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Loss of ERbeta expression as a common step in estrogen-dependent tumor progression.

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Table 1: Relative expression of ER α and ER β in breast tumor progression.

Studies	Tissues	Number	Methods	ER α	ER β	Comments
				SQ Ov.	SQ Ov.	
Roger <i>et al.</i> (2001)	Normal	118	IHC	+	+++	ER β + cells decrease during pre-invasive tumor progression
	NP-BBD	18		+	++	
	P-BBD	37		++	++	
	P-BBDWA	13		++	+	
	CIS	25		++	+	
High grade CIS	35	++	-			
Iwao <i>et al.</i> (2000)	Normal	11	Real Time-PCR	++	+++	Changes in ER β 1 and ER β 2 mRNA levels in breast cancer.
	Cancer	112	+++	++		
Park <i>et al.</i> (2003)	Normal	89	ISH	/	+++	ER β mRNA level decreases during tumor progression. High ER β level associated with poor differentiation.
	BBT	11			+++	
	Breast Cancer	85			+	
	Met. lymph node	10			+	
Skliris <i>et al.</i> (2003)	Normal	138	IHC	/	++++	Reduced expression of ER β in invasive breast cancer. Loss of ER β may be a reversible process involving methylation.
	PDCIS	16			+++	
	Invasive cancers	319			++	
	Met. lymph node	31			+	
	Recurrences	8			+	
Speirs <i>et al.</i> (1999)	Normal	23	RT-PCR	+	+++	22% of normal breast expressing exclusively ER β mRNA. 50% of breast tumors coexpressing ER α and ER β .
	Cancer	60	+++	+		
Leygue <i>et al.</i> (1998)	Normal (adjacent tissues)	18	Multiplex RT-PCR	+	++	Increase in ER α and decrease in ER β during tumor progression.
	Cancer	18 (7ER- /11ER+)		++/+++	+	
Gustafsson <i>et al.</i> (2000)	Normal BBD	Total of 30 samples	RT-PCR Western-Blot, IHC	↑	↓	ER β is the predominant form in normal mammary gland.
Cancer						

Table 2: Relative expression of ER α and ER β in ovarian tumor progression

References	Tissues	Number	Methods	ER α SQ Ov.	ER β SQ Ov.	Comments	
Pujol <i>et al.</i> (1998)	Normal	6	Competitive RT-PCR	+	+++	ER α /ER β mRNA ratio increase during tumor progression	
	Cysts	24		+	+++		↑
	Borderline tumors	3		++	++		↓
	Cancers	10		++	+		
Brandenberger <i>et al.</i> (1998)	Normal	10	Northern Blot RT-PCR	++	++	ER β mRNA level decreases in cancer	
	Cancer	10		+++	+		↓
Rutherford <i>et al.</i> (2000)	Normal	9	RT-PCR	++	++	ER β mRNA and protein levels decrease in ovarian cancer and metastases	
	Primary cancer	8	Western Blot	++	+		↓ ↓
	Met cancer	8		+++	-		↓ ↓

Table 3: Relative expression of ER α and ER β in prostate tumor progression

References	Tissues	Number	Methods	ER α SQ Ov.	ER β SQ Ov.	Comments	
Latil <i>et al.</i> (2001)	Normal Cancer	4 23	Real- Time RT-PCR	++ + to ++	+++ +	↓	Decreased expression of ER β mRNA in the hormone-resistant group
Pasquali <i>et al.</i> (2001a)	Normal Cancer	5 10	IHC	/	+++ +	↓	ER β protein expression decreases in cancer
Pasquali <i>et al.</i> (2001b)	Normal Cancer	6 5	RT-PCR Western blot	++	++	↓	ER β mRNA expression decreases in cancer
				++	+		
Horvath <i>et al.</i> (2001)	Normal Hyperplasia Cancer	5 157	IHC	/	+++	↓	Loss of ER β protein expression during tumor progression
		159			- or + - or +		
Leav <i>et al.</i> (2001)	Dysplasia	Total of 50 samples	IHC RT-PCR	-	+	↔ ↔	Decrease in ER β protein and mRNA expression in high grade dysplasia and carcinoma.
	- moderate grade			-	-		
	- high grade			-/+	+		
	- grade III			-/+	-/+		
- grade IV/V	-	+					
- grade IV/V							
Metastasis							
	HGPIN	47	IHC mono- clonal antibody	/	+++	↓	ER β protein expression decreases during tumor progression. ER β expression higher in Gleason grade IV than in grade III and V
	Adenocarcinoma						
	Gleason grade:						
	III	17			+		
IV	29	++					
V	14	+					
Metastatic	12	+					

Table 4: Relative expression of ER α and ER β in colon tumor progression

References	Tissues	Number	Methods	ER α SQ Ov.	ER β SQ Ov.	Comments
Campbell- Thompson <i>et al.</i> (2001)	Normal cancer	26 26	RT-PCR Southern	+ + \leftrightarrow	+++ + \downarrow	ER β 1 and ER β 2 mRNA expressions decrease in cancer
Foley <i>et al.</i> (2000)	Normal Cancer	11 11	RT-PCR Western	+ + \leftrightarrow	+++ + \downarrow	Decrease ER β protein but not mRNA expression in cancer. Post-transcriptional mechanism?

The number of + indicates the ERs relative expression. The arrows indicate a decrease (\downarrow), an increase (\uparrow) or no variations in expression (\leftrightarrow) between normal and cancer tissues. SQ= semiquantitative, Ov= overall trends, BBD= Benign Breast Disease, NP-BBD= Non Proliferative BBD, P-BBD= Proliferative BBD, P-BBDWA= Proliferative BBD with atypia, BBT= Benign Breast Tumors, CIS= carcinoma *in situ*, HGPIN= High grade prostatic intraepithelial neoplasia, IHS= *in situ* hybridization, IHC= immunohistochemistry, Met= metastatic, RT-PCR= reverse transcription polymerase chain reaction

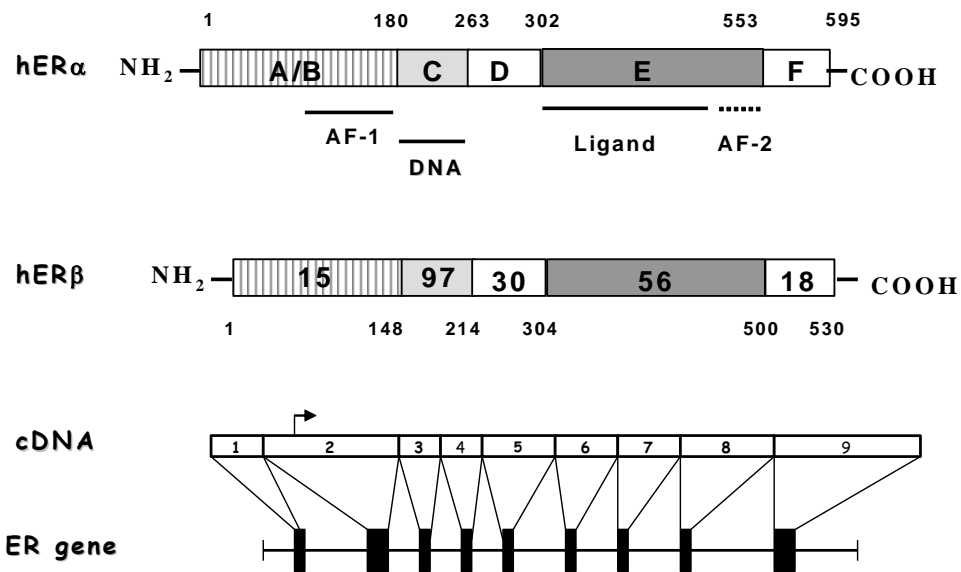


Figure 1 Schematic representation of the structure of human ER α and ER β nuclear receptors. The A/B domain at the NH₂ terminal contains the ligand independent transcriptional-activation function AF-1, the C domain represents the DNA-binding-domain, D corresponds to the hinge region, E domain contains the hormone binding domain and the hormone-dependent transcriptional-activation function AF-2. Numbers outside each box refer to amino acid number whereas the number inside each box of ER β refers to the percentage of amino acid identity. The arrow indicates the translation starting site in ER cDNA.

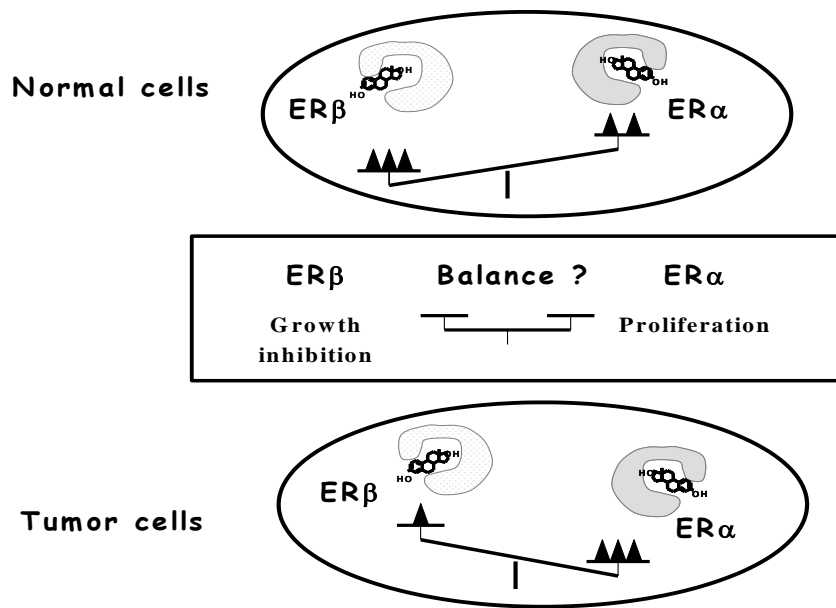


Figure 2 Schematic representation of ER α and ER β imbalance in estrogen dependent tumor progression

Hypothetical mechanism of antiproliferative effect of ER β

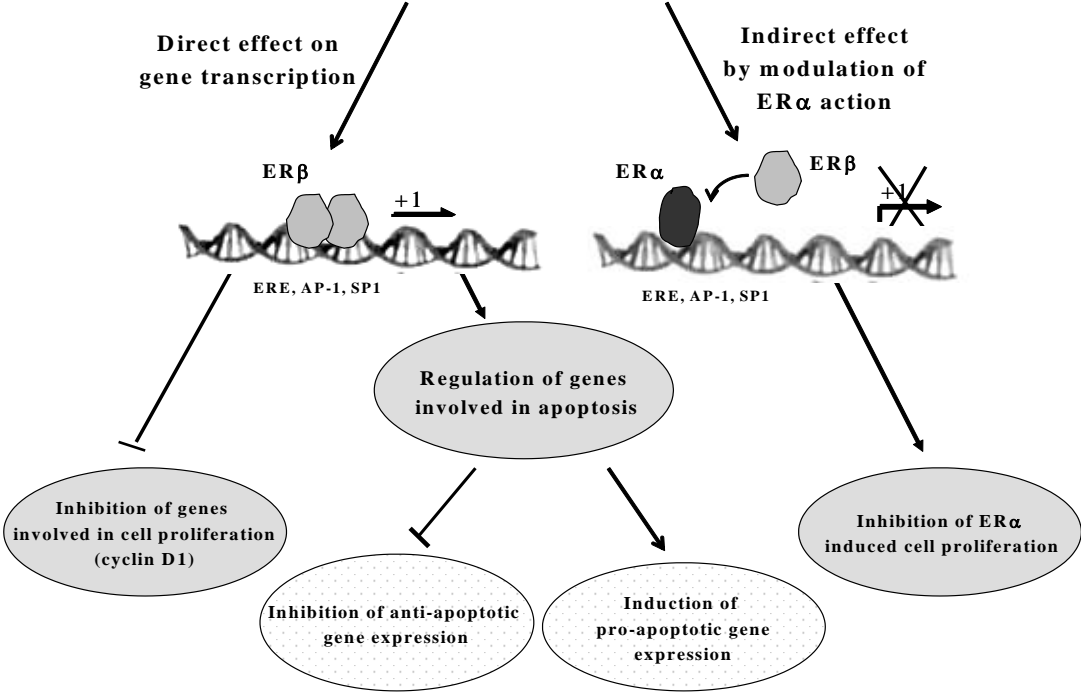


Figure 3 Hypothetical mode of ER β action on cell proliferation pathways.