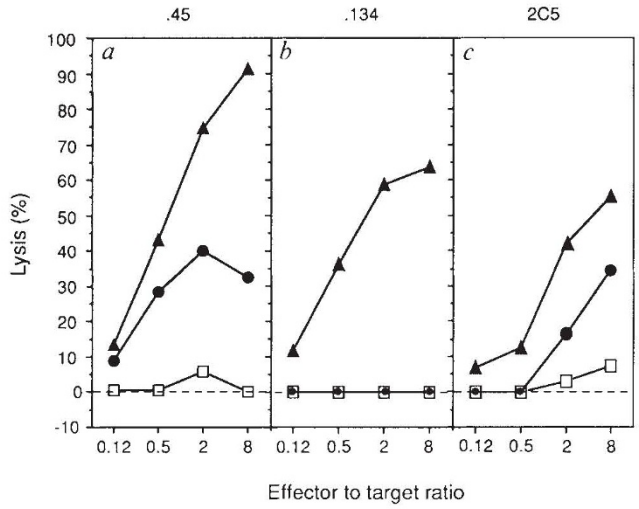

FIG. 4 A functional TAP is required for DR1-restricted presentation of a cytosolic H3 peptide but not for presentation of cytosolic H3. Lysis of uninfected (squares) or infected (filled symbols) cells was tested with the DR1-restricted H3-specific T-cell line E1.9 at the indicated effector to target ratios. Cells were infected with Vac-cytoH3 (triangles) or Vac-miniH3 (circles) as described for Fig. 2. *a*, Epstein–Barr virus-B cell line .45. *b*, TAP1-deficient mutant .134 derived from .45. *c*, Transfectant 2C5 of mutant .134 with restored TAP1 expression.

compartment occurs in a TAP-independent manner, or that a distinct pathway exists for the delivery of cytosolic antigen to a class II compartment. It is unlikely that cytoH3 presentation is mediated by the TAP2 subunit alone as mutant .134 cannot present the class I-restricted M1 epitope. Furthermore, mutant .134 infected with Vac-miniH3 was not recognized by E1.9 cells (Fig. 4*b*). The defect in presentation of endogenous miniH3 was clearly due to the lack of functional TAP and not to a secondary mutation, because transfected .134 cells expressing a complementary DNA for TAP1 (clone 2C5)[11] were lysed by E1.9 after infection with Vac-cytoH3 and Vac-miniH3 (Fig. 4*c*), even though the overall efficiency of lysis of transfectant 2C5 was somewhat reduced compared with .45 cells. Presentation of an endogenous cytosolic peptide by class II molecules is thus dependent on a functional TAP1. Therefore, presentation of endogenous cytoH3 in the absence of TAP1 probably does not involve translocation of short peptides into an early exocytic compartment.

These results define distinct pathways for the presentation of endogenous antigen by class II molecules. The first is similar to the class I pathway in that it uses short cytosolic peptides in a TAP-dependent process. But it is distinct from the class I pathway in its sensitivity to chloroquine. In addition, whereas presentation of cytosolic peptides by class I molecules is extraordinarily efficient, it is not yet clear how efficient or widespread this pathway may be for class II-restricted presentation. The second pathway is distinct from the class I pathway in that it does not require TAP1 function. Furthermore, it may not involve short peptides, but rather the delivery of larger cytosolic molecules to an endosomal/lysosomal compartment for processing, as was suggested earlier in a study on endogenous processing of cytosolic matrix protein[13,21].

It is now clear that antigenic epitopes recognized by $CD4^+$ T cells can be generated from processing of cytosolic proteins by several mechanisms. A potential use of such mechanisms is to accelerate the generation of T-cell help by class II-positive cells that are virus-infected. Although some viruses require endocytosis for infection, many others infect cells by fusion at the cell surface, delivering viral proteins directly into the cytosol. In the latter case, such as with human immunodeficiency virus, endogenous processing of cytosolic proteins for class II-restricted presentation may be an important defence mechanism. An important question raised by our findings is whether class II-resticted presentation of cytosolic proteins extends to self proteins in normal cells and to what extent such presentation may influence T-cell repertoire and tolerance. □

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ERRATUM

Myosin head movements are synchronous with the elementary force-generating process in muscle

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THE seventh sentence in the description of Fig. 1*b* on page 156 in this Letter should begin "The intensity before the step was $92 \pm 4\%$ of that in a tetanus without imposed steps", not $9 \pm 4\%$ as printed.