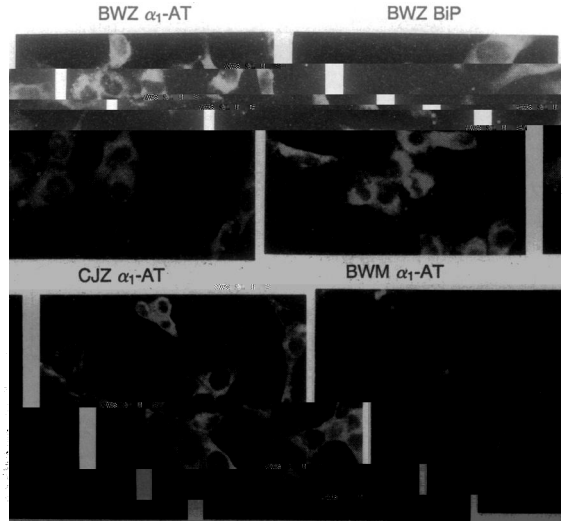
*Proc. Natl. Acad. Sci. USA*
Vol. 91, pp. 9014–9018, September 1994
Medical Sciences

# A lag in intracellular degradation of mutant $\alpha_1$-antitrypsin correlates with the liver disease phenotype in homozygous PiZZ $\alpha_1$-antitrypsin deficiency

YING WU*, INA WHITMAN*, ERNESTO MOLMENTI*, KENNETH MOORE*, PAUL HIPPENMEYER†, AND DAVID H. PERLMUTTER*

tibody to human calnexin (AF8) was provided by M. Brenner



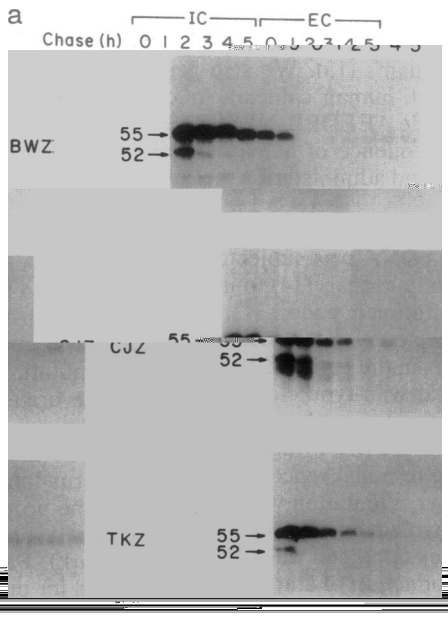
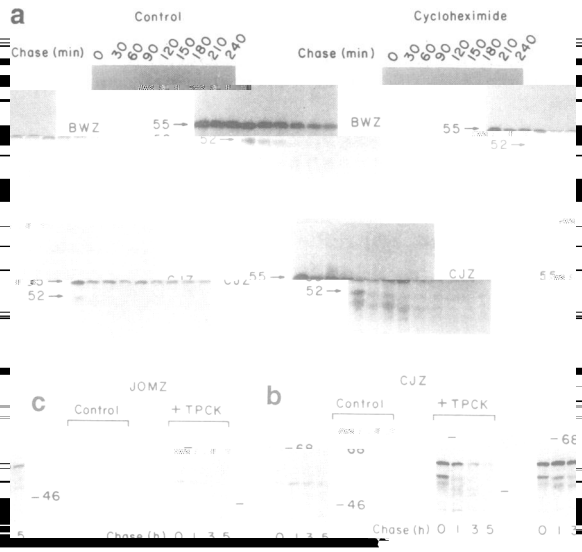



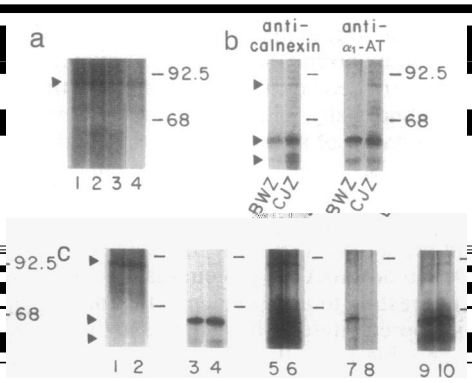

FIG. 2. Immunofluorescent staining of $\alpha_1$-AT and BiP in BWZ, BWM, and CJZ cells. The cells were stained for $\alpha_1$-AT or BiP and then with fluorescein isothiocyanate-conjugated anti-immunoglobulin.

were resistant to endo H. BWZ cells were also subjected to

cycloheximide on degradation of $\alpha_1$-AT Z in fibroblasts from BW (susceptible) and from CJ (protected) (Fig. 4*a*). In BWZ

naturing conditions, to optimize coprecipitation, and the resulting cell lysate was subjected to immunoprecipitation in



conditions of immunoprecipitated calnexin and $\alpha_1$-AT from each cell line is shown (lanes 1–4). Immunoprecipitation of calnexin (lanes 5 and 6) under nondenaturing conditions was associated with multiple bands including ones comigrating with the ≈88 kDa calnexin polypeptide and ≈52- and ≈55-

olytic cleavage in the juxtamembrane region (29). Because we could not detect a specific proteolytic fragment of $\alpha_1$-AT Z in our system, we predict that its degradation involves the major pathway for ER degradation. This would mean that the BWZ cell line is defective in this major ER degradative pathway