



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

Allison Bardin, Nathalie Boulle, Gwendal Lazennec, Françoise Vignon, Pascal
Pujol

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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 Cancer	Total of 30 samples	RT-PCR Western- Blot, IHC			ER β is the predominant form in normal mammary gland.

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	++	+	
	Met cancer	8	Blot	+++	-	

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	5 157 159	IHC	/	+++ - or + - or + ↓	Loss of ER β protein expression during tumor progression
Leav <i>et al.</i> (2001)	Dysplasia - moderate grade - high grade Carcinoma - grade III - grade IV/V Metastasis	Total of 50 samples	IHC RT-PCR	- - ↔ -/+ -/+ -	+ - ↔ + -/+ +	Decrease in ER β protein and mRNA expression in high grade dysplasia and carcinoma.
Fixemer <i>et al.</i> (2003)	HGPIN Adenocarcinoma Gleason grade: III IV V Metastatic	47 17 29 14 12	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

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

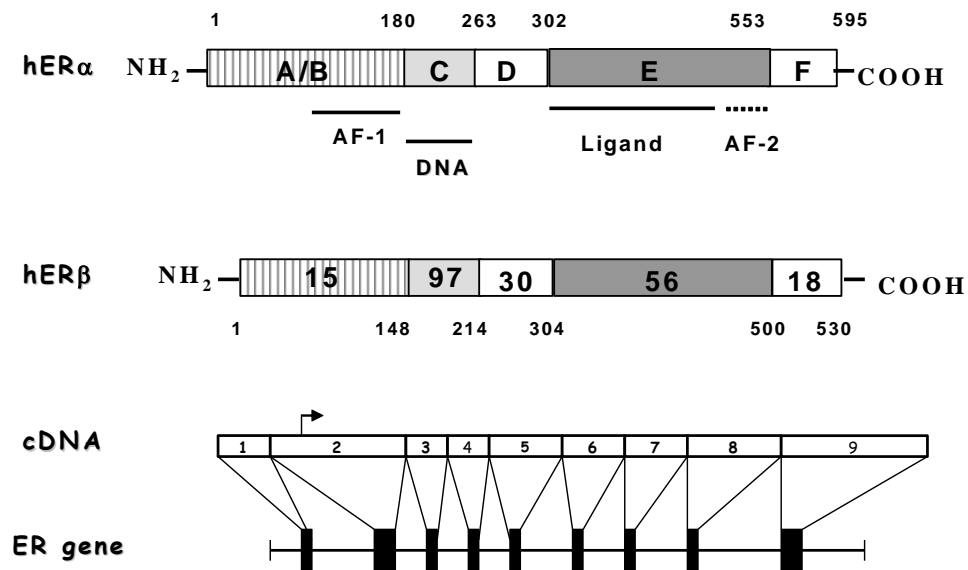


Figure 1 Schematic representation of the structure of human ERα and ERβ nuclear receptors. The A/B domain at the NH₂ terminal contains the ligand independent transcriptional-activation function AF-1, the C domain represents the DNA-binding-domain, D corresponds to the hinge region, E domain contains 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 ERβ refers to the percentage of amino acid identity. The arrow indicates the translation starting site in ER cDNA.

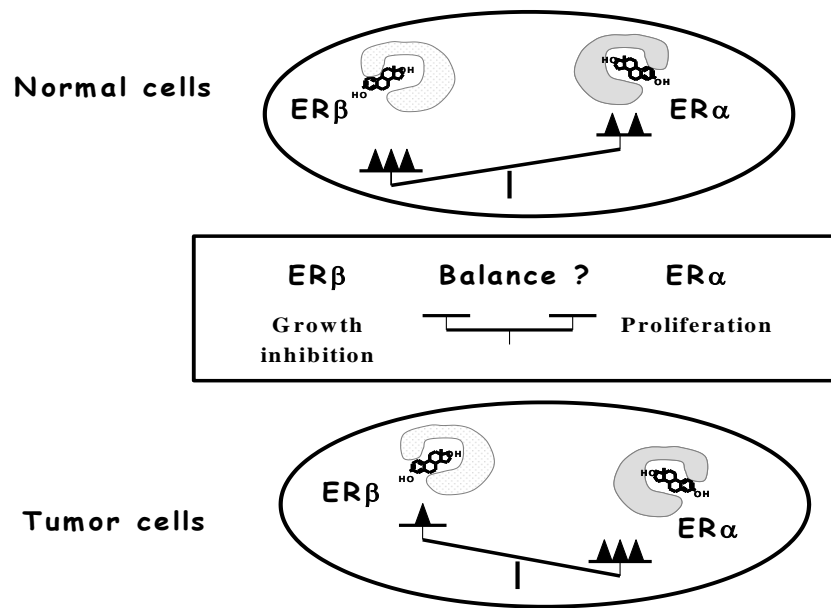


Figure 2 Schematic representation of ER α and ER β imbalance in estrogen dependent tumor progression

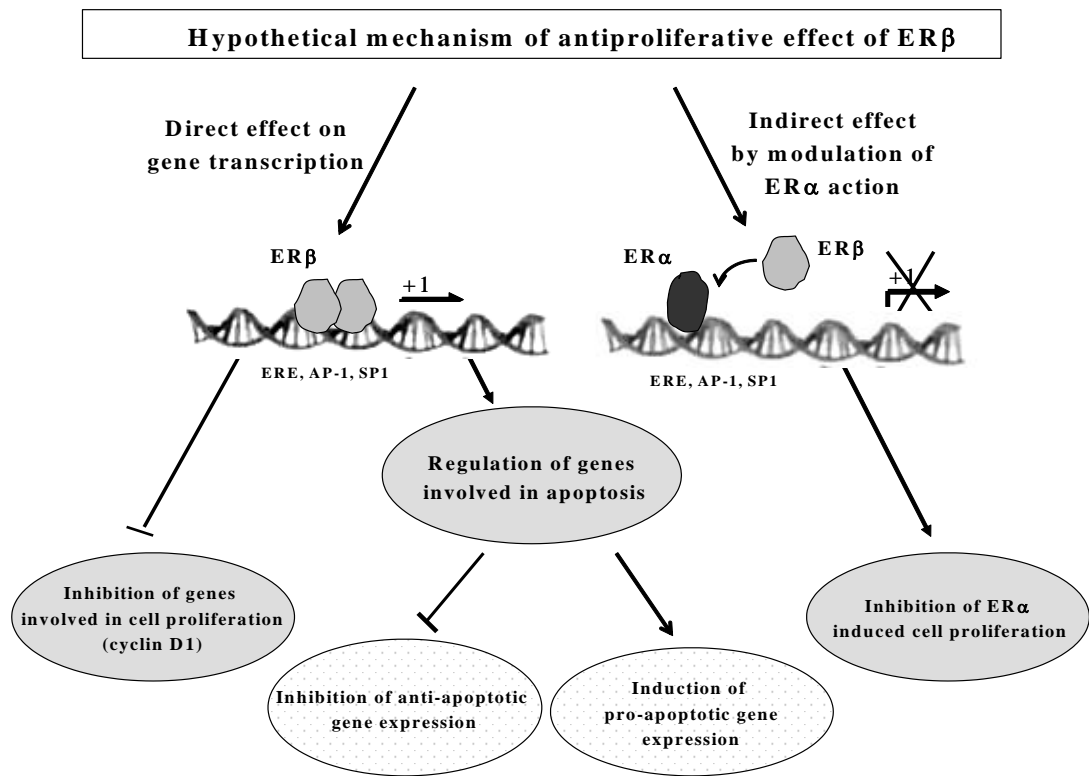


Figure 3 Hypothetical mode of ER β action on cell proliferation pathways.