ONLINE ISSN : 1880-313X
PRINT ISSN : 0388-6107

Biomedical Research
Vol. 28 (2007) , No. 1 February pp.33-42

Geldanamycin, a heat-shock protein 90-binding agent, induces thymocyte apoptosis through destabilization of Lck in presence of 12-*O*-tetradecanoylphorbol 13-acetate

Kazumasa OHTA[1)], Rintarou OKOSHI[1)], Maiko WAKABAYASHI[1)], Ayako ISHIKAWA[1)], Yutaka SATO[1)] and Harutoshi KIZAKI[1)]

1) Department of Biochemistry, Tokyo Dental College

(Received November 27, 2006)
(Accepted December 13, 2006)

ABSTRACT

Geldanamycin, a heat-shock protein 90 (Hsp90)-binding agent, modulates various cellular activities. The present study found that, although geldanamycin by itself had no effect on thymocyte viability, it induced apoptosis in thymocytes with a reduction of the mitochondrial transmembrane potential ($\Delta\Psi m$) in the presence of 12-*O*-tetradecanoylphorbol 13-acetate (TPA), an activator of protein kinase C (PKC). This apoptosis depended on transcription and translation, and on activation of caspase-8 and -3. Geldanamycin treatment in the presence of TPA also enhanced destabilization of Lck. This destabilization was independent of transcription and translation. It was inhibited, however, by conventional PKC inhibitors, preventing apoptosis. Proteasome inhibitor affected neither the degradation of Lck nor DNA fragmentation, although they inhibited reduction of $\Delta\Psi m$. These results suggest that the ubiquitin-proteasome system is not involved in Lck destabilization, and that $\Delta\Psi m$ reduction is not directly related to the progression of apoptosis. Furthermore, inhibition of Lck in the presence of TPA induced apoptosis in thymocytes. Our findings suggest that Hsp90 modulates thymocyte apoptosis in concert with PKC through the destabilization of Lck and in a caspase-8- and -3-dependent manner.

To cite this article:

Kazumasa OHTA, Rintarou OKOSHI, Maiko WAKABAYASHI, Ayako ISHIKAWA, Yutaka SATO and Harutoshi KIZAKI; "Geldanamycin, a heat-shock protein 90-binding agent, induces thymocyte apoptosis through destabilization of Lck in presence of 12-*O*-tetradecanoylphorbol 13-acetate", *Biomedical Research*, Vol. **28**, pp.33-42 (2007) .

doi:10.2220/biomedres.28.33

JOI JST.JSTAGE/biomedres/28.33