were obtained per condition, then corrected post hoc to match the time that the '1' was on screen after target foveation.

Ten subjects (9 male, mean age 30.5, s.d. 7.8) completed a control experiment. They estimated the duration of the first digit when a counter moved 24° to the point of fixation in 100 ms (six screen refreshes), compared with the usual stationary control. A further control experiment ($n = 10$, 9 male, mean age 31.4, s.d. 7.6) varied the time from saccade onset to the initial counter change by triggering this change either one fifth or four fifths of the way into a 55° saccade (randomly within the same block; separate self-terminating MOBS).

Experiment 2

The data of 12 subjects was included in experiment 2 (10 male, mean age 32.8, s.d. 9.3). In addition to a control, subjects completed two conditions requiring 12° saccades to a counter (as experiment 1) with or without deliberate, prior covert shifting of attention. Every other trial was a reaction time task in which subjects fixated the central target and then made a speeded 12° saccade to the appearance of a target '0' to the left or right. An uninformative cue (an arrow pointing to the left or right near fixation) directed attention before the appearance of the '0' in attention-shift blocks.

Experiment 3

Twenty-two subjects performed experiment 3 (16 male, mean age 30.8, s.d. 7.4). We tested three conditions: a 20° saccade to a stationary counter; a 20° saccade in which the counter shifted ± 0–9° synchronous with triggering of counter onset; and a control. All eye movement data were obtained within a single block type in which subjects made the standard timing judgment and also indicated whether the counter had moved during the saccade. Presentation was controlled by three randomly interleaved (equally probable) self-terminating MOBS. The first of these controlled target time intervals for the stationary counter trials (as in experiment 1), the latter two controlled the size of the target shift in a hypo- or hypermetric direction (0–9°) according to whether the movement was perceived. This ensured that most of the shift trials were close to the subject's point of shift perception, whether perceived or not. For shift trials, the target time interval was randomly generated in the range 400–1,600 ms. Trials were divided between perceived and unperceived shift conditions post hoc. For all conditions, matched time estimates were generated using logistic regression. Subjects initially completed four experimental blocks and four short control blocks, with a single additional block completed where fitted logistic regression lines exceeded $P = 0.05$.

Experiment 4

Ten subjects participated in experiment 4 (7 male, mean age 29.4, s.d. 7.5). We compared four conditions: a 20° saccade to a stationary counter; an identical saccade with a random, lower-case alphabetic character appearing 1° from the counter (hypo- or hypermetrically) at trigger time; a saccade with the character appearing 3° from the counter; and a control. Data for the first three conditions was obtained within a single block type, using three randomly interleaved and self-terminating MOBS.

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Haemoglobin C protects against clinical *Plasmodium falciparum* malaria

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Haemoglobin C (HbC; β6Glu → Lys) is common in malarious areas of West Africa, especially in Burkina Faso[1,2]. Conclusive evidence exists on the protective role against severe malaria of haemoglobin S (HbS; β6Glu → Val) heterozygosity[3], whereas conflicting results for the HbC trait have been reported[4–10] and no epidemiological data exist on the possible role of the HbCC genotype. *In vitro* studies suggested that HbCC erythrocytes fail to support the growth of *P. falciparum*[11,12] but HbC homozygotes with high *P. falciparum* parasitaemias have been observed[10]. Here we show, in a large case–control study performed in Burkina Faso on 4,348 Mossi subjects, that HbC is associated with a 29% reduction in risk of clinical malaria in HbAC heterozygotes ($P = 0.0008$) and of 93% in HbCC homozygotes ($P = 0.0011$). These findings, together with the limited pathology of HbAC and HbCC[13] compared to the severely disadvantaged HbSS and HbSC genotypes and the low β^S gene frequency in the geographic epicentre of β^C[1,2,14], support the hypothesis that, in the long term and in the absence of malaria control, HbC would replace HbS in central West Africa.

Since hominization the human genome has been under selective pressures for resistance to infectious diseases. For example, West African populations are able to escape the infection altogether, with complete protection from *Plasmodium vivax* achieved through the fixation of a Duffy silent allele (fy)[15]. In other cases, polymorphic

Table 1 Absence of age effect on β globin genotype frequencies

Age group (years)	Percentage genotype frequencies ± standard error*											
	AA		AC		AS		CC		SC		SS	
	Cases	Controls	Cases	Controls	Cases	Controls	Cases	Controls	Cases	Controls	Cases	Controls
0–3	76.7 ± 2.1	70.8 ± 5.4	19.2 ± 2.0	13.9 ± 4.1	3.3 ± 0.9	12.5 ± 3.9	0.25 ± 0.3	1.4 ± 1.4	0.5 ± 0.4	1.4 ± 1.4	0.0 (395)	0.0 (72)
>3–6	85.2 ± 2.2	66.7 ± 3.5	13.6 ± 2.1	19.4 ± 2.9	1.2 ± 0.7	11.1 ± 2.3	0.0 (257)	1.7 ± 1.0	0.0 (257)	1.1 ± 0.8	0.0 (257)	0.0 (180)
>6–10	80.2 ± 3.6	66.4 ± 1.4	15.7 ± 3.3	21.7 ± 1.2	3.3 ± 1.6	9.5 ± 0.9	0.0 (121)	1.4 ± 0.3	0.8 ± 0.8	0.9 ± 0.3	0.0 (121)	0.1 ± 0.1
>10	82.5 ± 5.0	66.2 ± 1.0	12.3 ± 4.3	22.2 ± 0.9	5.3 ± 3.0	9.3 ± 0.6	0.0 (57)	1.8 ± 0.3	0.0 (57)	0.4 ± 0.1	0.0 (57)	0.0 (2082)
P values	0.063	0.88	0.21	0.33	0.23	0.71	0.78	0.79	0.55	0.24	1.0	0.58

* When genotype frequency was zero, the number of individuals examined is indicated between brackets.
Cases, malaria patients; controls, healthy subjects; from Burkina Faso, West Africa.

gene mutants decreasing the susceptibility to severe forms of *P. falciparum* malaria have been selected in spite of a heavy segregational load (balanced polymorphisms). Since Haldane's malaria hypothesis[16], epidemiological and in some cases *in vitro* evidence on the protective role of thalassaemias[17,18]—HbS[3,19,20], human leukocyte antigen Bw53 (ref. 3), glucose-6-phosphate dehydrogenase deficiency[21] and haemoglobin E (HbE)[22]—have been obtained. Attempts to evaluate if HbC protects against malaria (both the infection and the disease) have yielded conflicting results. The first studies showed no correlations of HbC heterozygosity with parasitological indicators such as *P. falciparum* parasite rates and densities[4–7,14]. Clinical studies performed in Nigeria[8] and Mali[9,10], assessing the role of HbAC with respect to the susceptibility to severe forms of the disease, showed contrasting results: the Nigerian[8] and one study from Mali[9] indicated lack of protection, and the other Malian study[10] showed evidence for an association between HbAC and protection against severe malaria in the Dogon population. In the same study[10], episodes of non-complicated malaria with high *P. falciparum* parasitaemia were observed in HbCC patients, although *P. falciparum* was previously reported not to proliferate in HbCC erythrocytes *in vitro*[11,12].

None of the epidemiological studies mentioned above was designed or had the statistical power to evaluate the possible role of HbC homozygosity in the resistance or susceptibility to severe malaria. Moreover, a report on the possible reduced survival of the HbCC genotype[14], together with the need of extremely large clinical and control samples, did not encourage research in this direction.

In a large case-control study of *P. falciparum* malaria in Burkina Faso, we estimated the genotype and allele frequencies for the β globin gene in 3,513 healthy subjects and in 835 malaria patients recruited at the pediatric ward of the Ouagadougou University Hospital with a clinical picture of severe ($n = 359$) or non-severe ($n = 476$) malaria. The AA, AC and CC genotype frequencies were in Hardy–Weinberg equilibrium ($P > 0.6$) among healthy subjects but not among malaria patients ($P = 0.0005$). This disequilibrium is clearly dependent on the almost complete lack of the CC genotype in the clinical group (1 observed versus 13.8 expected). Among healthy subjects, HbSC and HbSS genotypes, in line with their known short life expectancy, were found at much lower frequencies than those expected by the Hardy–Weinberg equilibrium [23 versus 46.2 for HbSC ($P < 0.001$); 1 versus 9.2 for HbSS ($P < 0.01$)]. No evidence of any age effect on genotype frequencies was observed both in the case ($P = 0.40$) and control ($P = 0.73$) samples (Table 1).

As shown in Table 2, obvious indications of protection against clinical malaria were observed not only—as expected—for the HbAS genotype (odds ratio, OR 0.27, 95% confidence intervals, c.i. 0.17–0.42, $P \ll 0.001$) but also for HbAC (OR 0.71, 95% c.i. 0.58–0.87), $P = 0.0008$) and even more strongly for the HbCC genotype (OR 0.07, 95% c.i. 0.00–0.48, $P = 0.0011$). No differences were observed in HbC between severe and non-severe malaria patients, whereas significantly lower β^S allele ($P = 0.023$) and HbAS genotype ($P = 0.021$) frequencies were recorded among severe malaria patients than in those with non-severe malaria. No

Table 2 β globin genotype and allele frequencies in healthy subjects and in malaria patients from Burkina Faso, West Africa

Sample	*n*	Relative and (absolute) genotype frequencies						Relative and (absolute) allele frequencies		
		AA	AC	AS	CC	SC	SS	β^A	β^C	β^S
Healthy subjects	3,513	0.6641 (2333)	0.2172 (763)	0.0954 (335)	0.0165 (58)	0.0065 (23)	0.0003 (1)	0.8204 (5764)	0.1284 (902)	0.0512 (360)
Severe malaria	359	0.8078 (290)	0.1755 (63)	0.0111 (4)	0.0028 (1)	0.0028 (1)	0 (0)	0.9011 (647)	0.0919 (66)	0.0070 (5)
Non-complicated malaria	476	0.8004 (381)	0.1555 (74)	0.0399 (19)	0 (0)	0.0042 (2)	0 (0)	0.8981 (855)	0.0798 (76)	0.0221 (21)
Malaria patients (total)	835	0.8036 (671)	0.1641 (137)	0.0275 (23)	0.0012 (1)	0.0036 (3)	0 (0)	0.8994 (1502)	0.0850 (142)	0.0156 (26)
Comparisons		Odds ratio (95% confidence interval) and *P* values*								
Healthy subjects versus malaria patients		2.07† (1.71–2.50) ≪0.001	0.71‡ (0.58–0.87) 0.0008	0.27§ (0.17–0.42) ≪0.001	0.07‖ (0.00–0.48) 0.0011	n.s.	n.s.	≪0.001	≪0.001	≪0.001
Severe malaria versus non-severe malaria		n.s.	n.s.	0.27¶ (0.08–0.86) 0.021	n.s.	n.s.	n.s.	n.s.	n.s.	0.023

n, number of individuals examined; n.s., not significant.
* Although no evidence of any age effect on genotype frequencies was observed (Table 1) and the area of residence (urban or rural) of the case and control groups was almost overlapped, the possible confounding effect of these two factors was calculated by Mantel–Haenszel (M–H) weighted odds ratio (OR; 95% confidence intervals) and maximum likelihood estimate (MLE) of OR (exact 95% c.i.) after stratification by age (0–3 years, >3–6, >6–10, >10) and area of residence (urban or rural).
† M–H weighted OR: 2.15 (c.i. 1.66–2.79), $P \ll 0.001$; MLE of OR: 2.13 (c.i. 1.63–2.79); probability of MLE ≥ 2.13 if population OR = 1.0, $P \ll 0.001$.
‡ M–H weighted OR: 0.74 (c.i. 0.55–0.99), $P = 0.047$; MLE of OR: 0.75 (c.i. 0.56–1.00); probability of MLE ≤ 0.75 if population OR = 1.0, $P = 0.0268$.
§ M–H weighted OR: 0.26 (c.i. 0.15–0.45), $P \ll 0.001$; MLE of OR: 0.23 (c.i. 0.12–0.40); probability of MLE ≤ 0.23 if population OR = 1.0, $P \ll 0.001$.
‖ M–H weighted OR: 0.03 (c.i. 0.00–0.73), $P = 0.007$; MLE of OR: 0.07 (c.i. 0.00–0.59); probability of MLE ≤ 0.07 if population OR = 1.0, $P = 0.0028$.
¶ M–H weighted OR: 0.27 (c.i. 0.09–0.82), $P = 0.014$; MLE of OR: 0.28 (c.i. 0.07–0.85); probability of MLE ≤ 0.28 if population OR = 1.0, $P = 0.010$.

differences were recorded in the geometric means of *P. falciparum* parasite densities between malaria patients with HbAA (10,162 parasites μl^{-1}) and HbAC (11,066 parasites μl^{-1}) genotypes, whereas significantly lower values were observed among HbAS patients (1,995 parasites μl^{-1}; AS versus AA, $P = 0.004$; AS versus AC, $P = 0.013$). In contrast to previous observations from Mali[10], we did not record CC homozygotes among non-severe malaria patients. A very low parasite density (8 parasites μl^{-1}) was observed in the only CC subject with a clinical picture of severe malaria. These observations seem to be consistent with previous *in vitro* data indicating that HbCC erythrocytes fail to support the growth of *P. falciparum*[11,12].

Clearly, HbC provides protection against clinical *P. falciparum* malaria in both the heterozygous and homozygous state. The estimated reduction in the relative risk of clinical malaria associated with CC homozygosity (93%) is stronger than that of AC heterozygosity (29%) and similar to that of the HbAS genotype (73%). The estimated protection of HbAC (OR 0.71; c.i. 0.58–0.87) is lower than in ref. 10 comparing severe and non-complicated malaria (OR 0.25; c.i. 0.06–0.86) but the confidence intervals of the odds ratio partially overlap. We recorded no differences in HbAC frequency between severe and non-severe malaria: this discrepancy may to some extent derive from the fact that the Malian study[10] was performed in a hospital of a small town (Bandiagara, with 12,000 inhabitants) whereas this work was carried out in the main hospital of a city of about one million inhabitants (Ouagadougou). Our sample of non-severe malaria patients could be biased in the direction of high severity because the Ouagadougou University Hospital is the last level in the therapeutic itinerary of the patient. This may have resulted in the smoothing—though not the suppression (see the AS genotype frequencies in severe versus non-severe malaria)—of the clinical differences between the groups of severe and non-severe malaria. Given the genotype frequencies among healthy subjects (AC, 0.2172; CC, 0.0165; AS, 0.0954) and their respective protections, it can be estimated that in the Mossi population the proportion of potential clinical malaria cases prevented by HbC (AC + CC), that is, $[(0.29 \times 0.2172) + (0.93 \times 0.0165)] = 7.83\%$, is similar to that prevented by the HbAS genotype ($0.73 \times 0.0954) = 6.96\%$. Given the heavy genetic load of β^S due to the reduced fitness of the HbSS and HbSC genotypes (balanced polymorphism) and the probable absent or limited genetic load of β^C (transient polymorphism) it can safely be hypothesized that in those selective malaria contexts where these two alleles coexist the β^C gene is probably replacing β^S (refs 1, 2, 14). The restricted geographic distribution of the β^C gene and the evidence of its unicentric origin in central West Africa[23], together with the present results showing an obvious protection of HbC against clinical *P. falciparum* malaria, may suggest the recent origin of the β^C mutation. The β^C polymorphism has such a favourable cost/benefit ratio in highly malarious contexts that its relatively recent origin would seem puzzling: β^S and β^E, in spite of less favourable cost/benefit ratios, probably had polycentric origins and much wider diffusions. The most direct explanation would be that the rates of the $\beta^A \rightarrow \beta^S$ mutation (A → T single nucleotide substitution, SNS) and of the $\beta^A \rightarrow \beta^E$ (G → A SNS) are higher than that of the $\beta^A \rightarrow \beta^C$ (G → A SNS). This hypothesis is unlikely, not only with respect to β^E but even more so with respect to β^S, because the average G → A SNS rate is markedly higher than that of the other SNS[24,25]. Unlike HbS and HbE, which protect against malaria in the heterozygous state, HbC seems to protect mainly in the homozygous state: therefore, even considering higher or similar $\beta^A \rightarrow \beta^C$ mutation rates with respect to $\beta^A \rightarrow \beta^S$ and $\beta^A \rightarrow \beta^E$, the chance of β^C being selected (in spite of the initially strong adverse odds due to genetic drift) could be smaller, and the time it needs to reach significant frequencies could be longer, compared to β^S and β^E. Moreover, the fact that β^C protects mainly in the homozygous state may suggest a straightforward explanation for its very localized occurrence in West Africa: its selective advantage would be proportional to the allele frequency so that homozygous β^C would progressively fade out with increasing distance from the epicentre. The ideal epidemiological context for positive selection of a protective factor acting mainly in homozygosity is one with very high malaria transmission levels, such as sub-Saharan West Africa. A recent work[26] indicating a multicentric origin for β^C, as for HbS[27,28] and HbE[29], seems to support the positive selection of this allele in a non-African malarious context as well. □

Methods

Study area and subjects

The study was performed in Ouagadougou, Burkina Faso. The area has a rainy season lasting from June to October, which corresponds to the high malaria transmission season, and a long dry season from November to May. Inoculation rates range from 1 to 10 per person per year in urban areas of Ouagadougou, and from 50 to 200 in the surrounding rural zones. The main malaria vectors are *Anopheles gambiae*, *A. arabiensis* and *A. funestus*. About 95% of the population in the Ouagadougou area belongs to the Mossi ethnic group.

Healthy subjects were recruited in 12 primary schools in the urban area of Ouagadougou in the frame of a large programme for screening of haemoglobinopathies in Burkina Faso carried out by the Saint Camille Health Center of Ouagadougou. Of the total of 3,686 individuals examined, 3,513 belonged to the Mossi ethnic group and were considered in this study to be controls. Of the 3,513 control subjects, 3,056 (87%) were primary school children (aged 6–15), the remainder being either children aged 1–5 years ($n = 163$, 4.6%) or subjects more than 15 years old ($n = 294$, 8.4%). The presence of subjects aged 0–5 years was due to the sporadic request to include younger children in free-of-charge analyses and those aged over 15 years were repeater students, teachers and school personnel. The mean age ± standard deviation (s.d.) of the control group was 11.3 ± 3.9 years (range 1–40). Malaria patients were recruited during an epidemiological study on severe malaria performed in Burkina Faso[30]. A total of 835 malaria patients (359 severe and 476 non-severe malaria) belonging to the Mossi ethnic group were considered in the present analysis. The clinical study was carried out at the 158-bed paediatric ward of the Ouagadougou University Hospital. Patients aged 6 months to 15 years were included in the study. The mean age ± s.d. of the clinical sample [4.4 ± 3.2 (range 0.5–15 years)] was lower than that of the control sample. The majority of malaria patients, 93.7% ($n = 782$), came from urban areas of Ouagadougou; the remainder were from surrounding rural zones. Severe malaria was defined by the presence of *P. falciparum* in the thick blood film associated with at least one of the following conditions: prostration (that is, incapacity of the child to sit without help in the absence of coma), unrousable coma (score between 0 and 2 on the Glasgow modified coma scale), repeated generalized convulsions (more than two episodes in the preceding 24 hours), severe anaemia (haemoglobin $<0.05\ g\ ml^{-1}$), hypoglycaemia (blood glucose $<0.4\ mg\ ml^{-1}$), pulmonary oedema/respiratory distress, spontaneous bleeding and renal failure (plasma creatinine $<0.03\ mg\ ml^{-1}$). Non-severe malaria was defined as a clinical illness characterised by an axillary temperature >37.5 °C associated with a *P. falciparum*-positive blood film. Children with other detectable infections that were responsible for the hospital admission were not included in the study. All patients with a clinical picture of severe malaria were hospitalized whereas the majority (409/476) of non-severe malaria patients were recruited at the outpatients section of the paediatric ward of the Ouagadougou University Hospital; the remaining 67 patients with non-severe malaria were hospitalized because of high fever (≥40 °C) and/or anaemia (haemoglobin between 0.051 and $0.08\ g\ ml^{-1}$), high parasite densities ($>10^5\ \mu l^{-1}$), severe diarrhoea, severe vomiting. On admission or at outpatient examination and after oral informed consent of the parents, a blood sample was drawn for measurement of parasitaemia, blood glucose level, plasma creatinine concentrations, haemoglobin concentrations, haematocrit, complete cell count, humoral response to malaria antigens and genetic analyses. Patients were treated according to WHO guidelines with a complete regimen of drugs that were provided free of charge as part of the study. The study protocol was approved by the Centre National de Lutte contre le Paludisme of the Ministry of Health of Burkina Faso.

Haemoglobin typing

It was performed by cellulose acetate electrophoresis on the sample of healthy subjects and by polymerase chain reaction (PCR) restriction fragment length polymorphism (RFLP) on malaria patients. DNA samples were amplified with the following oligonucleotides: sense 5′AGGAGCAGGGAGGGCAGGA3′, and antisense 5′TCCAAGGGTAGACCACC AGC3′ (NCBI, NG_000007). The 358 base pair (bp) fragment was digested with *Mnl* I (5′CCTC(N)$_7$′3′;3′GGAG(N)$_6$′5′) which allows the discrimination among HbAA (173 bp, 109 bp and 60 bp), Hb SS/CC/SC (173 bp, 109 bp and 76 bp), HbAS/AC (173 bp, 109 bp, 76 bp and 60 bp), HbAE (249 bp, 173 bp, 109 bp and 60 bp) and HbEE (249 bp and 109 bp). A second digestion with *Dde* I (C/TNAG) was performed on those samples with the ambiguous result to further discriminate among HbSS (331 bp), HbCC (201 bp and 130 bp) HbSC (130 bp, 201 bp, and 331 bp), HbAS (130 bp, 201 bp, and 331 bp) and HbAC (130 bp, and 201 bp). Both digestions were carried out for 3 h at 37 °C and resolved on 3% agarose gel which allows a good detection of small size differences such as between 76 bp and 60 bp fragments. A total of 89 samples consisting of 64 AA, 17 AC, 4 AS, 2 CC, 1 SC and 1 SS, were typed both with electrophoresis and RFLP and no discordant results were observed.

Statistical analysis

P values of the comparisons were obtained by Yates corrected χ^2 test. Since no evidence of any age effect on genotype frequencies was observed (Table 1) and in view of the almost overlapped geographic origin (urban or rural) of the case and control group, unadjusted odds ratios (ORs) were calculated. Mantel–Haenszel weighted OR (95% confidence interval) and maximum likelihood estimate of OR (95% c.i.) were also calculated after stratification by age (0–3 years, >3–6, >6–10, >10) and area of residence (urban or rural). Student's *t*-test was used for the comparisons of age and parasite densities.

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Induction of *gadd45β* by NF-κB downregulates pro-apoptotic JNK signalling

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In addition to coordinating immune and inflammatory responses, NF-κB/Rel transcription factors control cell survival[1]. Normally, NF-κB dimers are sequestered in the cytoplasm by binding to inhibitory IκB proteins, and can be activated rapidly by signals that induce the sequential phosphorylation and proteolysis of IκBs[1]. Activation of NF-κB antagonizes apoptosis or programmed cell death by numerous triggers, including the ligand engagement of 'death receptors' such as tumour-necrosis factor (TNF) receptor[2]. The anti-apoptotic activity of NF-κB is also crucial to oncogenesis and to chemo- and radio-resistance in cancer[2]. Cytoprotection by NF-κB involves the activation of pro-survival genes[2]; however, its basis remains poorly understood. Here we report that NF-κB complexes downregulate the c-Jun amino-terminal kinase (JNK) cascade[3], thus establishing a link between the NF-κB and the JNK pathways. This link involves the transcriptional upregulation of *gadd45β*/*myd118* (ref. 4), which downregulates JNK signalling induced by the TNF receptor (TNF-R). This NF-κB-dependent inhibition of the JNK pathway is central to the control of cell death. Our findings define a protective mechanism that is mediated by NF-κB complexes and establish a role for the persistent activation of JNK in the apoptotic response to TNF-α.

To understand mechanisms controlling TNF-R-induced programmed cell death (PCD)- and NF-κB-dependent survival, we used the method of 'death trap' screening[5] in NF-κB null cells. Complementary DNA expression libraries derived from TNF-α-treated wild-type cells were transfected into NF-κB/RelA$^{-/-}$ fibroblasts[6]. Apoptosis was induced with TNF-α, and plasmids were recovered from surviving cells. After four cycles of selection, about 35% of the library cDNAs protected RelA null cells from killing by TNF-α. Known inhibitors of TNF-R-triggered apoptosis, including RelA, cFLIP (cellular FLICE inhibitory protein) and dominant-negative forms of FADD[7] (Fas-associated death domain protein), were highly enriched during selection.

A cDNA enriched by selection with TNF-α was found to encode full-length Gadd45β, a member of the Gadd45 family of inducible factors[8] associated with cell-cycle control and DNA repair[9]. *gadd45β* was strongly and rapidly induced by TNF-α in wild-type mouse embryo fibroblasts (MEFs), but not in RelA$^{-/-}$ cells (Fig. 1a). This mirrored the expression of *ikbα*, a target of NF-κB[1]. *gadd45β* was also upregulated by TNF-α in parental and Neo 3DO T cells, but not in 3DO clones expressing IκBαM, a variant of IκBα that blocks activation of NF-κB[10] (Fig. 1b; see also Supplementary Information Fig. 1). *gadd45β* was also induced by NF-κB after treatment with daunorubicin or phorbol 12-myristate-13-acetate (PMA) plus ionomycin (Fig. 1d and c, respectively).

In both MEFs and 3DO cells, expression of the other family members *gadd45α*/*gadd45* and *gadd45γ*/*oig37*/*cr6*/*grp17* (ref. 11) was independent of NF-κB (Fig. 1b–d; and data not shown). Thus, unlike these latter genes, *gadd45β* is a TNF-α-inducible gene and a physiological target of NF-κB. Mutational analyses confirmed the presence of three functional κB elements in the *gadd45β* promoter (R.J., E.D.S. and G.F., manuscript in preparation).