Targeted Therapy of HTLV-I Associated Adult T-cell Leukemia/Lymphoma: From the Bench to the Bedside

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Overview on ATL

Adult T-cell leukemia-lymphoma (ATLL) (reviewed in Bazarbachi and Hermine, 2001, Bazarbachi et al. 2004a) is an aggressive lymphoid proliferation associated with the human T cell lymphotropic virus type I (HTLV-I) (Hinuma et al. 1982). ATLL, the first human disease associated with a retroviral infection, usually occurs in native individuals from the HTLV-I endemic regions, i.e. the southern Japan, the Caribbean, inter-tropical Africa, Brazil and the Middle East (Gessain 1996). Although HTLV-I may be transmitted by intravenous route or sexual intercourse, vertical transmission through breast-feeding is required for ATLL development.

ATLL develops after a very long latency period in 3 to 5% of HTLV-I infected individuals, and is preceded by oligoclonal expansions of HTLV-I-infected activated T cells (Wattel et al. 1995). These clonal expansions, at least early after infection (Mortreux et al. 2001) result from the expression of the viral transactivator protein Tax, which activates the viral promoter and various cellular genes and creates an autocrine loop involving interleukin-2, interleukin-15 and their cognate receptors (Waldmann et al. 1985, Azimi et al. 1999). Tax alters many cellular pathways: it activates CREB/ATF, AP-1 and NF-κB, upregulates antiapoptotic proteins, represses p53, DNA polymerase beta, PCNA and MAD-1 and interferes with several cell cycle regulators including cyclins and cdk-inhibitors (reviewed in Franchini 1995, Yoshida 2001). Tax also influences the microenvironment: it induces the synthesis of TGF-ß, inhibits TGF-ß signal transduction in infected cells (Arnulf et al. 2002), induces angiogenesis, metalloproteinases and gap junction mediated communication between infected cells and endothelial cells, hence contributing to the extravasation and invasivness of ATLL cells (El-Sabban et al. 2002, Bazarbachi et al. 2004b).

Among the impressive properties of Tax, activation of the NF-κB pathway plays a mandatory role in the proliferation and transformation of infected T cells (Yamaoka et al. 1998). NF-κB plays a central role in the regulation of immune and inflammatory responses (reviewed in Ghosh and Karin 2002; Li and Verma 2002). In unstimulated cells, NF-κB is found in an inactive cytosolic form, associated with an inhibitory subunit known as IκB. Upon cell stimulation, the IκB proteins are phosphorylated by the IκB kinase (IKK) complex, then ubiquitylated and subsequently degraded by the 26S proteasome. Consequently, Rel-A containing NF-κB proteins translocate to the nucleus, bind specific promoters, and activate gene transcription (reviewed in Ghosh and Karin 2002; Li and Verma 2002). HTLV-1-infected and Tax-expressing cells demonstrate constitutive nuclear expression of NF-κB (Mori et al. 1999). Tax is indeed a powerful stimulator of the NF-κB pathway, which acts at multiple levels to initiate and maintain NF-κB activation (reviewed in Kfoury et al. 2005). We recently demonstrated that the lysine residues located in the carboxy-terminal domain of Tax are critical for Tax ubiquitylation and Tax-induced- NF-κB activation (Nasr et al. 2006). Specifically, we showed that these C-terminal lysines are important for Tax binding to IKK, IKK activation and nuclear translocation of NF-κB. We also showed that Tax is post-translationally modified by SUMO binding, and that sumoylation is critical for Rel A-enriched nuclear body formation and NF-κB activation (Nasr et al. 2006). Finally, we showed that K63-ubiquitylated Tax activates IKK in a centrosome-associated signalosome, leading to the production of Tax-free active cytoplasmic IKK (Kfoury et al. 2007). These observations highlight an unsuspected cellular and biochemical complexity in Tax-induced IKK activation and represent potential new targets for ATL therapy.

Targeted therapies for ATLL

Zidovudine and interferon alpha

ATL is an ideal model for targeted therapy because of its extremely poor prognosis due to chemotherapy resistance and to the presence in the leukemic cells of two well characterized targets: the HTLV-I oncoprotein Tax and the constitutive activation of the NF-κB pathway (reviewed in Shimoyama 1992, Bazarbachi and Hermine 2001, Bazarbachi et al. 2004). In multiple phase II clinical studies and more recently in a worldwide metaanalysis, we and others have shown that antiviral therapy using the combination of zidovudine (AZT) and interferon alpha (IFN) results in a high response and complete remission rates, resulting in impressive prolonged survival of more than 10 years in almost half of the patients (Gill et al., 1995; Hermine et al., 1995; Bazarbachi and Hermine, 1996). This targeted therapy is now considered as gold standard first line therapy. However, many patients eventually relapse, stressing the need for additional effective therapies (Hermine et al., 2002).

Arsenic trioxide

A very effective treatment for acute promyelocytic leukaemia, arsenic trioxide (As) synergizes with IFN to induce G1 arrest and apoptosis in ATLL (Bazarbachi et al., 1999) through shut-off of the NF-κB pathway and Tax degradation by the

proteasome (El-Sabban et al., 2000; Nasr et al., 2003). This combination yielded promising clinical results in relapsed/refractory ATL patients (Hermine et al. 2004). We recently demonstrated that the two agents cooperate to cure mouse ATL derived from these Tax transgenics and selectively eradicates leukaemia-initiating cells. Preliminary results from a phase II clinical study using a triple combination of arsenic, AZT and IFN are extremely encouraging.

Proteasome inhibitors

PS-341 is a selective inhibitor of 26S proteasome. PS-341 has demonstrated clinical effect in hematological malignancies. We demonstrated that PS-341 and its combination with doxorubicin or etoposide have a selective effect on fresh ATLL cells and HTLV-I transformed cells, supporting a potential therapeutic role for PS-341, either alone or in combination with chemotherapy in patients with ATLL and other HTLV-I negative T-cell lymphomas (Nasr et al., 2005). A study on another mice model of ATLL showed that PS-341 synergises with the human monoclonal antibody targeting the interleukin 2 receptor and decreases the DNA-binding activity of NFκB by preventing the degradation of the α subunit of inhibitors of NFκB (Tan and Waldmann, 2002).

Inhibitors of angiogenesis

The important role of angiogenesis in the growth and metastasis of solid tumours is well established. The invasive nature of ATLL with common visceral invasion, suggests a possible interaction between cells infected with HTLV-I and endothelial cells. We have shown that HTLV-I positive cells communicate with endothelial cells through paracrine stimulation and through direct heterocellular communication (El-Sabban et al., 2002). Furthermore, cells from ATLL specifically secrete high concentrations of the angiogenic factors VEGF and b-FGF, induce formation of endothelial tubes in vitro and establish functional communication with endothelial cells through gap junctions. Interaction of HTLV-I transformed cells with endothelial cells induces the production of functional matrix metalloproteinase by endothelial cells and results in the degradation of subendothelial basement membrane, allowing extravasation of transformed lymphocytes between endothelial cells (Bazarbachi et al., 2004). These results provide the rationale for a new therapeutic approach based on the inhibition of angiogenesis and on the modulation of adhesion or communication, such as use of kinase inhibitors. Preliminary results in vitro showed that angiogenesis inhibitors, such as monoclonal antibodies anti-VEGF (bevasizumab) or specific kinase inhibitors of the VEGF receptors (PTK-787), inhibit ATLL-induced angiogenesis and ATL cell invasion through an endothelial barrier.

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