Journal of Hematology & Multiple Myeloma

Editorial
Published: 30 Jan, 2018

Editorial-Immunoproteasome, A New Target for the Treatment of Multiple Myeloma

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Editorial

The Ubiquitin-Proteasome System (UPS) is the major non-lysosomal proteolytic system for the degradation of abnormal or damaged proteins no longer required. Proteasomeisinvolved in degradation of various proteins which regulate the cell cycle progression, thus playing a role in controlling cell proliferation; in view of these considerations defects in the UPS can lead to an uncontrolled cell proliferation and to a tumor development. The 26S proteasome is composed of a 20S catalytic core capped by two 19S regulatory complexes. The 20S proteasome possesses a barrel-like structure composed of four stacked rings of seven subunits each: α1-α7 subunits form the two outer rings, whereas the two inner rings are composed by seven different β1-β7 subunits that contain the proteolytic sites [1]. In eukaryotic proteasomes, β1, β2 and β5 subunits contain the proteolytically active sites, differing in substrate specificity: β1 subunit possesses a caspase-like(C-L) activity thus cleaving peptides with acidic residues at the P1 position; β2 subunit has a trypsin-like (T-L) activity and prefers substrates with basic residues at the P1 site; lastly β5 subunit displays a chymotrypsin-like (ChT-L) activity being involved in the degradation of peptides with hydrophobic residues at P1 position and it is currently considered the primary target for the development of novel agents for the treatment of hematologic malignancies, like multiple myeloma (MM) [2]. In addition to the constitutive proteasome, expressed in all cells and tissues, vertebrates possess a specialized form of proteasome, named immuno proteasome (i20S), predominantly expressed in monocytes and lymphocytes and responsible for the generation of antigenic peptides (also called MHC class I ligands) for cell-mediated immunity. Upon the exposure of specific stimuli, such as the inflammatory cytokines IFN-γ and TNF-α, the expression of constitutive subunits can be replaced by the synthesis of the immuno-core particles β1i, β2i and β5i. While β2i and β5i perform the same activities of β2c and β5c subunits, on the contrary β1i mainly performs a ChT-L activity where as its caspase-like activity is reduced to background levels [3]. It well known that i20S is the major form of the proteasome expressed in cells of hematopoietic origin, in particular in MM cells; thus, the inhibition of i20S could be a promising strategy to treat MM [4]. However, a selective inhibition of either β5i or β5c alone is insufficient to produce an antitumor response, where as inhibition of both β5i and β5c is required to induce an antitumor effect in MM, non-Hodgkin lymphoma, and leukemia cells, without causing cytotoxicity in non-transformed cells [5]. In view of these considerations at present, both non-selective and selective immuno proteasome inhibition has been validated as potential strategy for the treatment of MM [6].

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Received Date: *15 Jan 2018*
Accepted Date: *23 Jan 2018*
Published Date: *30 Jan 2018*

Citation:
Ettari R. Editorial-Immunoproteasome, A New Target for the Treatment of Multiple Myeloma. J Hematol Mult Myeloma. 2018; 3(1): 1011.