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ORIGINAL ARTICLE

In silico analysis of glycinamide ribonucleotide transformylase inhibition by PY873, PY899 and DIA

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Abstract In humans, purine *de novo* synthesis pathway consists of multi-functional enzymes. Nucleotide metabolism enzymes are potential drug targets for treating cancer and autoimmune diseases. Glycinamide ribonucleotide transformylase (GART) is one of the most important trifunctional enzymes involved in purine synthesis. Previous studies have demonstrated the role of folate inhibitors against tumor activity. In this present study, three components of GART enzyme were targeted as receptor dataset and *in silico* analysis was carried out with folate ligand dataset. To

Abbreviations: GAR, glycinamide ribonucleotide; GART, glycinamide ribonucleotide transformylase; DIA, 5-((4-carboxy-4-(4-(((2,4-diaminopyrido[3,2-*d*]pyrimidine-6-yl)methyl)amino)benzamido)butyl)carbamoyl)-isophthalic acid; DHFR, dihydrofolate reductase; PY899, 2,4-diamino-6-(3,4,5-trimethoxybenzyl)-5,6,7,8-tetrahydro-quinazoline; PY873, 2,4-diamino-6-(3,4,5-trimethoxyanilino)-methylpyrido[3,2-d]pyrimidine; HsGART, human GART tri-functional enzyme; GARS, glycinamide ribonucleotide synthetase; AIRS, aminoimidazole ribonucleotide synthetase; GARTfase, glycinamide ribonucleotide transformylase

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accomplish the task, Autodock 4.2 was used for determining the docking compatibilities of ligand and receptor dataset. Taken together, it has been suggested that folate ligands could be potentially used as inhibitors of GART.

1. Introduction

Nucleotide biosynthesis is an imperative phenomenon in the synthesis of nucleic acids and metabolic pathways. Nucleotide biosynthesis follows synergistic pathway involving coordination between *de novo* and salvage pathways. Since nucleotides play a pivotal role in human cells, the enzymes involved in nucleotide metabolism could be exploited as potential anti-proliferative drug targets against cancer and autoimmune diseases (Welin et al., 2010). During *de novo* purine synthesis, conversion of phosphoribosyl pyrophosphate to inosine monophosphate involves 10 individual steps (Hartman et al., 1959). However, six different multifunctional enzymes (three monofunctional, two bifunctional and one trifunctional enzymes) are engaged in catalysis of above-mentioned steps (Kappock et al., 2000).

Glycinamide ribonucleotide transformylase (GART) is one of the most important trifunctional enzymes involved in purine synthesis. Human GART (HsGART) is composed of three units: glycinamide ribonucleotide synthetase (GARS), glycinamide ribonucleotide transformylase (GARTfase), aminoimidazole ribonucleotide synthetase (AIRS) and all of which work in a synchronized manner to facilitate purine synthesis. These three units of human GART (HsGART) catalyze steps 2, 3 and 5 of the *de novo* purine synthesis pathway. The second step of purine synthesis is dependent on GARS (N-terminal enzyme unit) that results in the generation of glycinamide ribonucleotide (GAR), adenosine diphosphate and phosphate ion. The third step is catalyzed by GARTfase (C-terminal enzyme unit) resulting in conversion of GAR to N-formylglycinamide ribonucleotide using 10-formyltetrahydrofolate as a cofactor. AIRS (the middle enzymatic domain of HsGART) is important for the conversion of formylglycinamidine ribonucleotide and adenosine triphosphate to aminoimidazole ribonucleotide (AIR), adenosine diphosphate and phosphate ion (Welin et al., 2010). This whole process is shown in Fig. 1. The core fourth step of the purine pathway is performed by phosphoribosyl formylglycinamidine amidotransferase, encoded by a separate gene (*purL*). Interestingly, phosphoribosylamine, the substrate of GARS, is quite unstable and quickly hydrolyzes to ribose 5-phosphate within few seconds at physiological temperatures (Rudolph et al., 1995). Because of its transient nature, phosphoribosylamine might be transferred from phosphoribosyl pyrophosphate amidotransferase to GARS (Wang et al., 1998).

HsGART gene is localized on chromosome 21 and might be linked with trisomy disorders (Down syndrome) (Chadefaux et al., 1984). In addition, elevated serum purine levels associated with Down's syndrome may possibly be due to overexpression of HsGART (Brodsky et al., 1997). *In-vivo* studies have suggested that inhibitors of folate-dependent enzymes play a crucial role in anti-tumor activity. The C-terminal GARTfase domain uses folate cofactor and this has been associated with anti-tumor activity (Costi and Ferrari, 2001).

The compound (6R)-dideazatetrahydrofolate (lometrexol) belongs to the class of anti-folates that are specific inhibitors of *de novo* purine synthesis due to potent inhibition of GART (Bronder and Moran, 2002). A study of the activity of pemetrexed (a commercially available chemotherapy drug) against several recombinant mouse and human enzymes *in vitro* led

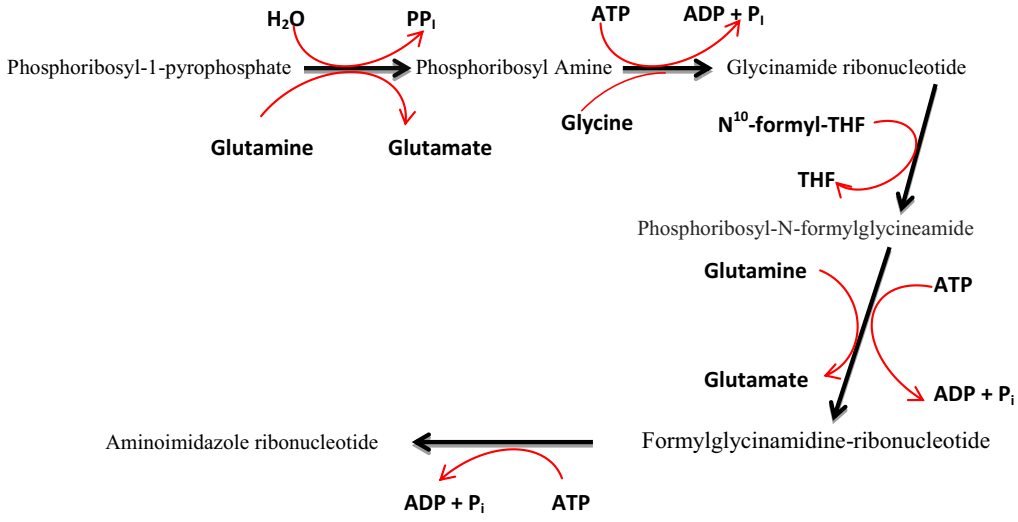

Figure 1 Presentation of step 1–5 of the purine de novo bio-synthesis pathway: Phosphoribosyl-1-pyrophosphate (PRPP) to aminoimidazole ribonucleotide (AIR).