

# Chaperone-related immune dysfunctions: an emergent property of distorted chaperone-networks

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Supplementary Table. Involvement of Hsp90-interacting proteins in immune function<sup>a</sup>

Name of human homolog	Hsp90-interacting yeast gene	Type of interaction <sup>b</sup>	Immune-related effect of human homolog	Refs <sup>c</sup>	Refs <sup>d</sup>
<b>Modulators of the immune response</b>					
ADA2	<i>YDR448W</i>	gs (0.25)	Growth factor for unspecific immune activation	[1]	
AKT			Involved in T cell activation	[2]	HIT
ARF1	<i>YDL192W</i>	sga (0.25)	Recruitment to lymphocyte Golgi apparatus	[3]	
ASK1	<i>YKL052C</i>		Apoptosis signal-regulating kinase 1, involved in Toll-like receptor-mediated innate immunity and HIV action	[4,5]	HIT
ATF1	<i>YOR377W</i>	2h (0.25)	Transcription factor modulating HTLV infection	[6]	[7]
BGGP	<i>YJR086W</i> and <i>YOR212W</i>		Free $\beta\gamma$ subunit of G protein, involved in lymphocyte chemotaxis	[8]	HIT
BRAF	<i>YLR362W</i>		B-Raf, serine/threonine kinase involved in B and T cell signaling	[9,10]	HIT
CAM	<i>YBR109C</i>		Calmodulin, involved in lymphocyte activation	[11]	HIT
CAT2	<i>YML042W</i>	2h (0.25)	Macrophage cationic amino acid transporter	[12]	
CDC37	<i>YDR168W</i>	tap (0.25)	Kinase-specific co-chaperone of Hsp90 for T cell kinases	[13]	HIT
CDK4			Involvement in B cell, T cell and macrophage proliferation	[14–16]	HIT
CDK6			Involvement in B and T cell proliferation	[17,18]	HIT
CDK9			Involvement in T and B cell proliferation and HIV action	[19,20]	HIT
CHIP			Ubiquitin ligase regulating antigen cross-presentation	[21]	HIT
CHP1			NOD1-modulating protein in its Hsp90 complex	[22]	HIT
CNA2	<i>YML057W</i>		Calcineurin, involved in T lymphocyte activation	[23]	HIT
CSF1	<i>YLR087C</i>	tap (0.25)	Macrophage colony-stimulating factor	[24]	[25]
CYP40	<i>YHR057C</i>		Receptor of cyclosporine A and regulator of steroid action	[26]	HIT
ERG2	<i>YMR202W</i>	gs (0.25)	Binding protein for the immunosuppressive agent SR31747a	[27]	
FES			src-type kinase involved in the regulation of inflammation and innate immunity	[28]	HIT
FGR			src-type kinase involved in the regulation of natural immunity	[29]	HIT
FIS1	<i>YIL065C</i>	sga (0.25)	Involvement in mitochondrial fission of T cells	[30]	
FKBP51			Regulator of glucocorticoid action	[31]	HIT
FKBP52			Regulator of glucocorticoid action and IL-12 secretion	[32]	HIT
FLT3			Cytokine receptor, role in dendritic cell and B lymphocyte development and function	[33]	HIT
FPS			src-type kinase involved in the regulation of inflammation and innate immunity	[28]	HIT
GRK2			G-protein-coupled receptor kinase, involvement in chemokine signaling of T cells	[34]	HIT
HCR1	<i>YLR192C</i>	sga (0.25)	Human complement receptor-1	[35]	
HDAC6	<i>YNL021W</i>		Histone deacetylase, involved in organization of the immunological synapse and in HIV infection	[36,37]	HIT
HSD1	<i>YOR311C</i>	sga (0.25)	Hydroxysteroid dehydrogenase involved in T lymphocyte regulation	[38]	[39]
IKK			Inhibitory $\kappa$ B kinase, involved in the survival and activation of lymphocytes and macrophages and in inflammatory response	[40]	HIT
IRAK1			Interleukin-1 receptor-associated serine/threonine kinase 1, involved in innate immunity signaling	[41]	HIT
IRE1	<i>YHR079C</i>		Inositol-requiring enzyme-1, involved in B cell differentiation	[42]	HIT
KSR			Scaffolding molecule kinase suppressor of Ras involved in T cell activation	[43]	HIT
LCK			src-type kinase involved in T cell signaling	[44]	HIT

MEK	<i>YOR351C</i>		Mitogen-activated protein kinase, involved in lymphocyte activation	[45]	HIT
MEKK1	<i>YJL095W</i>	sga (0.25)	Mitogen-activated protein kinase kinase kinase 1, involved in T cell and macrophage activation	[46,47]	HIT
MEKK3	<i>YLR362W</i>		Mitogen-activated protein kinase kinase kinase 3, involved in T cell regulation	[48]	HIT
MHC5	<i>YOR306C</i>	gs (0.25)	Caspase-8 involved in lymphocyte apoptosis	[49]	[50]
MIR1	<i>YGL035C</i>	sga (0.25)	Ubiquitin ligase for immune recognition-related molecules MHC-1, B7-2, ICAM-1	[51]	
MLK3			Mixed-lineage kinase 3, involved in T cell signaling	[52]	HIT
NIK			NF- $\kappa$ B-inducing kinase, involved in B and T cell activation	[53,54]	HIT
NKCC1	<i>YBR235W</i>		Na-K-Cl cotransporter 1 involved in T lymphocyte activation	[55]	HIT
NOD1			Participates in mammalian innate immune response	[22]	HIT
N-WASP			Wiskott-Aldrich syndrome (a rare X-linked primary immunodeficiency) homologous protein, involved in T lymphocyte actin signaling	[56]	HIT
P2X7			Proinflammatory purinergic receptor involved in T cell and macrophage activation	[57,58]	HIT
PKD1			Phosphoinositide-dependent kinase 1, involved in T cell-development and signaling	[59,60]	HIT
PER1	<i>YCR012W</i>	gs (0.5)	Circadian clock gene in human PBLs	[61]	
PGK1	<i>YCR012W</i>	tap (0.25)	Genetic linkage to X-linked SCID	[62]	
PIM1			Serine/threonine kinase involved in T cell signaling	[63]	HIT
PKR	<i>YMR123W</i>		dsRNA-dependent kinase, involved in antiviral response, innate immunity against viruses and bacteria, and inflammatory response	[64-66]	HIT
PLK1			Polo-like kinase 1, involved in HIV signaling	[67]	HIT
PPT2	<i>YGR123C</i>	2h + tap (0.5)	Palmitoyl protein thioesterase at the MHC class III locus with a cytokine receptor domain	[68]	
PPT5			NOD1-modulating protein in its Hsp90 complex	[22]	HIT
RAF1	<i>YLR362W</i>		Raf-1, serine/threonine kinase involved in B and T cell signaling	[10,69]	HIT
RIP			Death domain kinase, involved in T cell apoptosis and development	[70]	HIT
SHP1	<i>YBL058W</i>	sga (0.25)	Participates in chemokine signaling	[71]	
SKP1			Ubiquitin ligase, involved in chromosome segregation	[72]	HIT
SNF1	<i>YDR477W</i>	sga (0.25)	Protein kinase of hematopoietic cells	[73]	
SNF2	<i>YOR290C</i>	sga (0.25)	DNA helicase necessary for peripheral T lymphocyte proliferation	[74]	[75]
SRA			Macrophage scavenger receptor involved in host defense	[76]	HIT
SST2	<i>YLR452C</i>	sga (0.25)	Interleukin-1 receptor-like protein	[77]	
STAT3			Involvement in B and T cell proliferation	[78]	HIT
TAK1			Transforming growth factor- $\beta$ -activated kinase 1 involved in T cell and macrophage activation	[79,80]	HIT
TBK1			TANK-binding kinase-1 involved in innate immunity signaling	[81]	HIT
TERT	<i>YLR318W</i>		Telomerase, involved in regulation of cellular proliferation, senescence and lifespan	[82,83]	HIT
TLR4/MD2			Toll-like receptor-4 myeloid differential protein-2 involved in innate immunity	[84]	HIT
TRKB			Neurotrophin receptor B, involved in T lymphocyte development	[85]	HIT
VCP	<i>YLL034C</i>		Valosin-containing protein, becomes Tyr-phosphorylated after T cell activation and regulates cytokine transcription via T cell-specific adapter protein	[86]	HIT
WEE1	<i>YJL187C</i>		Tyrosine kinase regulating T cell mitosis	[87]	HIT
YES			src-type kinase involved in T cell signaling	[88]	HIT
<b>Role in autoimmune diseases</b>					
ADA2	<i>YDR448W</i>	gs (0.25)	Serum activity closely correlates with juvenile rheumatoid arthritis and systemic lupus erythematosus	[89]	
AKT			PKB, involved in the regulation of autoimmunity	[90]	HIT
GRK2			G-protein-coupled receptor kinase, involved in chemokine signaling of autoimmune responses	[91]	HIT
NIK			NF- $\kappa$ B-inducing kinase, involved in autoimmune signaling	[92]	HIT
P2X7			Proinflammatory purinergic receptor involved in apoptosis in systemic lupus erythematosus	[93]	HIT
PKR	<i>YMR123W</i>		dsRNA-dependent kinase, involvement in the autoimmune response in systemic lupus erythematosus	[94]	HIT
PPAR $\gamma$			Inhibitor, autoimmune response	[95]	HIT
RAF1	<i>YLR362W</i>		Raf-1, serine/threonine kinase, autoantigen in Menière's disease	[96]	HIT
SSA2	<i>YLL024C</i>	tap (0.25)	Part of the autoimmune Ro ribonucleoprotein complex	[97]	
TRNAS			Macromolecular His-tRNA-synthetase complex, autoantigen in myositis	[98]	HIT
VCP	<i>YLL034C</i>		Valosin-containing protein, autoantigen in primary biliary cirrhosis	[99]	HIT
AKT			Involved in the development of T and B lymphomas	[100]	HIT
APAF1			Apoptotic protease-activating factor-1 involved in B cell lymphoma survival	[101]	HIT
AUR2			Aurora kinase, involved in the development of B lymphomas	[102]	HIT
BCR-ABL			Tyrosine kinase involved in chronic myelogenous leukemia	[103]	HIT

BRAF	YLR362W		B-Raf, serine/threonine kinase involved in lymphomas and leukemias	[104]	HIT
CDC37	YDR168W	tap (0.25)	Hsp90 co-chaperone oncogene, overexpression in lymphomas	[105]	HIT
CDH1	YGL003C	sga (0.25)	E-cadherin involved in lymphoma development	[106]	
CDK4			Involvement in the development of leukemias and lymphomas	[16]	HIT
CDK6			Involvement in the development of leukemias and lymphomas	[16]	HIT
CDK9			Involvement in the development of lymphomas	[20]	HIT
CHIP			Regulator of nucleophosmin-anaplastic lymphoma kinase	[107]	HIT
CHK1	YBR274W		Checkpoint kinase 1, plays a role in the development of lymphoid tumors	[108]	HIT
CK2	YIL035C		Casein kinase II involved in lymphoma development	[109]	HIT
CSRC			Tyrosine kinase involved in lymphomas and leukemias	[110]	HIT
ENOS	YPR048W		Endothelial nitric oxide synthase involved in lymphoma survival	[111]	HIT
ERBB2			Mutant EGF receptor, involved in lymphoma development	[107]	HIT
FES			src-type kinase involved in lymphomas and leukemias	[112]	HIT
FGR			src-type kinase involved in lymphomas and leukemias	[113]	HIT
FLT3			Cytokine receptor, role in the antitumor response of dendritic cells	[114]	HIT
FPS			src-type kinase involved in in lymphomas and leukemias	[115]	HIT
HIF1			Hypoxia inducible factor, helps lymphoma survival	[116]	HIT
HIF2			Hypoxia inducible factor, helps lymphoma survival	[116]	HIT
IKK			Inhibitory $\kappa$ B kinase, involved in apoptosis regulation in leukemias and lymphomas	[40]	HIT
LCK			src-type kinase involved in T cell lymphomas	[117]	HIT
LEU1	YGL009C	tap (0.25)	Alternatively spliced in B cell leukemia	[118]	
MDM2			Oncogene, involved in leukemia and lymphoma development	[119]	HIT
MEK	YOR351C		Mitogen-activated protein kinase, involved in leukemia development	[120]	HIT
MLK3			Mixed-lineage kinase 3, involved in T cell leukemias	[52]	HIT
MTG8			A chimeric oncogene of AML1-MTG8 is generated in acute myelogenous leukemia	[121]	HIT
NALK			Nucleophosmin-anaplastic lymphoma kinase involved in lymphoma development	[101,103]	HIT
P2X7			Proinflammatory purinergic receptor involved in the development of B cell leukemia	[122]	HIT
PIM1			Serine/threonine kinase involved in lymphoma development	[123]	HIT
PKR	YMR123W		dsRNA-dependent kinase, involvement in Burkitt's lymphoma	[124]	HIT
PLK1			Polo-like kinase 1, involved in lymphomas and B cell malignancies	[125]	HIT
SAP30	YMR263W	sga (0.25)	Part of transcriptional repressor complex involved in lymphomas	[126]	
SIN3	YOL004W	sga+gs (0.5)	Part of transcriptional repressor complex involved in lymphomas	[126]	
SIP			Interacts with and modulates the function of the SIAH-1 tumor suppressor in T lymphomas	[127]	HIT
SKP2			F-box protein, p27(Kip1) ubiquitin ligase, involved in lymphoma development	[128]	HIT
STAT3			Helps tumor cells to evade immune attack	[129]	HIT
SURV			Survivin, involved in leukemia and lymphoma development	[130]	HIT
TERT	YLR318W		Telomerase, involved in B and T cell lymphomas	[131,132]	HIT
VEGFR2			Vascular endothelial growth factor receptor-2 involved in B cell chronic lymphocytic leukemias and T lymphomas	[133,134]	HIT

<sup>a</sup>The Hsp90-interacting yeast genes and the type of interaction are from Ref. [135]. Human and yeast homologues were found using the [www.yeastgenome.org](http://www.yeastgenome.org) database and Ref. [136]. The immune-related effects of human homologues are from PubMed. References for the interaction of human homologues with Hsp90 were from PubMed.

<sup>b</sup>The interaction types 2h, gs, sga, tap denote yeast two-hybrid experiments (2h), genetic screens for geldanamycin-hypersensitive strains (gs), synthetic lethal and synthetic slow-growth strains with a defective Hsp90 allele (sga) and tandem affinity purification-(TAP)-tagged affinity chromatographic proteome experiments (tap), respectively. The numbers in parentheses refer to the connection probability. For further details, see Ref. [135].

<sup>c</sup>Reference numbers for the immune related effect.

<sup>d</sup>Reference numbers for Hsp90 interactions. HIT refers to the Hsp90-interactor Table (version 06/2005) downloaded from <http://www.picard.ch/downloads/Hsp90interactors.pdf>. The original references for these interactions can be found in Refs [137–144] and at <http://www.picard.ch/downloads/Hsp90facts.pdf>.

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