MOLECULAR MECHANISMS OF APOPTOSIS

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Introduction

Apoptosis is the normal physiological process of cell death essential for the maintence of homeostasis (reviewed in 1-3). Because of its important role in development and recent evidence implicating dysregulation of this process underiying various pathological cónditions (3), there has been intense interest in the biochemical mechanism of apoptosis. Work in this laboratory has analyzed the apoptotic pathway using the human monocyte-like cell line U037 asa model system. Our studies indicate that both TNF and UV light initiate similar biochemicai processes culminating in internucleosómal DNA fragmentation. A key even in this pathway is the activation of a serine protease termed AP24 (apoptotic protease of 24 KD). This enzyme was purified from apoptotic U937 cells following exposure to UV light and was shown to initiate internucleosomal DNA fragmentation in nuclei isolated from normal U937 cells (4). Since protein synthesis is not required for apoptosis in this system (5), AP24 must be expressed in an inactive form or else in sequestered from its substrate in normal U937 cel! s. The upstream signaling events leading to activation of AP24 have been the subject of recent work. Recent work demonstrating a role for the caspase cascade (6) AOP-ribosylation (7) and calcium calmodulin kinase II (8) in the upstream activation of AP24 witl be presented.

1. Walker NI, Harmon BV, Gogê GC, Kerr JFK. Patterns of celi death. Meth Achiev Exp Pathol 1988;13:18-54.

2. Gerchenson LE, Rotello RJ. Apoptosis: a different type of cell death. FASEB J 1995; 6:2450.

3. Thompson CB. Apoptosis in the pathogenesis and treatment of disease. Science 1992;267:1456.

4. Wright SC, Wei QS, Zhong J, Zheng H, Kinder DH, Larrick JW. Purification of a 24 kD protease from apoptotic tumor cells that activates DNA fragmentation. J Exp Med 1994;180:2113.

5. Wright SC, Kumar P, Tam AW, Shen N, Varma M, Larrick JW. 1992. Apoptosis and DNA fragmentation preceed TNA-induced cytolysis in U937 cells. J Cell Biochem 1994;48:344.

6. Wright SC, Schellenberger U, Wnat H, Kinder DH, Larrick JW. Activation of C((32-like proteases is NOT sufficient to lead to apoptosis: Inhibition of apoptosis by agents that suppress activation of AP24 but not DEVD-cleaving activity. 1997(submitted).

7. Wright SC, Wei QS, Kinder Ok, Larrick JW. Biochemical pathways of apoptosis: NAD deficient cells are resistant to TNK or UV light activation of the 24kD apoptotic protease and DNA fragmentation. J Exp Med 1996; 183:463.

8. Wright SC, Ji L, Wang H, Larrick JW. 1997. Biochemical pathways of apoptosis: Calmodulin dependent protein kinase II mediates signal transduction in apoptosis. FASEB J (in press).