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Supplementary Information

Inhibition of JAK-STAT signaling with baricitinib reduces inflammation and improves cellular homeostasis in progeria cells

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Table S1 (Supplementary Dataset File 1). Excel file of the list of genes associated with vascular disease, arthritis, lipodystrophy and alopecia derived from the text mining analysis.

Table S3 (Supplementary Dataset File2). Excel file of the identified list of transcription factors that regulate the 17 genes derived from text mining.

Table S2: Differential regulation of the 17 genes altered in all four conditions. Vascular disease (VD), arthritis (AR), lipodystrophy (LD) and alopecia (AL). The level of expression according to curated literature (↑ = overexpressed; ↓ = downregulated) in of each gene in each disease is indicated.

Gene (swiss-prot gene ID)		**Expression**	**Function**
PPARγ (receptor) ID: 5468	**VD**	↓[1]	Protects endothelia, regulates the differentiation of adipocytes and lipid metabolism, inhibits proliferation and the migration of smooth muscle cells, and reduces inflammatory chemokines [1].
	AR	↓[2]	Inhibits major signaling pathways of inflammation and reduces the synthesis of cartilage catabolic factors responsible for articular cartilage degradation [3].
	LD	↓[4]	Essential in the differentiation of adipocytes [5].
	AL	↓[6]	Required for the maintenance of a functional epithelial stem cell compartment in murine hair follicles [7].
CCL2 (chemokine) ID: 6347	**VD**	↑[8]	Recruits macrophages and monocytes to the vessel wall [9].
	AR	↑[10]	Mediator of the migration of monocytes, macrophages and T cells. These are directly involved in the induction and perpetuation of synovitis and subsequent joint destruction [10].
	LD	↑[11]	Recruits macrophages to adipose tissue and induces an inflammatory response [12].
	AL	↑[13]	Recruits monocytes and lymphocytes T in the acute inflammatory condition and it may also be an important mediator in chronic inflammation [14].
TGFβ1 (growth factor) ID: 7040	**VD**	↑[15]	There is a link between increased levels of circulating TGFβ and hypertension, a cardiovascular risk factor which contributes to the development of organ damage such as renal sclerosis, stroke, and coronary heart disease [16].
	AR	↑[17]	Transforming growth factor beta1 (TGFbeta1) has been reported to have important roles in unresolved inflammation, immune suppression, fibrosing processes, and angiogenesis [18].
	LD	↑[19]	Potent inhibitor of adipocyte differentiation [19].
	AL	↑[20]	Influences the epithelial cell growth, and modulates androgen receptor transactivation and androgen sensitivity in dermal papilla cells [20].
CXCL8 (Chemokine) ID: 3576	**VD**	↑[21]	Stimulates the adhesion of monocytes to endothelial cells, and has a role in plaque destabilization [22,23].
	AR	↑[24]	Induces synovial inflammation, regulates leukocyte adhesion molecule expression, and it is a mediator of angiogenesis [25].
	LD	↑[26]	Major regulator of adipose tissue metabolism. Its overexpression in subcutaneous adipose tissue may be associated with wasting processes that lead to atrophy [26,27].
	AL	↑[28]	Plays a role in perturbing keratinocyte differentiation in the AA follicle [29].
ICAM1 (adhesion molecule) ID: 3383	**VD**	↑[30]	Key molecule in atherogenesis, when circulating monocytes adhere to the endothelium and subsequently transmigrate into the intima [31].
	AR	↑[32]	Promotes leukocyte adhesion to endothelial cells and synovial fibroblasts, and promotes leukocyte migration [33].

	LD	↑[34]	UNKNOWN
	AL	↑[35]	Together with gamma interferon mediates T cell trafficking in the skin [36].
CRP (pentraxin) ID: 1401	**VD**	↑[37]	Directly influences complement activation, apoptosis, vascular cell activation, monocyte recruitment, lipid accumulation and thrombosis. Associated with the formation and progression of atherosclerotic lesions [38,39].
	AR	↑[40]	Plays a role in the bony destructive process through the induction of RANKL expression and direct differentiation of osteoclasts precursors into mature osteoclasts [41].
	LD	↑[42]	Its levels are strongly associated with adipose tissue mass [43].
	AL	↑[44]	UNKNOWN
C3 (Chemokine) ID: 718	**VD**	↑[45]	Essential in the maturation of atherosclerotic lesions beyond the foam cell stage [46].
	AR	↑[47]	Contributes to inflammation and tissue injury. Has a role in the induction and progression of the disease [47].
	LD	↓[48]	Excessive consumption of C3 in the alternative complement pathway leads to an increased expression of Factor D. Lipodystrophy and tissue destruction are more significant in tissues where Factor D expression is increased [49,50].
	AL	↑[51]	C3 deposition reflects the morphological state of hair follicles in each stage of the hair cycle, suggesting a relationship between the hair cycle and C3 deposition [52].
TRAF1 (tumor necrose factor associated) ID: 7185	**VD**	↑[53]	Involved in monocyte recruitment to the vessel wall [54].
	AR	↑[55]	Plays a crucial role in the pathogenesis of autoantibodies and may serve as a serologic inflammatory marker of disease activity [55].
	LD	↑[56,57]	UNKNOWN
	AL	↑[58]	UNKNOWN
IL18 (Interleukin) ID: 7185	**VD**	↑[59]	Has a proatherogenic effect through stimulation of IFN-γ secretion. It polarizes T helper 1 cells and induces the production of inflammatory cytokines, chemokines, and vascular adhesion molecules [60,61].
	AR	↑[62]	Promotes articular Th1 responses, acts directly on macrophages to induce proinflammatory cytokine production, and contributes to cartilage degradation [63].
	LD	↑[64]	Induces apoptosis of subcutaneous adipocytes in lipoatrophic areas, and it contributes towards HALS by downregulating the production of adiponectin [64,65].
	AL	↑[66]	Induces the production of IFN-γ, a factor that induces alopecia [67].
IGF1 (growth factor) ID: 3479	**VD**	↓[68]	Reduces atherosclerosis burden and improves features of atherosclerotic plaque stability through induction of the reduction of oxidative stress, cell apoptosis, proinflammatory signaling, and endothelial dysfunction [68].
	AR	↓[69]	Enhances the synthesis of components such as proteoglycan and collagen in normal cartilage, and blocks cytokine-stimulated cartilage degradation. It is an important regulator of the repair processes during joint diseases [70,71].

	LD	↓[72]	IGF1 signaling is essential for the development and function of adipose tissue. The IGF1 receptors play a role in gene expression in white adipose tissue and in the maintenance of normal serum leptin and adiponectin levels [72].
	AL	↓[73]	Stimulates follicular epithelial cell growth [74].
IL6 (Interleukin) ID: 3569	**VD**	↑[75]	Plays a central role in propagating the downstream inflammatory response responsible for atherosclerosis. Contributes to both atherosclerotic plaque development and plaque destabilization [76,77].
	AR	↑[78]	Contributes to the induction and maintenance of the autoimmune process through B cell modulation and Th17 cell differentiation, and it plays a role in angiogenesis by inducing intracellular adhesion molecules [79].
	LD	↑[80]	Leads to increased apoptosis and thus contributes to the loss of subcutaneous fat [81].
	AL	↑[82]	Induces a rise in immunoglobulin G which can have a key role in long-standing disease due to humoral autoimmune pathology, and plays a partial role in hair growth inhibition [82,83].
TNFα (tumor necrosis factor) ID: 7124	**VD**	↑[84]	Promotes cholesterol uptake into monocytes and macrophages and cholesteryl ester-laden cell formation from differentiating monocytes, resulting in foam cell accumulation; it is involved in the production of chemokines and in the recruitment of leucocytes during inflammatory reactions; induces VSMCs proliferation; increases adherence of leucocytes to endothelial cells by inducing the expression of cell adhesion molecules; stimulates apoptosis of VSMCs; and it can induce autophagy in plaque VSMCs [84-86].
	AR	↑[87]	Stimulates the production of cytokines, chemokines and prostaglandins in RA synovium; stimulates the production of matrix-degrading enzymes like MMPs; leads to an increase of the destructive potential of RASF; induces the expression of RANKL and synergizes with RANKL to directly promote osteoclast differentiation; and stimulates bone loss by mobilizing $CD11b^{+}$ osteoclast precursors from the bone marrow and by reducing bone formation by inhibiting osteoblast differentiation and function [88-90].
	LD	↑[91]	Stimulates lipolysis; induces insulin resistance, leptin production, suppression of lipogenesis, adipocyte dedifferentiation, and apoptosis in preadipocytes and adipocytes; and impairs preadipocyte differentiation [92,93].
	AL	↑[94]	Causes the condensation and distortion of the dermal papilla, marked vacuolation of the hair follicle matrix, abnormal keratinization of the follicle bulb and inner root sheath, disruption of follicular melanocytes and the presence of melanin granules within the dermal papilla, resulting in the formation of dystrophic anagen hair follicles [95,96].
HMOX1 (oxygenase) ID: 3162	**VD**	↓[97]	Its expression in macrophages increases antioxidant protection and decreases inflammatory components of atherosclerotic lesions, having a role in the protection against atherogenesis [98].
	AR	↓[99]	Inhibits cartilage erosion, decreases proinflammatory cytokine secretion, and suppresses osteoclastogenesis and bone destruction [100].
	LD	↓[101]	UNKNOWN

	AL	↓[102]	Its decreased expression causes the impairment of the protective mechanism from oxidative stress in the scalp [102].
LEP (adipokine) ID: 3952	**VD**	↑[103]	leptin as an important mediator in endothelial dysfunction and neointimal hyperplasia, both key steps in the evolution of atherosclerotic vascular changes.Additionally, aracrine leptin release from perivascular adipose tissue (PVAT) has deleterious effects on the underlying endothelium and vascular smooth muscle cells (SMC), including the coronary circulation [103].
	AR	↑[104]	Adipocyte-derived leptin induces proinflammatory cytokine release from innate and adaptive immune cells, producing an inflammatory milieu that encourages cartilage damage and rheumatoid arthritis [104].
	LD	↓[105]	Leptin has key roles in the regulation of energy balance, body weight, metabolism, and endocrine function. Leptin levels are undetectable or very low in patients with lipodystrophy, hypothalamic amenorrhea, and congenital leptin deficiency (CLD) due to mutations in the leptin gene [105].
	AL	↑[106]	The plasma leptin level was significantly higher in AGA subjects, compared to non-AGA subjects (4.45 vs 2.76 ng/mL, P<.05). Leptin from the circulation might impact the development of AGA [106].
IL4 (Interleukin) ID: 3565	**VD**	↑[107]	IL-4 can induce apoptosis of human vascular endothelial cells through the caspase-3-dependent pathway, suggesting that IL-4 can increase endothelial cell turnover by accelerated apoptosis, the event which may cause the dysfunction of the vascular endothelium [107].
	AR	↑[108]	IL4 improves anti-inflammatory effect and suppresses several pro-inflammatory cytokines and systemic IL4 treatment protects the cartilage and bone destruction in established murine type II collagen-induced arthritis. IL-4 has an inhibiting effect on the degradation of proteoglycans in the articular cartilage, by inhibiting the secretion of MMPs metalloproteinases, as well as reducing the variation in the production of proteoglycans that are visible in the course of OA [108].
	LD	↓[109]	IL-4 has important role in lipid metabolism and regulation of glucose by promoting insulin sensitivity and glucose tolerance.Lower insulin sensitivity reduced uptake of fatty acids, reduced glucose transport, and increased free fatty acids (FFA) in the general circulation and that can lead to lipodystrophy [109].
	AL	↑[110]	Alopecia development is associated with CD8(+) T cell activation, migration into the intrafollicular region, and hair follicle destruction. The disease may be adoptively transferred with T lymphocytes and is class I and not class II MHC-dependent. Pathologic T cells primarily express IFNG and IL-17 early in disease, with dramatic increases in cytokine production and recruitment of IL-4 and IL-10 production with disease progression [110].
IFNG (Interferon) ID: 3458	**VD**	↑[111]	IFN-g, known to be a pro-inflammatory cytokine, can also display anti-inflammatory properties. it is likely that it acts in both ways in atherosclerosis. it is possible that its proatherogenic actions out-weigh its anti-atherogenic ones or vice versa. IFN-g promotes

			foam cell formation, plaque development and a Th1-driven adaptive immune response. These effects can be attributed to an array of key genes, involved in atherosclerosis, that are regulated by IFN-g [111].
	AR	↓[112]	IFN-γ activity associated with necroptosis suggests that IFN-γ may modulate necroptosis and improve RA progression by preventing or reducing inflammatory cell death [112].
	LD	↑[113]	Cytokines play important roles in the pathogenesis of lipodystrophy syndrome. Single nucleotide polymorphisms (SNPs) at position +874 (T/A) of the interferon-gamma gene are related to the expression of these cytokines [114].
	AL	↑[115]	IFN-γ rapidly inhibited hair elongation in cultured human anagen hair follicles and induced morphological signs of catagen transformation. IFN-γ can also inhibit proliferation, increase apoptosis and follicular melanogenesis [115].

Table S4. Primers used for the real-time quantitative PCR analysis of the 17 genes identified by text mining

Primer	Target Gene	Product size(bp)	Melting Temp	Info
FW:5′-AATGGCGAGATCCCCTTGA-3′ REV:5′-GCACCGGCTTTCATAGAATCTCT-3′	JAK1	66	62.9℃ 63.0℃	[116]
FW:5′-TGATTTTGTGCACGGATGGA-3′ REV:5′-ACTGCCATCCCAAGACATTCTT-3′	JAK2	72	63.4℃ 62.1℃	[116]
FW:5′-GCCTGGAGTGGCATGAGAA-3′ REV:5′-CCCCGGTAAATCTTGGTGAA-3′	JAK3	55	62.4℃ 62.0℃	[117]
FW:5′-GGGACCGTGGGCAGGAGCTA-3′ REV:5′-GTGCGTGTGGGAGACCTGGC-3′	TYK2	116	69.0℃ 68.7℃	[116]
FW:5′-TTCAGAGCTCGTTTGTGGTG-3′ REV:5′-AGAGGTCGTCTCGAGGTCAA-3′	STAT1	419	60.0℃ 60.0℃	[118]
FW:5′-CCAAGGCTACCATGCTATTC-3′ REV:5′-GCTGGTCTTTCAGTTGGCTG-3′	STAT2	336	57.3℃ 61.0℃	[119]
FW:5′-CAGGAGGGCAGTTTGAGTCC-3′ REV:5′-CAAAGATAGCAGAAGTAGGAGA-3′	STAT3	218	62.1℃ 53.4℃	[120]
FW:5′-CCTGACATTCCCAAAGACAAAGC-3′ REV:5′-TCTCTCAACACCGCATACACAC-3′	STAT4	203	64.2℃ 61.2℃	[121]
FW:5′-TTACTGAAGATCAAGCTGGGG-3′ REV:5′-TCATTGTACAGAATGTGCCGG-3′	STAT5A	104	59.3℃ 61.9℃	[122]
FW:5′-CATTTTCCCATTGAGGTGCG-3′ REV:5′-GGGTGGCCTTAATGTTCTCC-3′	STAT5B	103	63.6℃ 60.7℃	[122]
FW:5′-CCTTGGAGAACAGCATTCCTGG-3′ REV:5′-GCACTTCTCCTCTGTGACAGAC-3′	STAT6	116	65.3℃ 59.1℃	[123]
FW:5′-GAGCCAGGAGTGGACTATGTGTA-3′ REV:5′-CAATGGCCATGATGTACTCG-3′	C3	85	60.6℃ 59.9℃	[124]
FW:5′-AGCATGAAAGTCTCTGCCGC-3′ REV:5′-GGCATTGATTGCATCTGGCTG-3′	CCL2	93	62.9℃ 66.0℃	[125]
FW:5′-CTTTTGGCCAGACAGACATG-3′ REV:5′-GTGTAGAAGTGGAGGCACA-3′	CRP	130	59.3℃ 54.5℃	[126]
FW:5′-CTGGCCGTGGCTCTCTTG-3′ REV:5′-CCTTGGCAAAACTGCACCTT-3′	CXCL8	69	63.2℃ 62.5℃	[125]
FW:5′-TGAAGGACATGGCTTAGAAGTG-3′ REV:5′-GGTGCAAGGGTCACAGTGTT-3′	FAS	118	59.4℃ 61.0℃	[127]
FW:5′-ACTGCGTTCCTGCTCAACATC-3′ REV:5′-GCTCTGGTCCTTGGTGTCATG-3′	HMOX1	75	62.7℃ 63.0℃	[128]
FW:5′-ATGCCCAGACATCTGTGTCC-3′ REV:5′-GGGGTCTCTATGCCCAACAA-3′	ICAM1	112	61.0℃ 62.2℃	[129]
FW:5′-GTCCAACGCAAAGCAATACATG-3′ REV:5′-CCTTTTTCGCTTCCCTGTTTTAG-3′	IFN-G	81	62.6℃ 62.4℃	[130]
FW:5′-GGCACAATTACTGCTCCAAAGAC-3′ REV:5′-CAAGGCCCTTTCTCCCCAC-3′	IGF1	121	62.2℃ 64.1℃	[131]
FW:5′-ATCGCTTCCTCTCGCAACAA-3′ REV:5′-CTTCTACTGGTTCAGCAGCCATCT-3′	IL18	64	63.3℃ 63.3℃	[132]

FW:5′-AACAGCCTCACAGAGCAGAAGAC-3′ REV:5′-GTGTTCTTGGAGGCAGCAAAG-3′	IL4	74	62.4°C 62.2°C	[130]
FW:5′-GGTACATCCTCGACGGCATCT-3′ REV:5′-GTGCCTCTTTGCTGCTTTCAC-3′	IL6	81	63.6°C 62.4°C	[133]
FW:5′-TCCCCTCTTGACCCATCTC-3′ REV:5′-GGGAACCTTGTTCTGGTCAT-3′	LEP	110	60.0°C 58.8°C	[134]
FW:5′-TGATTTTGTGCACGGATGGA-3′ REV:5′-ACTGCCATCCCAAGACATTCTT-3′	PPARG	105	55.4°C 54.6°C	[135]
FW:5′-CCCAGCATCTGCAAAGCTC-3′ REV:5′-GTCAATGTACAGCTGCCGCA-3′	TGFB1	101	62.1°C 63.4°C	[136]
FW:5′-TCAGATCATCTTCTCGAACCCC-3′ REV:5′-ATCTCTCAGCTCCACGCCAT-3′	TNFa	134	62.7°C 62.3°C	[137]
FW:5′-CATGAGAGGGGAGTATGATG-3′ REV:5′-GAAGAAGAGTGGGCATCCAC-3′	TRAF1	181	55.4°C 59.7°C	[138]
FW:5′-CTCTGCTCCTCCTGTTCGAC-3′ REV:5′-TTAAAAGCAGCCCTGGTGAC-3′	GAPDH	144	60.1°C 60.2°C	[139]

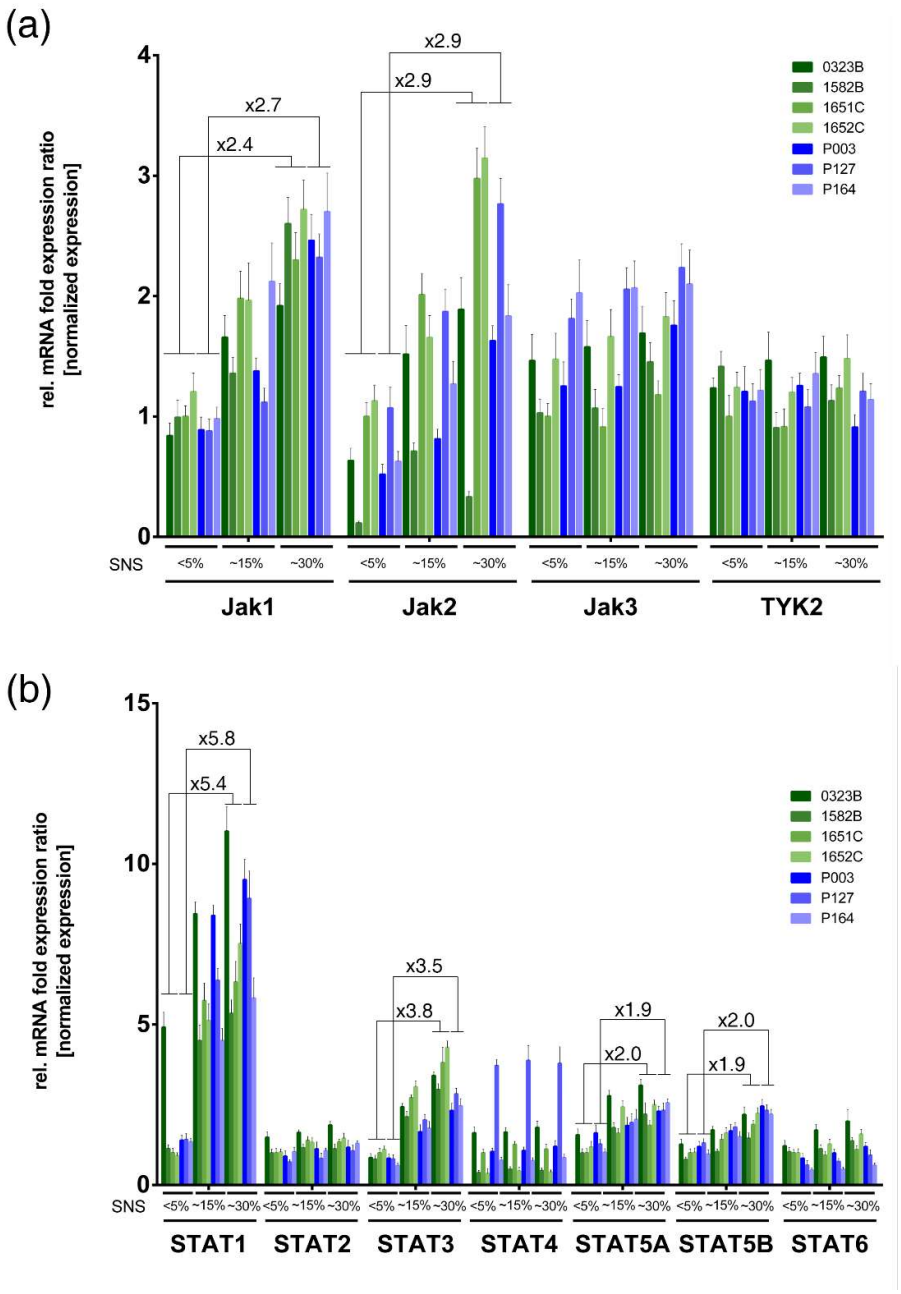

Figure S1. Real-time PCR analysis of the JAKs and STATs gene families in normal and HGPS cells. (**a**) mRNA levels of JAK1, 2, 3, and TYK2 in control (GMO1651c, GMO1652c, GMO1582B, and GMO0323B) and HGPS (HGADFN003, HGADFNP127, and HGADFNP164) cells from cultures of indicated senescence index. (**b**) mRNA levels of STAT1,2,3,4,5a,5b and 6 in cell strains as in (**a**). Relative expression was normalized to the expression of GAPDH. Due to the heterogeneity in the expression levels between cell strains, we only calculated the indicated fold change.

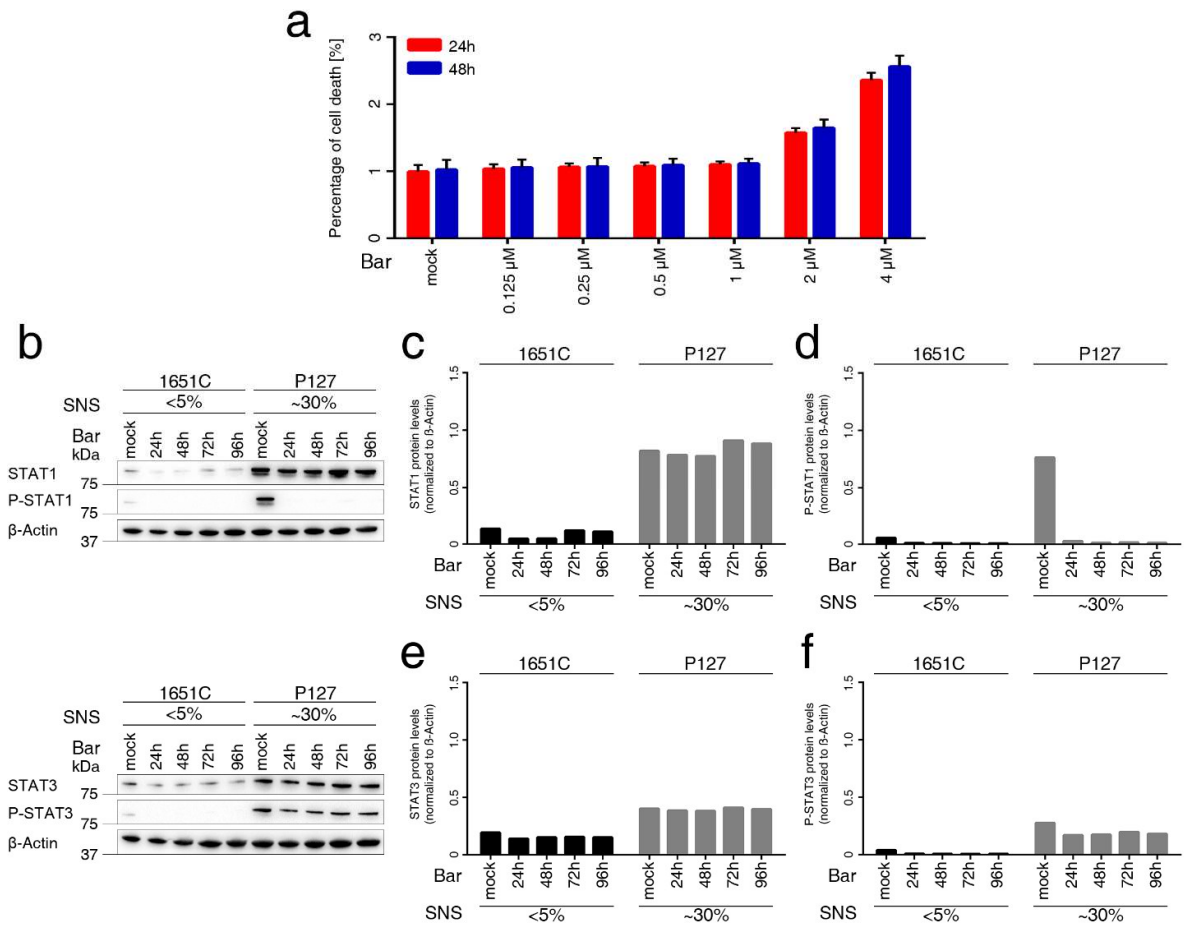

Figure S2. Cytotoxicity and stability of Bar in a cell-based aging model. (**a)** Cell cytotoxicity was determined by CellTox™ Green Cytotoxicity Assay kit in control fibroblasts GMO1651C. Cells were treated with Bar at different concentrations (0.125 µM, 0.25 µM, 0.5 µM, 1 µM, 2 µM, 4 µM) for 24 and 48 hours. (**b)** Representative western blot images for STAT1/3 and p-STAT1/3 and ß-actin in the control (GMO1651) and HGPS (HGDFN127) cells at the indicated senescence index were treated with Bar or DMSO for indicated period without medium change. (**C-f)** Quantifications of STAT1/3, and p-STAT1/3 are shown. Graphs show the mean (n>3).

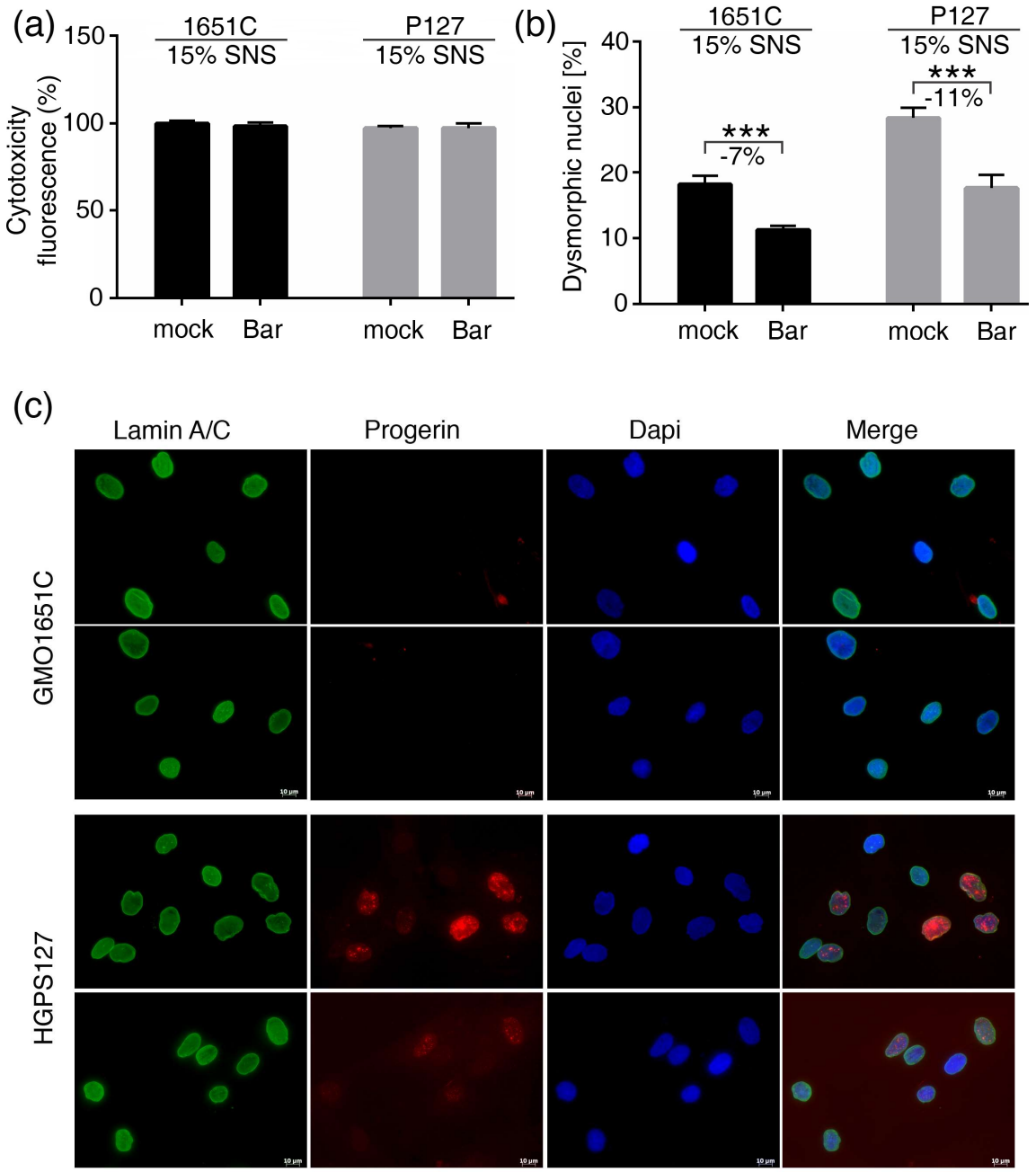

Figure S3. Bar treatment ameliorates HGPS nuclear morphology. (a) Cell cytotoxicity was determined using CellTox™ green cytotoxicity assay on mock-treated or Bar-treated control (GMO1651C) and HGPS (HGADFN127) fibroblasts at the indicated senescence index (48 hours treatment). (b) The frequency of misshapen nuclei (dysmorphic) after 20 days of treatment with either DMSO or 1.0 μM Bar. An average of 1000 nuclei were examined for each condition, and each experiment was repeated 3 times. (c) Immunochemistry was performed on mock-treated or Temsirolimus-treated control (GMO1651C) and HGPS (HGADFN127) fibroblasts after 20 days using antibodies against the indicated proteins (lamin A/C, and progerin). Representative images are shown. Scale-bar: 10 μm.

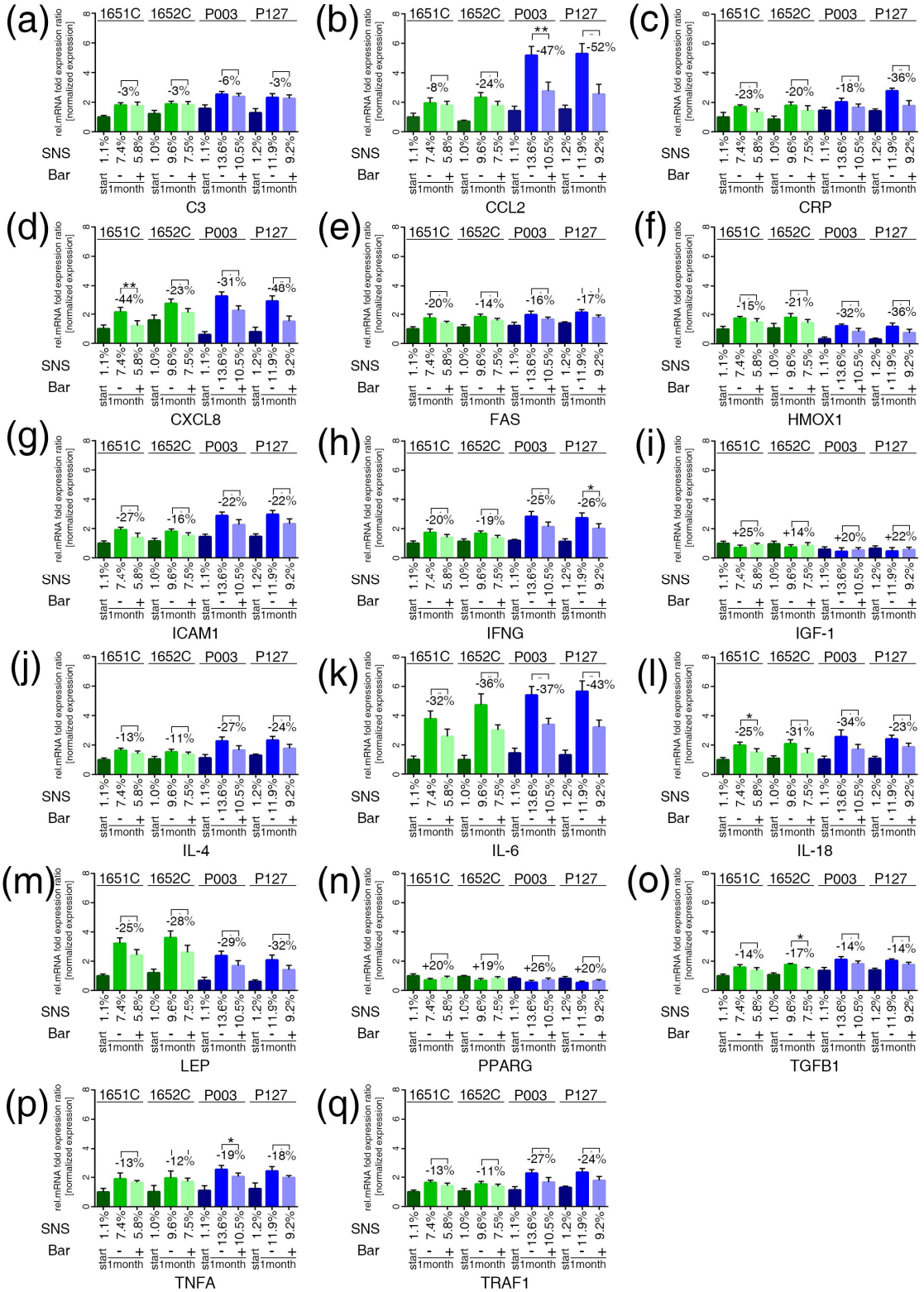

Figure S4. Real-time PCR analysis of the 17 genes identified by text mining in normal and HGPS cells treated with Bar for 1 month. (**a-q**) mRNA levels of indicated genes were determined in controls (GMO1651c, GMO1652c) and HGPS (HGADFN003 and HGADFN127) cell strains. The starting senescence index of the culture is indicated (Start SNS). The senescence index of the cultures at the end of the treatment is indicated. Relative expression was normalized to the expression of GAPDH. Graphs show mean ± SD (n ≥ 3). Comparisons were performed by two-tailed t test (* P<0.05, **P<0.01, ***P<001). The percent change between Bar-treated cells and mock-treated counterparts is indicated.

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