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T-cell apoptosis in ICF syndrome

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To the Editor:

Immunodeficiency-centromeric instability-facial anomalies (ICF) syndrome is characterized by hypogammaglobulinemia, recurrent infections, and facial anomalies.¹ Rearrangements involving the heterochromatin of chromosomes 1, 9, and 16 are detected almost exclusively in T lymphocytes.¹ In some patients with ICF who have lymphopenia or an inverted CD4/CD8 ratio,^{2,4} T cells and/or their subsets can be particularly vulnerable to apoptosis.

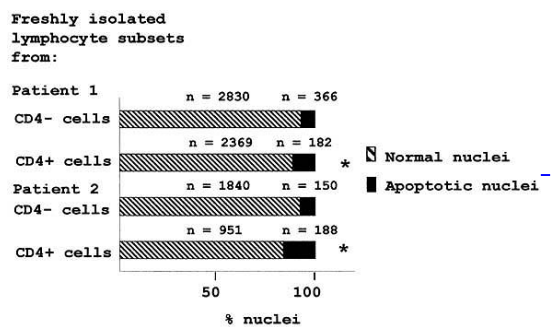
To test this hypothesis, we investigated the occurrence of apoptosis in peripheral blood T lymphocytes, as well as in the CD4⁺ and CD4⁻ subsets, from 2 patients with ICF, one displaying an inverted CD4/CD8 ratio and the other displaying T-cell lymphopenia with an abnormal expansion of NK cells (CD3⁻, CD56⁺, CD16⁺, and CD8^{+/-}).

The number of apoptotic lymphocytes in phytohemagglutinin-stimulated cells was significantly higher in patients than in 4 age-matched normal controls ($P < .001$ for each patient; χ^2 test). Apoptosis involved significantly more CD4⁺ lymphocytes than CD4⁻ lymphocytes (freshly isolated by immunomagnetic bead manipulation) from both patients with ICF (Fig 1).

The simultaneous presence of apoptotic nuclei and of 1qh and 16qh chromosomal rearrangements in the aforementioned cell fractions was investigated through use of a newly developed technique whereby the TdT-mediated-dUTP nick end labeling (TUNEL) and fluorescence in situ hybridization (FISH) assays are carried out sequentially on the same sample (Fig 2). In case 1, more CD4⁺ cells than CD4⁻ cells showing 1qh abnormalities were found to undergo apoptosis ($P < .05$), whereas no significant difference was observed between CD4⁺ and CD4⁻ cells with 16qh abnormalities. In case 2, CD4⁺ lymphocytes bearing 1qh or 16qh rearrangements contained more apoptotic cells than CD4⁻ cells with the same abnormalities ($P < .01$ for both rearrangements).

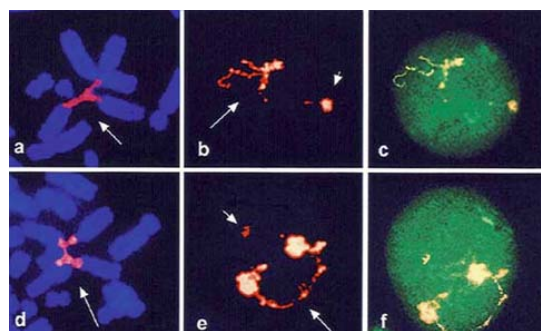
Despite the detection of spontaneous T-cell apoptosis, no clinical evidence of T-cell immunodeficiency was found in our patients. Recent studies have shown that mutations in the DNA methyl transferase 3B gene occur in a fraction of patients with ICF.^{5 6} Notably, however, no such mutations have been detected in the present cases.⁷ The general relevance of these results remains to be established by further studies.

Fig. 1. Detection of apoptosis by the TUNEL assay in CD4⁺ and CD4⁻ cells from patients with ICF. Each result is the percent of nuclei; *dashed areas* indicate normal nuclei, and *black areas* indicate apoptotic nuclei. *n*, Absolute number of nuclei counted for the area. *Asterisk* indicates statistically significant difference ($P < .001$).



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Fig. 2. Simultaneous detection of apoptosis by the TUNEL assay and of chromosomal rearrangements by FISH on interphase nuclei from freshly isolated lymphocytes of ICF patient 1. **a**, Chromosome 1qh hybridization signal with triradial configuration (*arrow*) in a partial metaphase. **b**, A similar triradial configuration is detected in an interphase nucleus subjected to FISH with the 1qh-specific probe pMG1; *arrow* indicates heterochromatic chromosome 1 hybridization signal, and *arrowhead* points to the hybridization signal of the normal chromosome 1. **c**, The same nucleus shown in Fig 2, *b* displays chromatin fragmentation, an early feature of apoptosis, as assessed by the TUNEL assay (bright green staining with FITC-dUTP). This finding demonstrates unambiguously that apoptosis affects a cytogenetically abnormal cell. **d**, Chromosome 1qh hybridization signal (pMG1 probe) of large size in an intertwined network of multibranched chromosomes (*arrow*) in a partial metaphase. **e**, In an interphase nucleus subjected to FISH with the pMG1 probe, the heterochromatic hybridization signal shows 2 large blocks joined by a thin stretch. This figure is the equivalent of the metaphase signal shown in Fig 2, *d*; however, heterochromatin appears more decondensed, as expected in interphase. *Arrowhead* points to the hybridization signal of normal chromosome 1. **f**, The same nucleus shown in Fig 2, *e* displays chromatin fragmentation, an early feature of apoptosis (bright green staining with FITC-dUTP). The signals shown in red in Fig 2, *e* and in Fig 2, *b* appear here in yellow because of the use of the filter for FITC-dUTP detection, showing again that apoptosis affects a cytogenetically abnormal cell.



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