ***Lung cancer in women has been increased recently and some research found that it was not related to smoking habit. Increasing lung cancer risk in women with early onset of menopause and hormonal contraception using more than five years. Those indicated a connection of female hormon to the development of lung cancer. Estrogen is one of steroid hormon classes related to reproductive organs in female. Effect of estradiol is mediated by ERα and ERβ. Both ER encoded by different gene, expressed to the same or different tissues in variated levels. Expression of ERα was mostly observed in breast cancer cells, while ERβ commonly found in normal breast. The absence of ERβ in knock out mice showed abnormality in lungs structure development and hypoxia. ERs expression was higher in NSCLC than normal lung tissues. ER expression highly connected with tumor differentiation. ERβ with strong full length expression in cytoplasm and nucleus. As ER probably indicate prognosis of breast cancer, in lung cancer overexpression of ERβ leads to poor prognosis in postmenopausal women and also agresive tumor. Furthermore the expression of ERα, ERβ along with EGFR mutation possibly as biomarker and prognostic markers for lung cancer as well as breast cancer.***

Keywords: estrogen receptor α, estrogen receptor β, lung cancer, breast cancer

1. Introduction

Lung cancer has been known to be in high cancer case worldwide and the greatest cause of cancer-related death. In 2012, the rate of lung cancer was 1.82 million new lung cancer cases (1.24 million men and 0.58 million women), it is increasing from 2002 estimates. Lung cancer in women has been increased recently and some research found that it was not related to smoking habit.[1] As the other, lung cancer also undergoing accumulation process of genetic changes, different signaling pathway, and not well functioned cell growth, survival, proliferation, and apoptosis. Study of non small cel lung carcinoma in Indonesia found 28% patients are women with the highest case is adenocarcinoma. Most of them are not related to cigarettes exposion or smoking habit.[2][3]

Case-control study to lung cancer women exhibited an increasing lung cancer risk in women with early onset of menopause and hormonal contraception using more than five years. Moreover,epidermal growth factor receptor (EGFR), Kirsten rat sarcoma viral oncogen homolog (KRAS), and TP53 mutation were found in non smoking women patient.[3]Mutation of EGFR was on exon 19 and exon 21.[4] In patient with EGFR mutation lung cancer also high expression of ERβ.[5] Those indicated a connection of female hormon to the development of lung cancer.[6][7][8]This article is about to discuss the estrogen receptor expression in breast cancer, well-known estrogen-related cancer, and lung cancer.

1) Estrogen receptorsregulation

Estrogen is one of steroid hormon classes related to reproductive organs in female. It consists of estrone (E1), stradiol (E2), and estriol.The most potent estrogen in circulatory is 17β-estradiol. Effect of estradiol is mediated by estrogen receptor α (ERα) and estrogen receptor β (ERβ). Furthermore estrogen also has known to take part in other organ function. ERα predominant on uterus, mamary glands, pituitary gland, skeletal muscle, adipose tissue, and bones. While ERβ has role in ovarium, prostate, lungs, cardiovascular system, and central nervous system.[9] ERα-related estrogen was important in premenopausal women. Then after entered menopause estrogen produced byperipheral estrogene-metabolizing enzim (EMEs), as aromatase, from androgen through ERβ.[10]

Both ER encoded by different gene, expressed to the same or different tissues in variated levels. Gene that express ERα located in cromosome 6, q24-27, with 595 amino acid. Gene that express ERβ (ESR2) located in cromosome 14, q22-24, with 530 amino acid. Interaction of 17β-estraiol with ER mediated by some location, such as membrane, mitochondria activities, and nuclear signaling.[9] In point mutant homozigous nucelear only estrogen receptor (NOER) knock in mice showed ER on nucleus was stronger than in wild-type mice. However some abnormalities were pointed in mice with depleted ER membrane such as hipoplastic utery, small ovarium with lack of corpora lutea, fail to ovulate, thin uterine epitelial, and established unsignificant effect to ovariectomy or E2 treatment. The absence of ER membrane lead to imbalance hypotalamic-pituitary-ovarian axis. Prolactin serum also decreased significantly, depletion of ductus branch and blunt trigemini ductus formation in mamary glands.[11]

17β-estradiol was notable increasing DNA-encoded mRNA, mitochondrial ATP synthesis subunit E, COVII, and other genes. Furthermore E2-ERα induce expression of Nuclear Respiratory Factor (NRF)-1 by direct interaction with nuclear DNA, then increase transcription TFAM and TFB2, nuclear-encoded gene, and also MRC gen in breast cancer and lung cancer models. E2-ER signal producing NRF-1 enhance mtDNA-encoded gene expression, mithocondrial biogenesis, and oxidative phosporilation. Those leads to ATP escalation, ROS production, manganese superoxide dismutase (MnSOD) activity and expression. Enhancement of superoxide products detoxified by MnSOD activities to prevent apoptosis.[9]

2) Estrogen Receptor Expression in Breast Cancer

Normal breast exhibited location of ERα and adrogen receptor (AR) in luminal epitelial cells. Meanwhile ERβ located in luminal and basal epitelial cells, stroma, fat cells, endothelial cells, and macrophages. ERα induce cell cycle and stimulate cell growth. Some studies using MCF-7 cell in vitro with suppressed ERα induced migration and invasion of cells through EGFR/ERK signaling pathway. ERβ was found to inhibit cell growth by mitigating cyclin D expression leads to G1 arrest. Overexpression of ERβ downregulated major DNA replication and cell cycle-related genes.[12]

Estrogen receptor endogen purified by rapid immunorecipitation mass spectometry of endogenous protein (RIME) from breast cell lines, MCF-7. Amount of 108 ER-related protein were found, including pioneer factor ER FoxA1, TLE1, and AP2-γ, ER putative factor like GATA3, known co-factor RIP140 (NRIP1), AIB1 (NCOA3), p300, CBP, and CARM1 and also RAR family. More than 25% of those proteins validated before to interact with ER. Then ER RIME was repeated to treated cell lines with estrogen 3 hour and tamoxifen 3 hour. Some proteins bind to ER after the treatment. Growht regulation by estrogen breast cancer (GREB1) was found as the most estrogen-ER-interacting protein. GREB1 was esstimated to stabilize classic active coactivator interaction in ER bound specific sites. Study using breast cancer found that not all ER+ breast cancer express ER-EGRB1 bound. ER+ breast cancer corelated with good clinical outcome.[13]

Expression of ERα was mostly observed in breast cancer cells.[14][15] In the other side, ERβ commonly found in normal breast. Hence low expression of ERβ leads to poor prognosis. ERβ was established to inhibit cell proliferation thwough MAPK and PI3K signaling pathway.[16][17] Overlapping binding region of ERβ1 and ERα influenced the effects of both receptors in MCF-7 cell lines. ERβ1 effects on ERα lower than the effect of ERα to ERβ1, thus ERβ1 would occupy new sites.[18] Some other studies discovered ERα potentially used as a good indicator for endocrine therapy and prognosis.[19] Patient with high ESR1 provided response to aromatase inhibitor therapy but more risk to first distand recurrance or late distant recurrence.[20][21]

3) Estrogen Receptor Expression in Lung Cancer

In lung cancer cells, ERβ expression were found in pneumosit and epitelial cell of bronchus. ERβ has function to maintain extracellular matrix in lungs. The absence of ERβ in knock out mice showed abnormality in lungs structure development and hypoxia.[22] Both ERs present in non small cell lung carcinoma (NSCLC) to mediate cell proliferation and prevent cell death.[23] ER positive staining pointed ER positive as yellow nucleus and brown granule. ER expression was higher in NSCLC than normal lung tissues. ER expression highly connected with tumor differentiation.[24]ERβ expression was higher in lung tumor patients.[25]Some studies detected ERs location in lung cancer, altough the results differ based on the method and antibody performed. ERα was found higher with epitope on C-terminus and in cytoplasm. Then ERβ with strong full length expression in cytoplasm and nucleus.[26]

Metastasis associated in lung adenocarcinoma transcript 1 (MALAT1) was upregulated in ER-positive breast cancer. ER target genes, PGR and CCND1, also overexpressedin MALAT1, which indicate MALAT1 function in ER expression in breast cancer. MALAT1 execute gene separation, gene expression and nucleus organization. MALAT1 also has a role in carcinogenesis including tumor cells, apoptosis, migration and metastasis.[27]Other than MALAT1, 27-hydricholesterol (27HC), a metabolite cholesterol, in human circulation also related to breast and lung cancer.Enzyme producing 27HC, CYP27A1, was invented higher in lung cancer. The cholesterol related to lung cancer proliferation in ERβ positive. 27HC effets mediated by PI3K-Akt signaling pathway, one of the downstream EGFR mediators. Mutasi EGFR berhubungan dengan estrogen pada kanker paru.[28]Those indicated the relation of ER in lung cancer and breast cancer.

As ER indicate prognosis of breast cancer, ER also investigated to be used as marker in lung cancer.Some studies found overexpression of ERβ leads to poor prognosis in postmenopausal women and also agresive tumor. ERβ1 was related to worse prognosis in women with stage I lung cancer and nuclear ERβ1 has possible link to poor survival in metastatic cancer, but not in the early stage.[29] EGFR mutation and ERα overespression associated with the lung cancer. ERα leads to good prognosis or not connected to prognosis.[22]A newest data established that ERα leads to worse prognosis and invasiveness in vitro.[30]

2. Conclusion

Expression of ER in lung cancer mostly nuclear and genome-related. There posibly a correlation between ER in lung cancer and breast cancer. Furthermore the expression of ERα, ERβ along with EGFR mutation highy possible to be biomarker and prognostic markers for lung cancer.

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