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Short Communication

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Relationship between Cellular Senescence and Redox Potential on Adult T-Cell Leukemia Cells

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Abstract

Human T-cell leukemia virus type I (HTLV-I) is a human retrovirus and an etiologic agent of adult T-cell leukemia/lymphoma (ATL/ATLL). The subtypes acute and lymphoma have a poor prognosis with median survival rate of approximately 6 months. Some excellent therapeutic strategies for ATL are required. Retinoids [all-*trans* retinoic acid (ATRA) and tamibarotene (Am-80) have been reported to inhibit the *in vitro* growth of HTLV-1 [+] T-cell lines and that of fresh cells obtained from patients with adult T-cell leukemia (ATL). We showed a clinical efficacy of retinoid therapy in treating ATL has also been evaluated. Further, we found that retinoid induced cellular senescence on ATL cells and tight relationship between cellular senescence and redox potential on ATL cells.

Keywords

HTLV-I; Retinoid; Senescence; ROS; Redox

Introduction

Human T cell leukemia virus type I (HTLV-I) is a human retrovirus that is an etiologic agent of adult T cell leukemia/lymphoma (ATL/ATLL) [1]. We previously reported the clinical efficacy of all-*trans* retinoic acid (ATRA) for patients with adult-T-cell leukemia (ATL) [2]. Additionally, we found that retinoids including ATRA could facilitate cellular senescence in HTLV-I-positive T-cell lines and fresh primary cells obtained from patients with acute ATL [3]. Cellular senescence was detected by staining for senescence-associated β-galactosidase (SA β-Gal) [4]. It has known that senescence is a well-established anti-cancer mechanism [5] and can be caused by telomere attrition, DNA damage, oncogene and oxidative stress [6].

In our previous study, significant cellular senescence was observed for *Tax* mRNA expressing cells (HUT102, MT-2, MT-4, and ATL-2 cells) than ED40515 cells, which do not express *Tax* mRNA because of a nonsense mutation [3]. Thus, we assume that *Tax* is an oncogene that could possibly be involved in oncogene-induced senescence (OIS) by retinoids. It has been reported that OIS does occur in human and mouse tumor cells *in vivo* [7,8]. Furthermore, it is caused by accumulation of DNA damage, which in turn causes oncogene-driven accumulation of reactive oxygen species (ROS) [9]. Our hypothesis is that the *Tax* oncogene may induce cellular senescence via ROS, but the number of these senescing cells is easily reduced by retinoid. These results indicated that Tax mRNA expression may be a critical factor in retinoid therapy for patients with ATL and retinoid may be a reasonable agent for ATL with facilitating cellular senescence.

The balance of oxidative/anti-oxidative influences may play an important role in the modulation of cellular function. It has been reported that L-cysteine and L-cystine act as a buffer of the redox potential of the environment in cells or serum [10,11]. In our previous study, to study the effects of exogenous thiol compounds on the sensitivity to retinoid in a HTLV-I positive T cell line, ATL2 cells [12] were cultured with thiol compounds (L-cystine, GSH and TRX), following addition of ATRA or 13-*cis* RA [13,14]. Pre-incubation of ATL-2 with L-cystine or GSH resulted in complete restoration of growth despite the inhibitory effects of RA; this suggested that it helped to increase the redox potential of the intracellular environment [10]. These processes are antagonized by antioxidants such as cysteine and GSH [11]. Moreover, the effects of thiol compound, N-acetyl cysteine (NAC) for cellular senescence was examined. Figure 1 showed that spontaneous senescence was induced on HTLV-I positive T-cell lines (HUT102 and MT-2) but not on HTLV-I negative T-cell lines (Jurkat and MOLT-4). Furthermore, ATRA treatment induced more senescence on just HTLV-I positive T-cell lines. However, pretreatment with NAC for 24 hrs blocked cellular senescence by following addition with ATRA. These results suggest that the imbalance of intracellular redox potential in HTLV-I [+] T cell lines may be associated strongly with the sensitivity to RA and exogenous thiol compounds may prepare the intracellular environment to become resistant to RA. Further, pre-treatment with NAC for those cells was sufficient to recover from cellular senescence and finally rescue cell proliferation on HTLV-I positive T-lymphocytes. Having obtained those results described above, it has been suggested tight relationship between cellular senescence and redox potential on HTLV-I positive cells.

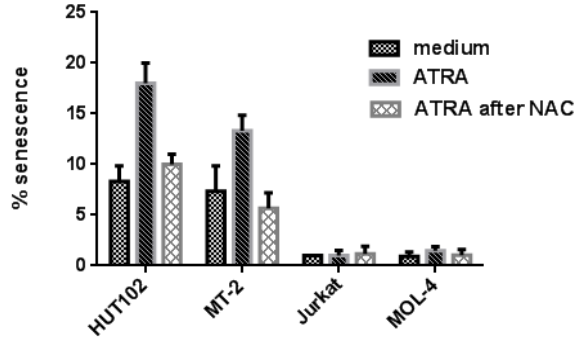

Figure 1: The effects of NAC for cellular senescence.

Note: Both HTLV-I positive cell lines [HUT102 and MT-2] and HTLV-I negative T-cell lines [Jurkat and MOLT-4] with 10-5 M NAC for 24 hrs were pre-incubated, and then 10-5 M ATRA was added to those cells for 24 hrs. Cellular senescence was detected by staining for senescence-associated β-galactosidase [SA β-Gal]. Values for the calculation were the mean of triplicate culture.

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