PRIMA-1 restores (R245S)-p53-mutant function indirectly

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Abstract

Minor conformational changes due to G245S mutation on p53 have removed its capability to induce apoptosis. Recent experimental results show that PRIMA-1 was able to restore the conformational changes on several mutants into wild type like conformation. In order to study the restoration mechanism, we have chosen two docked PRIMA-1 positions on the mutant to dynamically-studied by means of molecular dynamics simulation. One of those sites has keeping PRIMA-1 at the position for about 7 ns. This long time interaction is occurred at the cystein rich region of p53. This result suggests the necessity of extensive interactions between PRIMA-1 and cystein which is in a good agreement with experimental results.

Keywords: cystein, dynamics, G245S, p53, PRIMA-1.

Introduction

Understanding the process of apoptosis provides the basis for chemotherapy through induction of cancer cell death (Ghobrial et al. 2005). Apoptosis occurs through several pathways. One pathway which has strong relations to cancer is through the induction of apoptosis by p53-tumor-suppressor. p53 response to DNA damage or other cells stress by arresting cell cycle or induce apoptosis (Alberts et al., 2002). In normal cells p53 is very unstable and only exist in very low concentration because of its interaction with Mdm2 protein. This protein causes degradation of p53 in normal conditions, so that apoptosis does not take (Moll and Petrenko 2003). Approximately 50% of tumor cells in humans due to loss of p53 function in the mutant. The loss of p53 function, causing DNA damage or other defects in cells is not accompanied by cell cycle arrested and/or apoptosis, despite the increase in p53 concentration. The restoration of a mutated p53 function could potentially trigger a massive apoptosis that can effectively kill tumor cells (Bykov et al., 2002a).

Researches to restore the function of mutant p53 using small molecules have been carried out. Evidence suggests that p53 function can be restored by adjusting the conformation of mutant p53 so as to resemble the wild-type p53. Compounds used in these studies are vary (e.g. PRIMA-1 (Bykov et al., 2002b), maleimide derivatives (Bykov et al., 2005), CP-31 398 (Wang et al., 2003), RITA (Issaeva et al., 2004) and several short specific peptide (Issaeva et al., 2003)) with different effectiveness. Restoration of mutant p53 function requires specific interactions between small molecules with mutant p53. Dynamics properties of these interactions provide an advantage to this study. Recently, (Lambert et al., 2009) reported that covalent modification is needed to restore p53 function.

In this article we present a possible initial point of p53 restoration mechanism by means of molecular dynamics simulation.

Materials and Methods

Structural and dynamical properties of biologically interesting macromolecules such as protein and DNA, have been extensively studied by means of molecular dynamics (MD) simulation (von Kitzing, 1992; Beveridge and Ravishanker, 1994; Feig and Pettitt, 1999; Castrignano et al., 2000). This method provides an excellent tool for investigation of biomolecules in their biologically active form. The inclusion of the long range interactions via the Ewald summation in the form of the particle mesh Ewald method and improved parameterization of the force fields allows stable calculation of protein trajectories in the nanosecond time range.

Computational Details

Wild-type p53 and (R245S) mutant were taken from x-ray structure with pdb code 1GZH and 2JIY respectively. PRIMA-1 was optimized with GAUSSIAN98 (Frisch M. J. et al., 1995) at HF/6-31G* level of theory. Complexes structures were chosen from the lowest docked energy and another