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10. The IS task was a modification of the CF task. Five hundred milliseconds into the delay period, the visual fixation point jumped. The monkey responded by making a saccade to the new location of the red LED. Another 600 ms of delay period ensued before both fixation LEDs were extinguished to trigger the reach. This task was interleaved with the two conditions of the CF task depicted in Fig. 1, C and D. In one of these conditions gaze was directed at the initial eye position for the IS trials. In the other condition, gaze was directed at the final eye position for the IS trials. The delay epochs for the two CF conditions were lengthened to 1100 ms to more closely match the overall delay period in the IS task. In all three tasks the initial hand position was at the center button, so the same reach was always performed. Typically, 10 repetitions of each task were performed.
11. Neurons that showed a significantly different response (Mann-Whitney test, $P < 0.05$) during the final 500 ms of the delay period for the two CF conditions were analyzed further. A cell was considered to update if its response during the 500 ms after the saccade and before the reach in the IS task was significantly greater (Mann-Whitney test, $P < 0.05$) than its response during the 500 ms before the reach for the CF condition with the target out of the response field. Fifteen neurons from monkey D, 16 from monkey O, and 3 from monkey G were studied.
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BLyS: Member of the Tumor Necrosis Factor Family and B Lymphocyte Stimulator

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The tumor necrosis factor (TNF) superfamily of cytokines includes both soluble and membrane-bound proteins that regulate immune responses. A member of the human TNF family, BLyS (B lymphocyte stimulator), was identified that induced B cell proliferation and immunoglobulin secretion. BLyS expression on human monocytes could be up-regulated by interferon-γ. Soluble BLyS functioned as a potent B cell growth factor in costimulation assays. Administration of soluble recombinant BLyS to mice disrupted splenic B and T cell zones and resulted in elevated serum immunoglobulin concentrations. The B cell tropism of BLyS is consistent with its receptor expression on B-lineage cells. The biological profile of BLyS suggests it is involved in monocyte-driven B cell activation.

A 285–amino acid protein was identified in a human neutrophil-monocyte–derived cDNA library that shared identity within its predicted extracellular receptor-binding domain to APRIL (28.7%) (*1*), TNFα (16.2%) (*2*), and lymphotoxin-α (LT-α) (14.1%) (Fig. 1A) (*3*). This cytokine has been designated B lymphocyte stimulator (BLyS) on the basis of its biological activity. Analyses of the BLyS protein sequence have revealed a potential transmembrane spanning domain between amino acid residues 47 and 73 that is preceded by nonhydrophobic amino acids, suggesting that BLyS is a type II membrane-bound protein (*4*). Expression of this cDNA in mammalian cells [HEK 293 and Chinese hamster ovary (CHO)] and Sf9 insect cells identified a soluble form, 152 amino acids in length, with an NH_2-terminal sequence beginning with Ala^{134} (arrow in Fig. 1A). Reconstruction of the mass-to-charge ratio defined a mass for BLyS of 17,038 daltons, a value consistent with that predicted for this 152–amino acid protein with a single disulfide bond (17037.5 daltons). BLyS has been mapped to human chromosome 13q34 (*5*).

The expression profile of BLyS was assessed by Northern blot and flow cytometric analyses. BLyS is encoded by a single 2.6-kb mRNA expressed in peripheral blood mononuclear cells, spleen, lymph node, and bone marrow (Fig. 1B). Lower expression was detected in placenta, heart, lung, fetal liver, thymus, and pancreas. BLyS mRNA was also detected in HL-60 and K-562, but not in Raji, HeLa, or MOLT-4 cells. Surface expression was analyzed by flow cytometry with the BLyS-specific monoclonal antibody (mAb) 2E5. BLyS was not detected on T- or B-lineage cell lines, but was restricted to cells of myeloid origin, including K-562, HL-60, THP-1, and U-937 (*6*). Analyses of normal blood cell types showed expression on resting monocytes that was upregulated four times after exposure of cells to interferon-γ (IFN-γ) (100 U/ml) for 3 days (Fig. 1C). A concomitant increase in BLyS-specific mRNA was also detected by quantitative polymerase chain reaction using a TaqMan machine (Perkin-Elmer Applied Biosystems) (*6*). BLyS was not expressed on freshly isolated blood lymphocytes or on activated T cells [anti-CD3 mAb + interleukin-2 (IL-2)], B cells (SAC + IL-2), or NK cells (IL-2 + IL-12) (*6*).

Purified recombinant BLyS (rBLyS) was assessed for its ability to induce activation, proliferation, differentiation, or death in numerous cell-based assays involving B cells, T cells, monocytes, natural killer (NK) cells, hematopoietic progenitors, and a variety of cell types of endothelial and epithelial origin. A biological response to BLyS was observed only among B cells in a standard costimulatory proliferation assay in which purified tonsillar B cells were cultured in the presence of either formalin-fixed *Staphylococcus aureus*

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Cowan I (SAC) or immobilized anti-human immunoglobulin M (IgM) as priming agents (*7, 8*). The rBLyS induced a concentration-dependent proliferation of tonsillar B cells similar to that of recombinant IL-2 (rIL-2) (Fig. 2A). BLyS also induced B cell proliferation when cultured with cells costimulated with graded doses of anti-IgM (Fig. 2B). A concentration-dependent response was readily observed as the amount of cross-linking agent increased in the presence of a fixed concentration of either IL-2 or rBLyS.

Biotinylated BLyS protein (which retained biological function in the standard B cell proliferation assays) (*6*) was used to assay for receptor expression. Lineage-specific analyses of human peripheral blood cells indicated that binding of biotinylated BLyS was undetectable on T cells, monocytes, NK cells, and granulocytes as assessed by CD3, CD14, CD56, and CD66b, respectively (Fig. 3A). Activation of normal human T cells with anti-CD3 mAb and IL-2 did not induce BLyS receptor expression (*6*). In contrast, biotinylated BLyS bound peripheral CD20$^+$ B cells. Receptor expression was also detected on the B cell tumor lines REH, ARH-77, Raji, Namalwa, RPMI-8226, and IM-9 but not any of the myeloid-derived lines tested, including THP-1, HL-60, K-562, and U-937 (Fig. 3B). Thus, BLyS displays a B cell tropism in both its receptor distribution and biological activity.

To examine the species specificity of BLyS, mouse splenic B cells were cultured in the presence of human BLyS (HuBLyS) and SAC. Recombinant BLyS induced in vitro proliferation of murine splenic B cells and bound to a cell-surface receptor on these cells. Immature surface Ig-negative B cell precursors isolated from mouse bone marrow did not proliferate in response to BLyS, nor did they bind the ligand (*6*).

To assess the in vivo activity of rBLyS, BALB/c mice (three mice per group) were injected intraperitoneally (i.p.) twice a day for 4 days with buffer only or with BLyS (2 mg/kg body weight). Upon treatment with BLyS, normal splenic architecture was altered by an expansion of the white pulp and an increase in nucleated cells within the red pulp (RP) (Fig. 4A). The B cell regions within the periarterial lymphatic sheaths (PAL) and the marginal zone were expanded but appeared to stain less intensely with the B cell marker CD45R (also known as B220). In addition, the T cell–dense regions surrounding the central arterial (CA) were also infiltrated by moderate numbers of CD45R$^+$ cells. This suggests the white pulp changes were due to increased numbers of B cells. The densely packed cell population that fre-

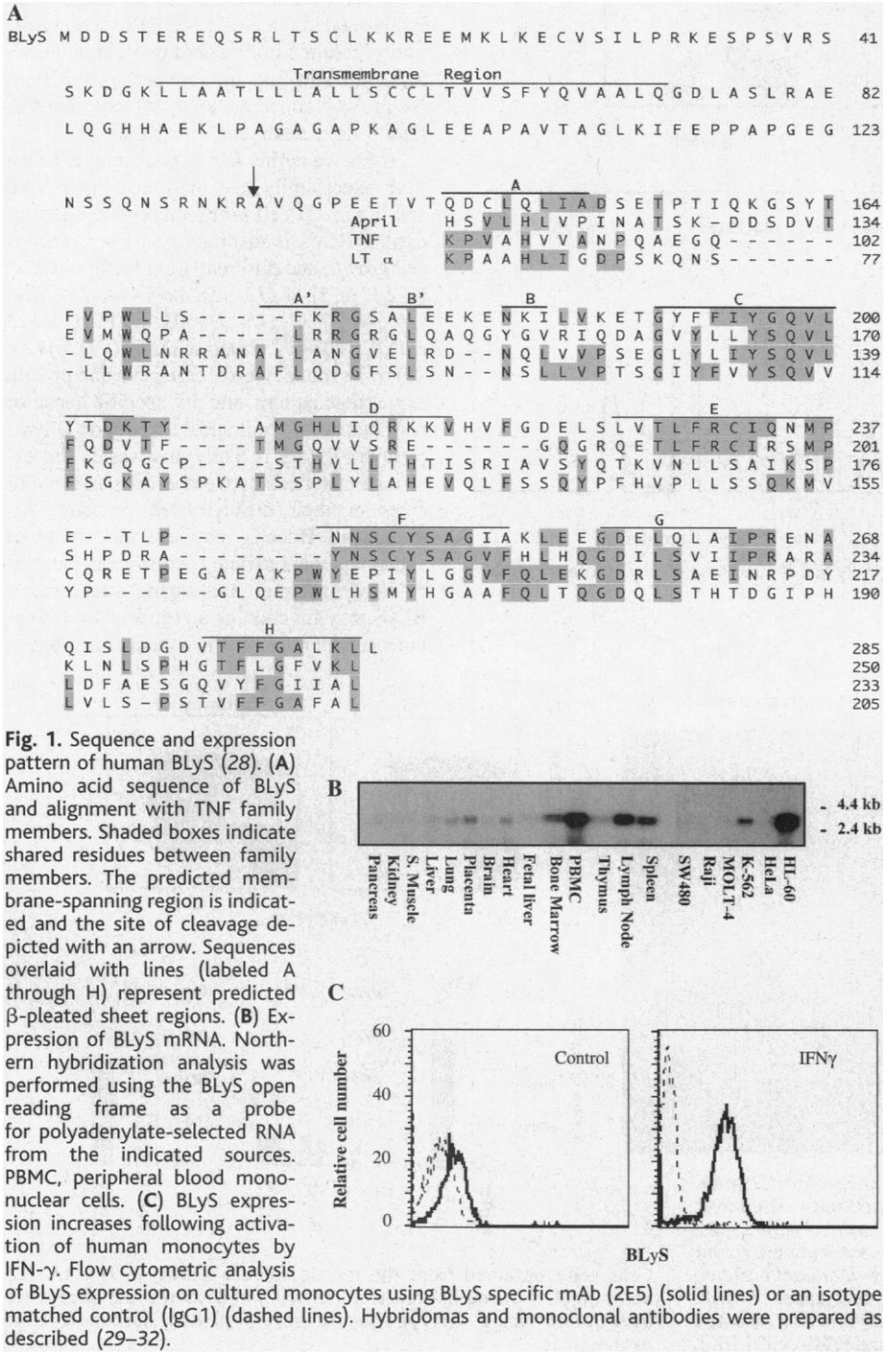

Fig. 1. Sequence and expression pattern of human BLyS (*28*). (**A**) Amino acid sequence of BLyS and alignment with TNF family members. Shaded boxes indicate shared residues between family members. The predicted membrane-spanning region is indicated and the site of cleavage depicted with an arrow. Sequences overlaid with lines (labeled A through H) represent predicted β-pleated sheet regions. (**B**) Expression of BLyS mRNA. Northern hybridization analysis was performed using the BLyS open reading frame as a probe for polyadenylate-selected RNA from the indicated sources. PBMC, peripheral blood mononuclear cells. (**C**) BLyS expression increases following activation of human monocytes by IFN-γ. Flow cytometric analysis of BLyS expression on cultured monocytes using BLyS specific mAb (2E5) (solid lines) or an isotype matched control (IgG1) (dashed lines). Hybridomas and monoclonal antibodies were prepared as described (*29–32*).

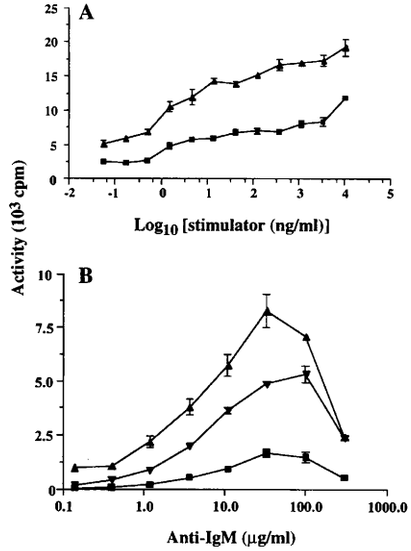

Fig. 2. BLyS is a potent B lymphocyte stimulator. (**A**) The biological activity of BLyS was assessed in a standard B lymphocyte costimulation assay (*33*) (▲, SAC + IL-2; ■, SAC + BLyS). (**B**) Proliferation of tonsillar B cells with BLyS and costimulation with anti-IgM [■, anti-IgM only; ▲, anti-IgM + IL-2 (100 ng/ml); ▼, anti-IgM + BLyS (100 ng/ml)].

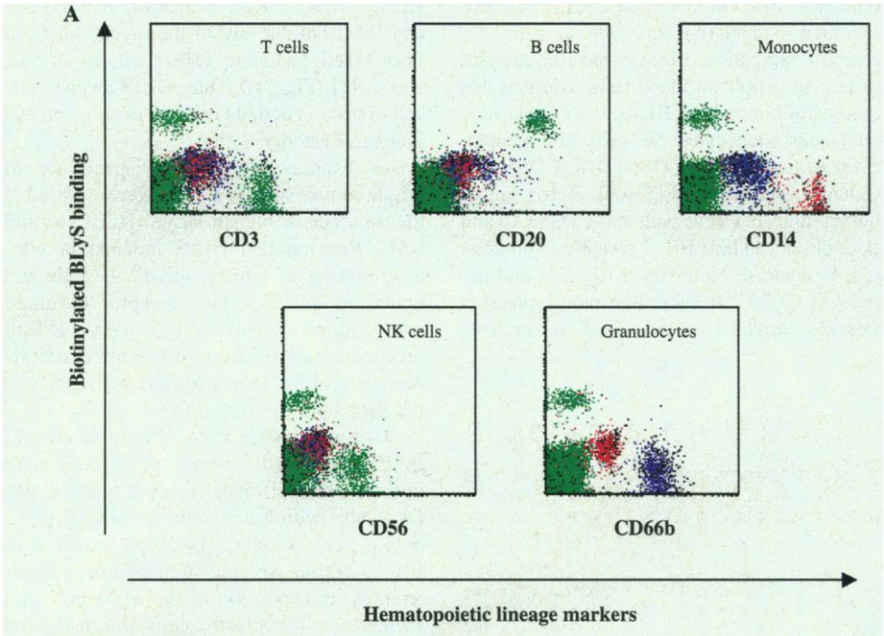

Fig. 3. BLyS receptor expression among normal human peripheral blood nucleated cells and tumor cell lines. (**A**) Human peripheral blood nucleated cells were obtained from normal volunteers and isolated by density gradient centrifugation. Cells were stained with biotinylated BLyS followed by PE-conjugated streptavidin and fluorescein isothiocyanate (FITC)–coupled mAbs specific for CD3, CD20, CD14, CD56, and CD66b. (**B**) BLyS binding to U-937 and the myeloma line IM-9. Similar results were also obtained using a biologically active FLAG-tagged BLyS protein instead of the chemically modified biotin-BLyS (*6*).

quently filled RP spaces did not stain with CD45R.

Flow cytometric analyses of the spleens from BLyS-treated mice indicated that BLyS increased the proportion of CD45R^{dull}, Ly6D^{bright} (also known as ThB) B cells approximately 10-fold over that observed in control mice (Fig. 4B). This phenotype is rare among normal splenocytes but is characteristic of terminally differentiated plasma cell populations (*9, 10*). A potential consequence of increased B cell representation in vivo is a relative increase in serum Ig titers. Accordingly, serum IgM, IgG, and IgA concentrations were compared between buffer- and BLyS-treated mice (Fig. 4C). BLyS administration resulted in five- and twofold increases in serum IgM and IgA, respectively. Circulating IgG concentrations did not increase after 4 days treatment with BLyS.

Here, we define BLyS as a member of the TNF superfamily that induces both in vivo and in vitro B cell proliferation and differentiation. BLyS is distinguished from other B cell growth and differentiation factors such as IL-2 (*11*), IL-4 (*12, 13*), IL-5 (*14, 15*), IL-6 (*16, 17*), IL-7 (*18, 19*), IL-13 (*20*), IL-15 (*21*), CD40L (*22, 23*), or CD27L (CD70) (*24, 25*) by its monocyte-specific gene and protein expression pattern and its specific receptor distribution and biological activity on B lymphocytes. BLyS is likely involved in the exchange of signals between B cells and monocytes or their differentiated progeny. Although all B cells may use this mode of signaling, the restricted expression patterns of BLyS receptor and ligand suggest that BLyS may function as a regulator of T cell–independent responses in a manner analogous

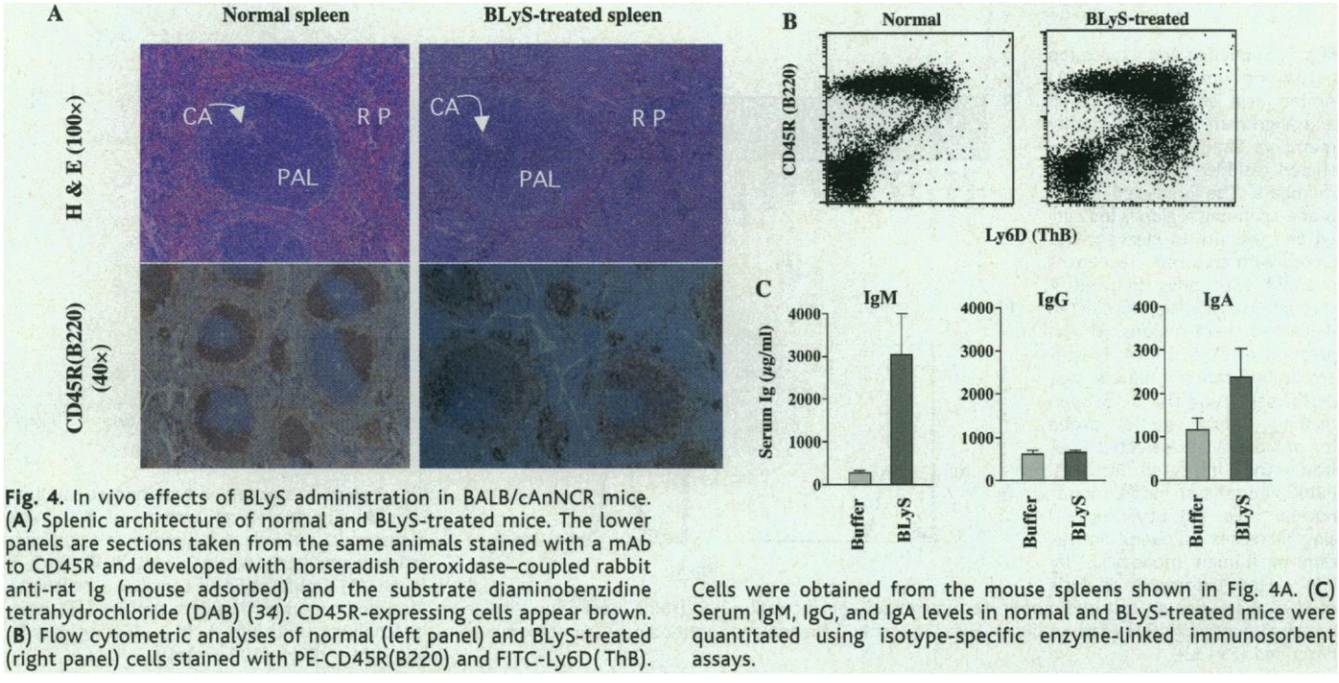

Fig. 4. In vivo effects of BLyS administration in BALB/cAnNCR mice. (**A**) Splenic architecture of normal and BLyS-treated mice. The lower panels are sections taken from the same animals stained with a mAb to CD45R and developed with horseradish peroxidase–coupled rabbit anti-rat Ig (mouse adsorbed) and the substrate diaminobenzidine tetrahydrochloride (DAB) (*34*). CD45R-expressing cells appear brown. (**B**) Flow cytometric analyses of normal (left panel) and BLyS-treated (right panel) cells stained with PE-CD45R(B220) and FITC-Ly6D(ThB). Cells were obtained from the mouse spleens shown in Fig. 4A. (**C**) Serum IgM, IgG, and IgA levels in normal and BLyS-treated mice were quantitated using isotype-specific enzyme-linked immunosorbent assays.

to that of CD40 and CD40L in T cell–dependent antigen activation (*26, 27*). As such, BLyS, its receptor, or related antagonists may find medical utility in the treatment of B cell disorders associated with autoimmunity, neoplasia, or immunodeficiency syndromes.

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28. A full-length BLyS clone was identified, sequenced, and submitted to GenBank (accession number AF132600). BLyS was expressed in baculovirus and purified from Sf9 cell supernatant using a combination of ion exchange (poros HQ-50, poros HS-50, poros PI-50; PE Biosystems, Framingham, MA), size exclusion (Sephacryl S100 HR; Amersham Pharmacia Biotech, Piscataway, NJ), and hydrophobic interaction (Toyopearl Hexyl 650C; Tosohass, Montgomeryville, PA) columns. Purification of BLyS was monitored by SDS-PAGE analysis and the B cell costimulation assay. BLyS was formulated in 0.15 M NaCl and 50 mM sodium acetate at pH 6. Endotoxin concentrations were below the detection limit in the LAL assay (Associates of Cape Cod, Falmouth, MA). Single-letter abbreviations for the amino acid residues are as follows: A, Ala; C, Cys; D, Asp; E, Glu; F, Phe; G, Gly; H, His; I, Ile; K, Lys; L, Leu; M, Met; N, Asn; P, Pro; Q, Gln; R, Arg; S, Ser; T, Thr; V, Val; W, Trp; and Y, Tyr.
29. BLyS expression was assessed on the indicated cell types using BLyS-specific mAb 2E5 (IgG1) followed by phycoerythrin (PE)-conjugated F(ab')2 goat antibody to mouse IgG (CALTAG Laboratories, Burlingate, CA). Purified monocytes were cultured in tissue culture–treated plastic wells (Falcon #3043; Becton-Dickinson, Lincoln Park, NJ) for 3 days in RPMI-1640 medium supplemented with 10% fetal bovine serum (FBS), 2 mM l-glutamine, 100 U/ml penicillin and 100 μg/ml streptomycin in the presence or absence of IFN-γ (100 U/ml). Comparable results were obtained with monocytes purified from three different donors in three independent experiments. BLyS binding was assessed using rBLyS biotinylated with a *N*-hydroxy-succinimidobiotin reagent (Pierce, Rockford, IL) and PE-conjugated streptavidin (Dako Corp., Glostrup, Denmark).
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32. BALB/cAnNCR mice (6 to 8 weeks old) from Charles River Laboratories were maintained according to recommended standards in microisolator cages with recycled paper bedding (Harlan Sprague-Dawley, Indianapolis, IN) and were provided with pelleted rodent diet (Harlan Sprague-Dawley) and bottled drinking water on an ad libitum basis. The animal protocols used in this study were reviewed and approved by the Human Genome Sciences Institutional Animal Care and Use Committee.
33. Human tonsillar B cells were purified by magnetic bead (MACS) depletion of $CD3^+$ cells. Purified cells were > 95% B cells as assessed by expression of CD19 and CD20. We placed rHuBLyS or the control protein rHuIL-2 into individual wells of a 96-well plate, to which we added 10^5 B cells suspended in medium (RPMI-1640 containing 10% FBS, 5×10^{-5} M 2ME, 100 U/ml penicillin, 100 μg/ml streptomycin, and 10^{-5} dilution of SAC or anti-IgM). Proliferation was quantitated by a 20-hour pulse (0.5 μCi/well) of [^{3}H]thymidine (6.7 Ci/mM) beginning 72 hours after factor addition. Analyses of both human and mouse B cell cultures indicated that the proliferative response was evident 24 hours after BLyS addition and progressively increased with a maximal response observed between 72 and 92 hours after culture initiation. The positive and negative controls were IL-2 and medium, respectively. SAC alone yielded background counts of 1427 ± 316. Values are reported as mean ± standard deviation of triplicate wells. Anti-IgM costimulation was performed as described for SAC with the exception that individual wells were precoated with 50 μl of a 10 μg/ml solution of anti-human IgM mAb (IgG1) for 12 hours at 4°C, after which wells were washed before addition of cells. An isotype-matched (IgG1) control antibody was included as a control for nonspecific Ig effects. Similar results were obtained using rBLyS purified from stable CHO transfectants and transiently transfected HEK-293T cells.
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hRAD30 Mutations in the Variant Form of Xeroderma Pigmentosum

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Xeroderma pigmentosum (XP) is an autosomal recessive disease characterized by a high incidence of skin cancers. Yeast *RAD30* encodes a DNA polymerase involved in the error-free bypass of ultraviolet (UV) damage. Here it is shown that XP variant (XP-V) cell lines harbor nonsense or frameshift mutations in *hRAD30*, the human counterpart of yeast *RAD30*. Of the eight mutations identified, seven would result in a severely truncated hRad30 protein. These results indicate that defects in *hRAD30* cause XP-V, and they suggest that error-free replication of UV lesions by hRad30 plays an important role in minimizing the incidence of sunlight-induced skin cancers.

Xeroderma pigmentosum (XP) patients are hypersensitive to sunlight, and they suffer from a high incidence of skin cancers. Cells from seven different XP complementation groups (A to G) are defective in nucleotide excision repair (*1*), whereas cells from the variant form of XP (XP-V) excise UV photoproducts at a normal rate (*2*). XP-V cells, however, are much slower than normal cells in replicating DNA containing UV photoproducts (*3*), and XP-V cell-free extracts are deficient in bypass replication of a *cis-syn* thymine-thymine (T-T) dimer (*4*). XP-V cells are hypermutable with UV light and exhibit an unusual mutational spectrum (*5*). The *RAD30* gene of *Saccharomyces cerevisiae* functions in error-free bypass of UV lesions (*6*, *7*). RAD30 encodes a DNA polymerase, Polη, which can efficiently replicate past a *cis-syn* T-T dimer in template DNA, and Rad30 inserts two adenines across from the dimer (*8*). Here, we determine if the human homolog of yeast *RAD30* is responsible for XP-V.

A human cDNA clone, H96386 [345 base pairs (bp)], that encodes a peptide with homology to the NH_2-terminus of yeast Rad30 protein was used to screen a spleen cDNA library (*9*), and a single clone that contains a 3-kb cDNA insert was isolated. Sequence analysis (*10*) of this cDNA (*11*) (GenBank accession number AF158185) indicated that the protein encoded by the human gene displays significant homology to the *S. cerevisiae* Rad30 protein (Fig. 1A). We have named the human gene *hRAD30*. Excluding the intervening region from amino acid residues 452 to 606 in hRad30, the human and yeast Rad30 proteins share 23% identical and 53% conserved residues, and the two proteins have several highly conserved motifs throughout their length (Fig. 1A).

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