Journal of Hematology & Thromboembolic Diseases

Gouri et al., J Hematol Thrombo Dis 2015, S1:e101
DOI: 10.4172/2329-8790.1000S1e101

Editorial Open Access

Urokinase Plasminogen Activator System and Hematologic Malignancies: Potential Role in Diagnosis and Therapy

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Received date: July 27, 2015, **Accepted date:** July 28, 2015, **Published date:** July 30, 2015

Editorial

The urokinase plasminogen activating system (uPAS) consists of the urokinase plasminogen activator (uPA), its cognate cell membrane receptor (uPAR or CD87) and two main inhibitors belonging to the serine proteinase inhibitors (serpin) superfamily, the plasminogen activator inhibitor-1 (PAI-1) and -2 (PAI-2) [1,2].

For over a decade, the uPA system has been implicated in cancer invasion and metastasis. uPA was originally believed to mediate these processes by catalysing degradation of the extracellular matrix (ECM) thus allowing malignant cells to invade locally and eventually spread to distant sites. Recently, additional functions have been described for uPA and uPAR, particularly in cell adhesion and chemotaxis, the amounts of uPA and uPAR in various tumor types and in the tissue/serum samples of cancer patients have been shown to correlate with survival prognosis, indicating the relevance of these molecules in malignancy [3].

The distribution and expression of uPAS in different hematological disorders was reported in several studies, a high level of plasma soluble uPAR (suPAR) at diagnosis was correlated with poor response to chemotherapy in acute leukemia [4].

Literature data show that uPAR (CD87) expression has a potential role in the diagnostic or prognostic work-up of several hematologic malignancies, particularly acute leukemia and multiple myeloma (MM) [5].

Wada H et al. found that the level of the tissue type PA (t-PA) antigen was highest in acute myeloblastic leukemia (AML) and that of the urokinase type PA (u-PA) was highest in acute promyelocytic leukemia (APL). The PAI-I antigen showed no marked cell specificity, but the PAI-II antigen was markedly increased in myelomonocytic leukemia and acute monocytic leukemia (AMOL). From these findings, various PAs and PAIs are considered to be present in leukemia cells and to be involved in hemostatic disorders, thus they are of diagnostic value in leukemia. CD87 expression has also been correlated in AML patients with higher frequency of bleeding complications, mucocutaneous infiltration, hepatosplenomegaly and lymphadenopathy. These observations suggest that uPAS activity is associated with clinical features predicting a more aggressive course of the disease [5,6].

In addition, high levels of soluble uPAR appear to represent an independent factor predicting worse prognosis and extramedullary involvement in multiple myeloma (MM) [7].

Hjertner et al. showed that uPA and uPAR are expressed by myeloma cells and that this proteolytic system is functionally active in both primary myeloma cells and in myeloma cell lines. Therefore, the uPAS can also potentially influence important biological events in MM such as bone matrix degradation, tumour invasion and homing of plasma cells to the bone marrow [8]. Moreover, positive correlation was observed between number of leukocytes and of granulocytes and u-PA concentration in the blood of patients with myeloproliferative syndromes which could confirm the above hypothesis and explain fibrinolysis system activation reported in these patients [4].

Finally, recent results from preclinical studies show that inhibition of uPA protease activity or blockage of uPA from binding to its receptor prevents tumor progression. Several therapeutical approaches have been shown to possess anti-tumor effects in preclinical assays, including selective inhibitors of uPA activity, antagonist peptides, monoclonal antibodies able to prevent uPA binding to uPAR and gene therapy techniques silencing uPA/uPAR expression. The recent development of anti-urokinase receptor antibodies, may further underline the possibility that the uPAR molecule could represent a suitable target for new therapeutic options. [9,10].

The most interesting approach, as far as hematological disorders are concerned, is represented by the development of such fusion proteins as the diphtheria toxin/urokinase fusion protein, which has been demonstrated, in vitro, to be toxic to CD87 AML blasts. Overall, these preliminary observations suggest that the uPAR molecule could represent a suitable target for new therapeutic strategies in hematological malignancies [11].

In conclusion, further studies are needed to increase the comprehension of the molecular mechanisms implicating the uPAS system in tumorigenesis, along with more exhaustive clinical investigations to prove the efficacy of uPAS inhibitors, in monotherapy or in combination with conventional or novel anti-cancer therapies.

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This article was originally published in a special issue, entitled: **"Epigenetics in Hematology",** Edited by Adel Gouri