Chapter 13

THE ROLE OF THE UBIQUITIN-PROTEASOME PATHWAY IN CANCER AND PROTEASOME INHIBITORS

Miriş DİKMEN[1], Zerrin CANTÜRK[2]

Introduction

Cancer is one of the important diseases, largely on account of its reputation for having high rates of mortality; yet, the new therapies that have recently been developed offer new hope and possibilities for beating the disease. The ubiquitin-proteasome system, which has been at the focus of cancer studies is the main degradation mechanism for oxidatively damaged proteins.[Catalgol, 2012]. The proteasome is a multimeric protease complex, and central to cellular protein regulation. Proteins conjugated to multiple units of the polypeptide ubiquitin are degraded by the proteasome[Teicher &Tomaszewski, 2015]. Protein oxidation, which is mainly a function of proteasome, is involved in the development of cancer, in which the ubiquitin proteasome system (UPS) is a key point in many cell pathways. Proteasome takes away irregular proteins that were misfolded, aged, or damaged, also regulates the short-lived regulatory proteins, such as cyclins, which include in the control of cell cycle and transcription regulators. Proteasome has important role in the degradation of protein stacks, like oncogene and tumor suppressor proteins, transcription factors and some signaling molecules [Wustrow, Zhou&Rolfe, 2013] . In this section, the importance of proteasome in the degradation of cancer-related proteins and the use of proteasome inhibitors in cancer treatment are reviewed [Catalgol, 2012].

The Ubiquitin–Proteasome System (UPS)

The degradation of cellular proteins is extremely complex for regulating cellular function and preserving homeostasis. More than 80% of cellular proteins are degraded during the cell cycle, apoptosis, transcription, DNA repair, protein quality control and antigen presentation. But the failures of degradation are cause many diseases, is located including cancer [Crawford, Walker & Irvine 2011] .

The proteasome located in the cytoplasm and nuclei of cells. Timed degradation/recycling of proteins is essential for cell viability. Malignant cells, due to their genetic instability and rapid proliferation, are particularly more dependent upon the protea-

[1]Doç. Dr., Anadolu Üniversitesi, Eczacılık Fak., Eskişehir. mirisd@anadolu.edu.tr
[2]Doç. Dr., Anadolu Üniversitesi, Eczacılık Fak., Eskişehir. zkcanturk@anadolu.edu.tr

proteasome inhibitors and prevent the development of drug resistance [Wua et al., 2010; Stein & Groll, 2014].

The clinical and commercial success of bortezomib has driven many firms to search for second-generation proteasome inhibitors with developed therapeutic indices and oral bioavailability compared to bortezomib. Bortezomib is a boronic acid requiring intravenous administration, while ixazomib and delanzomib are boronic acids that are taken orally. Carfilzomib is an irreversible epoxyketone requiring intravenous administration, while oprozomib is an epoxyketone that is taken orally. These compounds are generally very effective cytotoxics, all of them focus on inhibiting the proteasome chymotrypsin-like protease. As a matter of fact, multiple myeloma came from clinical observations during early bortezomib clinical trials. Thus, discovery and development of the proteasome inhibitor class of anticancer agents have progressed through a classic route of serendipity and scientific investigation and never will finish up developing till it reaches the top. [Canturk et al., 2016; Teicher &Tomaszewski, 2015; Crawford, Walker &Irvine 2011].

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