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Extracellular Ubiquitin: New Potential Therapeutics for Hematological Diseases

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Bone marrow generates functional cells of peripheral blood. This is attained by regulation of hematopoietic stem cells activity to balance proliferation, differentiation and maturation. Protein regulation by the ubiquitin proteasome system is pivotal for normal functioning of hematogenesis. Deregulation of ubiquitin proteasome system can lead to abnormal transformation and leucosis. Understanding how UPS regulates hematogenesis may lead to targets for therapy of leukemia. The finding that proliferating cells are more sensitive to defects in protein degradation and that inhibitors of proteasomes are useful in certain types of cancer therapy suggests that further emphasis on this pathway could provide new therapeutic strategies to target disorders in haematogenesis after irradiation and chemotherapy.

UPS is the principal mechanism for protein catabolism in the mammalian cytosol and nucleus. Ubiquitin is found in intra- and extracellular fluids and is involved in regulation of numerous cellular processes including apoptosis, cell cycle and division, DNA transcription and repair, differentiation and development, immune response and inflammation.

Injected proteins can be used as effective tests of the action of endogenous proteins. Exogenous ubiquitin has been used in numerous experiments for elucidation the role and pathways of extracellular and exogenous ubiquitin. Extracellular ubiquitin regulates intracellular processes [1]. It inhibits proliferative activity of cells in intact animals, but stimulates it in modeled diseases [2]. In vivo injected exogenous ubiquitin inhibits mitotic activity of bone marrow cells by about 53% in intact rats [3]. Extracellular ubiquitin regulates spontaneous regeneration of leucopoiesis in rats after chemically induced leucopoenia. It enhances proliferation and retains passage of bone marrow cells to peripheral blood. Extracellular ubiquitin ascribed a role in differentiation of hematopoietic cells. Experimental data suggest an influence of extracellular ubiquitin on the ratios of the heterogeneous population of bone marrow and peripheral blood [4]. Recent observations showed that extracellular ubiquitin can suppress immune response and prevent inflammation [5]. Ubiquitin was suggested as a promising anti-inflammatory protein therapeutic [6,7].

Investigation of regulation of spontaneous regeneration of leucopoiesis by using biologically active agent like extracellular ubiquitin seems to be very important for further elucidation of mechanisms underlying regeneration disorders in bone marrow after irradiation and chemotherapy, as well as ubiquitilation pathways playing an essential role in leukemogenesis.

Understanding the molecular mechanisms controlling normal hematopoietic differentiation is critical to develop new treatment for haematological malignancies and to manipulate stem cells. The treatment of patients suffering from blood cancers relies on therapies that lessen inflammation and are able to repopulate the bone marrow. Based on these characteristics, extracellular ubiquitin seems to be a good candidate as therapeutics for haematological diseases of different etiologies.

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