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Perspective

Translation inhibitors and their unique biological properties

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ABSTRACT

In eukaryotes, many translation inhibitors have been widely used as bioprobes to evaluate the contribution of translation to signaling pathways and cellular functions. Several types of translation inhibitors are also known to trigger the activation of the mitogen-activated protein kinase superfamily in an intracellular mechanism called ribotoxic stress response. This perspective focuses on the biological properties of recently identified translation inhibitors that trigger ribotoxic stress response, particularly glutarimides as well as triene-ansamycins.

1. Introduction

Translation is the fundamental process of decoding an mRNA sequence into the amino acids of a protein. It is divided into three stages: initiation, elongation, and termination. The elongation process proceeds through three main steps: binding of aminoacyl tRNA to the ribosome A-site, peptide bond formation by transferring a nascent peptide in the P-site peptidyl tRNA to the A-site aminoacyl tRNA, and translocation of the P-site deacylated tRNA to the E-site and the A-site peptidyl tRNA to the P-site, which enables the next aminoacyl tRNA to enter the A-site. In eukaryotes, many translation inhibitors, such as cycloheximide, are known to block the elongation steps and have been widely used as bioprobes to evaluate the contribution of translation to signaling pathways and cellular functions (Schneider-Poetsch et al., 2010a). In addition, several types of translation inhibitors are able to trigger the activation of the mitogen-activated protein (MAP) kinase superfamily in an intracellular mechanism called ribotoxic stress response (Iordanov et al., 1997; Shifrin and Anderson, 1999; Sidhu and Omiecinski, 1998). This perspective focuses on recently identified translation inhibitors that trigger ribotoxic stress response and their unique biological activities in relation to tumor necrosis factor (TNF)-α-dependent signaling pathways leading to nuclear factor-κB (NF-κB) activation and apoptosis (Fig. 1).

2. NF-κB and apoptosis signaling pathways

Pro-inflammatory cytokines, such as TNF-α and interleukin (IL)-1, mainly induce the activation of the NF-κB signaling pathway, leading to the expression of a variety of genes essential for inflammation and other cellular functions. TNF receptor 1 (TNF-R1) and IL-1 receptor possess different cytoplasmic domains termed as the death domain and the Toll-IL-1 receptor domain, respectively, and trigger distinct signaling pathways by recruiting different sets of adaptor proteins (Bhoj and Chen, 2009; Hayden and Ghosh, 2008). However, these bifurcated signaling pathways converge to induce inhibitor of κB (IκB) kinase as the common signaling molecule. Phosphorylated IκB is subsequently ubiquitinated and hydrolyzed by 26S proteasome, leading to the liberation of NF-κB dimers from a cytosolic inactive complex pre-associating with IκB and their translocation to the nucleus where they activate the transcription of various target genes (Karin and Greten, 2005). Many types of natural and synthetic compounds have been identified to block the NF-κB signaling pathway induced by pro-inflammatory cytokines (Kataoka, 2009).

In the apoptosis signaling pathway, death receptors, such as TNF-R1 and Fas, recruit the adaptor protein Fas-associated death domain (FADD) and the initiator procaspase-8 to their death domains and trigger the auto-activation of procaspase-8 into its fully active form that induces apoptosis by cleaving various substrates, such as effector procaspases (Danial and Korsmeyer, 2004). However, TNF-R1 and even Fas do not always cause apoptosis, mainly due to the expression of endogenous anti-apoptotic proteins, such as the caspase-8 modulator cellular FLICE-inhibitory protein (c-FLIP). c-FLIP is capable of preventing the death-receptor-induced apoptosis via the interaction of FADD and procaspase-8 and is regulated by various transcription factors,

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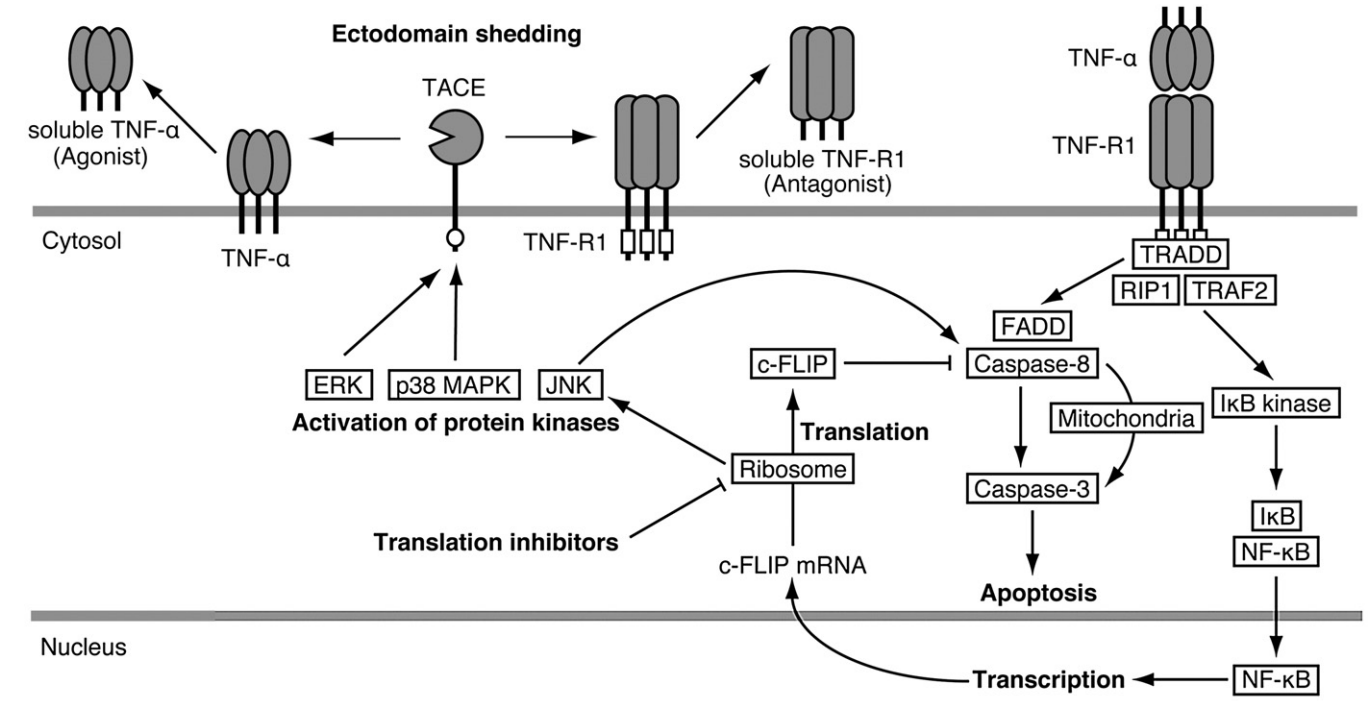

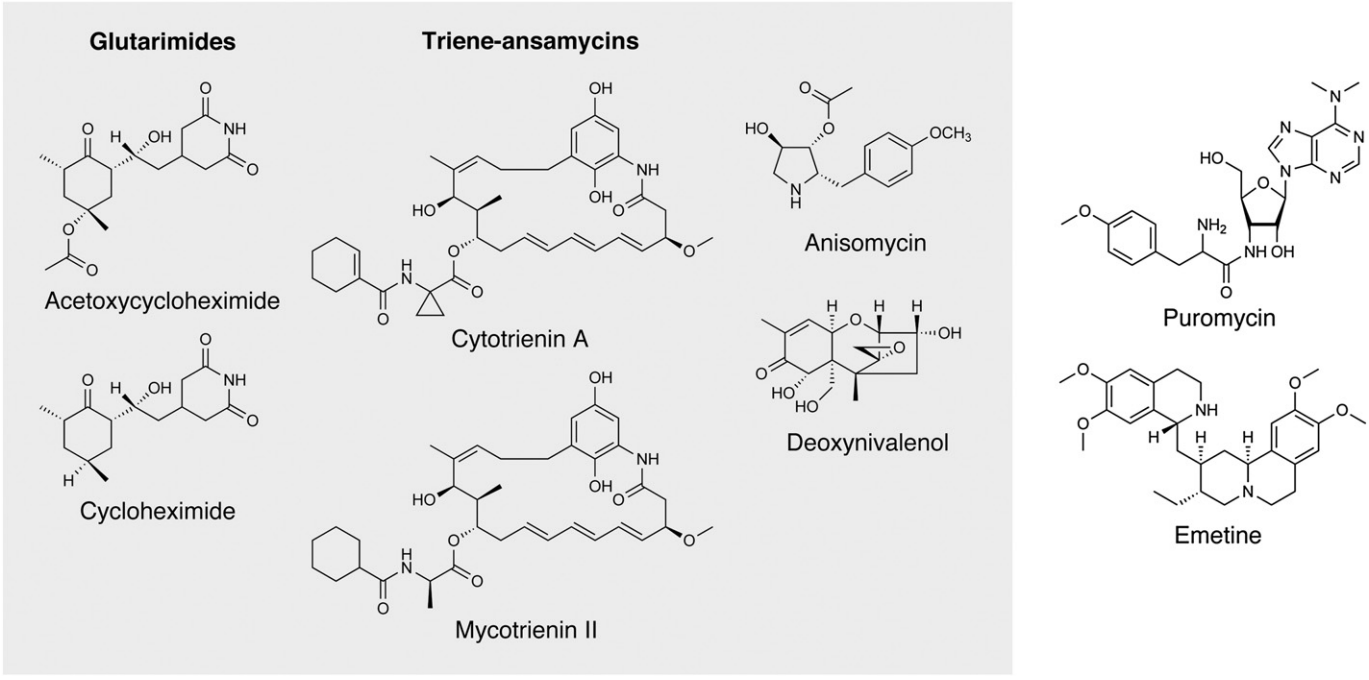

Fig. 1. Translation inhibitors and their mechanisms of actions on TNF-α-dependent signaling pathways. TNF-α induces NF-κB activation and upregulates c-FLIP expression, which blocks caspase-8 activation. Translation inhibitors prevent c-FLIP upregulation and thus sensitize many types of cells to TNF-α-induced apoptosis. TACE mediates the ectodomain shedding by converting membrane-anchored substrates, such as TNF-α and TNF-R1, into their soluble forms. Glutarimides, triene-ansamycins, anisomycin, and deoxynivalenol (gray box), but neither puromycin nor emetine, are able to induce ribotoxic stress response, leading to the activation of protein kinases. The MAP kinase superfamily members regulate the TACE-mediated ectodomain shedding and the apoptosis signaling pathway.

including NF-κB (Budd et al., 2006). It is well characterized that such translation inhibitors as cycloheximide diminish constitutive and NF-κB-inducible c-FLIP expression and allow the activation of procaspase-8 during death-receptor-mediated apoptosis (Kataoka, 2005).

3. TNF-α-converting enzyme (TACE) and ectodomain shedding

TNF-α-converting enzyme (TACE), also referred to as a disintegrin and metalloproteinase 17, is a cell-surface metalloproteinase required for the ectodomain shedding of many membrane-anchored proteins, such as cytokines (e.g., TNF-α) and receptors (e.g., TNF-R1 and TNF-R2) (Seals and Courtneidge, 2003). TACE plays a bifunctional role in the TNF-α signaling pathway in that the TACE-mediated ectodomain shedding generates soluble TNF-α as pro-inflammatory agonists and conversely downregulates cell-surface levels of TNF receptors, accompanied by the augmentation of soluble TNF receptors acting as anti-inflammatory antagonists (Scheller et al., 2011).