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Transglutaminase 2 inhibitors and their therapeutic role in disease states

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Abstract

Transglutaminase 2 (TG2) is a multi-domain, multi-functional enzyme that post-translationally modifies proteins by catalyzing the formation of intermolecular isopeptide bonds between glutamine and lysine side-chains. It plays a role in diverse biological functions, including extracellular matrix formation, integrin-mediated signaling, and signal transduction involving 7-transmembrane receptors. While some of the roles of TG2 under normal physiological conditions remain obscure, the protein is believed to participate in the pathogenesis of several unrelated diseases, including celiac sprue, neurodegenerative diseases, and certain types of cancer. A variety of small molecule and peptidomimetic inhibitors of the TG2 active site have been identified. Here, we summarize the biochemistry, biology, pharmacology and medicinal chemistry of human TG2.

Keywords: Transglutaminase; Inhibitors; Chemical structures; Celiac sprue; Neurodegeneration; Cancer

Abbreviations: ECM, extracellular matrix; GDP, guanosine diphosphate; GPR56, G protein-coupled receptor 56; GTP, guanosine triphosphate; HLA, human leukocyte antigen; NF-κB, nuclear factor κB; ROCK, rho-associated coiled-coil containing serine/threonine protein kinase; TG2, transglutaminase 2; TGF-β, transforming growth factor β.

Contents

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1. Introduction

Transglutaminases were first discovered in the 1950s as enzymes found in mammalian liver homogenates capable of catalyzing calcium-dependent covalent bonds between small molecule amines and certain proteins with the corresponding release of ammonia (Borsook et al., 1949; Clarke et al., 1959). Since that time, 9 members have been added to the transglutaminase family of enzymes, including transglutaminases 1–7, factor XIIIA, and the enzymatically inactive erythrocyte band 4.2 (for reviews, see Griffin et al., 2002; Lorand & Graham, 2003). Of these 9 family members, transglutaminase 2 (TG2, tissue transglutaminase, transglutaminase C, tTG, $G_{\alpha h}$) is among the most well studied and biologically characterized presumably because it is present in most bodily tissues (Thomazy & Fesus, 1989) and has been implicated to play a role in a number of diseases, such as celiac sprue (Molberg et al., 2000), Alzheimer's disease, Huntington's disease (Hoffner & Djian, 2005), and certain types of cancer (Mangala & Mehta, 2005).

In an effort to treat patients that have these debilitating and often fatal diseases, small molecule and peptidomimetic inhibitors capable of blocking TG2 enzymatic activity have been designed and biochemically characterized. In this review, we will briefly summarize what is known about the biology of TG2, compare the different classes of TG2 inhibitors that have been reported, and discuss the application of these inhibitors to biological systems.

2. Functions of transglutaminase 2

TG2 is an ~ 80 kDa protein with enzymatic, G-protein, and non-enzymatic biological functions (for reviews, see Aeschlimann & Paulsson, 1994; Chen & Mehta, 1999; Griffin et al., 2002; Lorand & Graham, 2003; Zemskov et al., 2006). As an enzyme, TG2 is able to catalyze the calcium-dependent ($K_a \sim 1$ mM; Piper et al., 2002) covalent modification of protein-bound glutamine side chains through transamidation or deamidation reactions. The first step in both types of modifications is the acylation of the active site cysteine (Cys^{277}) of TG2 by a protein-bound glutamine residue, resulting in the liberation of ammonia and the formation of a thioester intermediate between TG2 and the glutamine bearing protein substrate (see Fig. 1). In TG2 catalyzed transamidation, the thioester intermediate is attacked by a nucleophilic primary amine, either a small molecule amine such as putrescine or the ε-amino group of protein-bound lysine residues. This results in the formation of relatively stable isopeptide bonds. In TG2 catalyzed deamidation, water acts as the nucleophile that attacks the thioester intermediate, resulting in the conversion of the glutamine residue into a glutamate residue (Case & Stein, 2003; Lorand & Graham, 2003). The transamidation reaction is kinetically favored over deamidation at pH > 7, but the deamidation reaction becomes kinetically competitive as the pH is lowered below 7 or as the concentration of amine substrates is lowered below their K_m values (Fleckenstein et al., 2002). Despite a certain level of substrate specificity, the

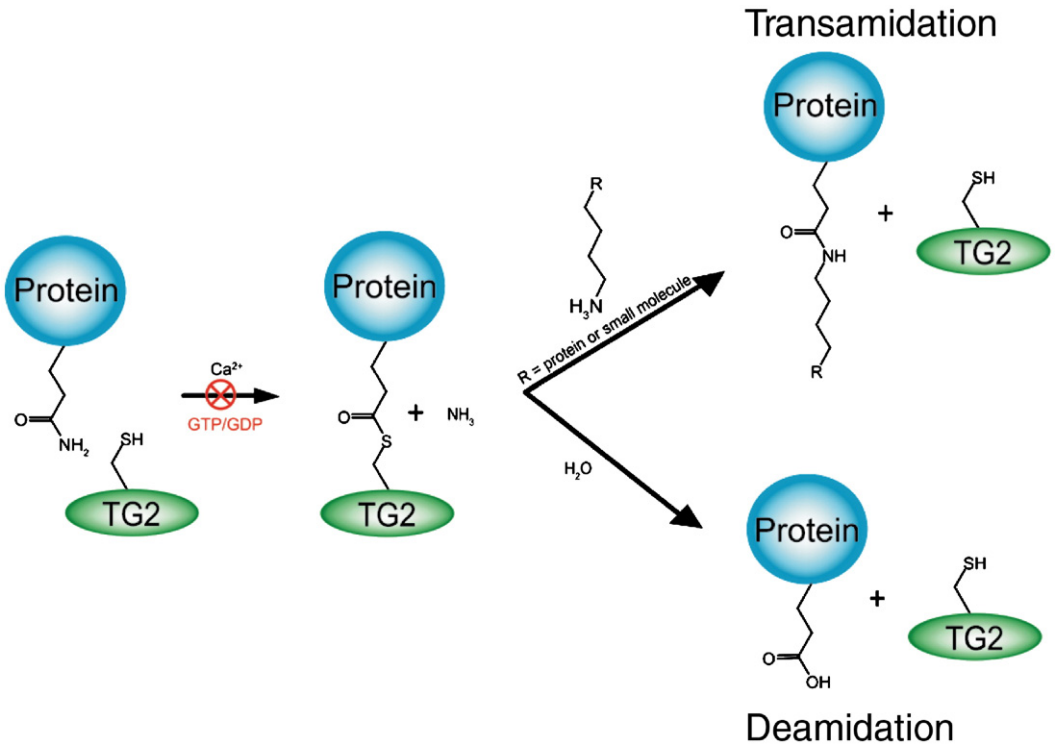

Fig. 1. TG2 catalytic mechanism. In the presence of calcium, the TG2 active site cysteine (Cys^{277}) thiol attacks the γ-glutaminyl side chain of a protein- or peptide-bound glutamine residue forming a thioester intermediate with the release of ammonia. In transamidation, a primary amine nucleophile attacks the thioester carbonyl displacing the TG2 thiol and resulting in an isopeptide crosslink between the glutamine side chain and the primary amine. In deamidation, water acts as the thiol-displacing nucleophile resulting in the net conversion of glutamine to glutamate. The presence of GTP or GDP inhibits transglutaminase activity.