A DNA/HDAC dual-targeting drug CY190602 with significantly enhanced anticancer potency

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Abstract

Genotoxic drugs constitute a major treatment modality for human cancers; however, cancer cells' intrinsic DNA repair capability often increases the threshold of lethality and renders these drugs ineffective. The emerging roles of HDACs in DNA repair provide new opportunities for improving traditional genotoxic drugs. Here, we report the development and characterization of CY190602, a novel bendamustine-derived drug with significantly enhanced anticancer potency. We show that CY190602's enhanced potency can be attributed to its newly gained ability to inhibit HDACs. Using this novel DNA/HDAC dual-targeting drug as a tool, we further explored HDAC's role in DNA repair. We found that HDAC activities are essential for the expression of several genes involved in DNA synthesis and repair, including TYMS, Tip60, CBP, EP300, and MSL1. Importantly, CY190602, the first-in-class example of such DNA/HDAC dual-targeting drugs, exhibited significantly enhanced anticancer activity in vitro and in vivo. These findings provide rationales for incorporating HDAC inhibitory moieties into genotoxic drugs, so as to overcome the repair capacity of cancer cells. Systematic development of similar DNA/HDAC dual-targeting drugs may represent a novel opportunity for improving cancer therapy.

Keywords DNA repair; dual-targeting anticancer drug; HDAC; nitrogen mustard

Subject Categories Cancer; Pharmacology & Drug Discovery

Introduction

A significant challenge for treating cancer is to enhance the efficacy of existing drugs. Genotoxic drugs represent an important branch of chemotherapy, which kill cancer cells by attacking cellular DNA. Double-strand breaks (DSBs) resulting from such attacks are extremely toxic, and one irreparable DSB is sufficient to induce cell death (Jackson & Bartek, 2009). Despite such potent lethality, DNA damage caused by anticancer drugs can be mitigated by cellular DNA repair machinery, thus enabling some cancer cells to survive and ultimately cause treatment failure. Drugs that inhibit DNA repair, such as ATM and DNAPK inhibitors, have been intensely investigated as potential means to improve chemotherapy (Hickson et al., 2004; Helleday et al., 2008; Willmore et al., 2008; Jiang et al., 2009).

Nitrogen mustards are a major type of genotoxic anticancer drugs. They work by attacking the N7 position of guanines on opposing DNA strands, thereby causing DNA interstrand cross-linkings (ICLs), which impede DNA replication forks and ultimately cause DSBs. Several pathways exist in mammalian cells to repair such damage, including the Fanconi anemia (FA) pathway, translesional synthesis (TLS), and homologous recombination (HR) (Knipscheer et al., 2009; Moldovan & D’Andrea, 2009). As a result, nitrogen mustards are generally well tolerated by cancer cells. Consequently, these drugs exhibit poor potency and limited treatment success. An emerging approach is to suppress DNA repair in order to enhance the efficacy of nitrogen mustards. Several lines of evidence support the potential benefits of this approach. For example, human patients with inherited deficiencies in FA pathway are extremely sensitive to ICLs (Taniguchi & D’Andrea, 2006), and tumors with mutations in the FA and HR pathways are hypersensitive to ICL agents (Van der Heijden et al., 2005; Kennedy &