Toxicology 271 (2010) 1–4

Contents lists available at ScienceDirect

Toxicology

journal homepage: www.elsevier.com/locate/toxicol

Review

Possible involvement of DEC1 on the adverse effects of quinolone antibiotics

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ARTICLE INFO

Article history:
Received 8 February 2010
Accepted 2 March 2010
Available online 7 March 2010

Keywords:
Quinolones
Antibiotics
Adverse effects
DEC1

ABSTRACT

Quinolone antibacterial agents are widely used in the clinic because of their high antibacterial activity, broad spectra and favorable pharmacokinetics. However, the adverse effects induced by quinolones, such as tendon/articular toxicity, central nervous system toxicity, phototoxicity and dysglycemia, have greatly restricted their therapeutic use. Differentiated embryo-chondrocyte expressed gene 1 (DEC1), an important transcription factor that has a basic helix-loop-helix domain and is ubiquitously expressed in both human embryonic and adult tissues, has a pivotal function in various biological phenomena, including neurogenesis, neuroregulation, chondrogenesis, cell growth, oncogenesis, immune balance and circandian rhythm. Recently, DEC1 has received increasing attention for its role in maintaining the homeostasis of metabolism and energy. Research has shown that DEC1 may play a vital role in metabolic disease. Although the mechanism of the adverse reactions caused by quinolones has not been clarified, the distribution of these serious adverse effects in tissues and organs is consistent with the expression of DEC1 in corresponding normal tissues. In the present paper, we review evidence showing that DEC1 may take part in the adverse effects induced by quinolone antibiotics. The investigation of the molecular details of the toxicity caused by quinolones may help overcome the shortcomings of the antibiotics and reveal new, useful therapeutic functions besides their antimicrobial effect.

Contents

1. Introduction

Quinolone antibacterial agents (quinolones) and their fluoro derivatives are a family of synthetic broad-spectrum chemotherapeutic bactericidal drugs. These drugs may prevent bacterial DNA from unwinding and duplicating during replication (Neu, 1992). Because of their high antibacterial activity, broad spectra and favorable pharmacokinetics, these drugs are widely used in the clinic. Quinolones have safety profiles similar to those of

Abbreviations: DEC1, differentiated embryo-chondrocyte expressed gene 1; bHLH, basic helix-loop-helix; SHARP-2, enhancer-of-split- and hairy-related proteins; Stra13, stimulated by retinoic acid 13; ROS, reactive oxygen species; LXR, liver X receptor.

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doi:10.1016/j.tox.2010.03.001

other antimicrobial classes (Neu, 1992). However, serious adverse effects frequently occur in some individuals such as children and adolescents with arthropathy (Iannini, 2007). These adverse effects, including neurotoxicity, chondrotoxicity, dysglycemia, phototoxicity, cardiotoxicity and hepatotoxicity, have restricted the therapeutic use of these antimicrobial agents (Fish, 2001).

The basic helix-loop-helix (bHLH) transcription factor differentiated embryo-chondrocyte expressed gene 1 (DEC1), also known as SHARP-2/Stra13, was identified independently by three research laboratories, each through studies of different systems of mammalian differentiation (Boudjelal et al., 1997; Rossner et al., 1997; Shen et al., 1997). DEC1 is expressed ubiquitously in both embryonic (Shen et al., 1997) and adult tissues in humans (Ivanova et al., 2005; Turley et al., 2004). Although the precise role of DEC1 in human physiology is unclear, recent studies have shown that DEC1 is one of the major circadian molecules (Honma et al., 2002; Nakashima et al., 2008) and is involved in maintaining the homeostasis of metabolism and energy in mammals (Iizuka and Horikawa, 2008; Zvonic et al., 2006). The gene expression of DEC1 is regulated by various extracellular stimuli in a cell type-specific manner (Yamada and Miyamoto, 2005a). In addition to the potential adaptive and protective role of DEC1 with environmental stimuli, many studies have shown that DEC1 has a pivotal function in various biological phenomena, including neurogenesis, neuroregulation, chondrogenesis, cell growth, oncogenesis and immune balance (Yamada and Miyamoto, 2005a).

Although the mechanism of the adverse reactions caused by quinolones has not been clearly elucidated, the distribution of these serious adverse effects in tissues and organs is consistent with the expression of DEC1 in corresponding normal tissues (Iannini, 2007; Ivanova et al., 2005; Shen et al., 1997; Turley et al., 2004), and some evidence indicates that DEC1 might be involved in the process of the adverse effects induced by quinolones. This paper describes evidence of DEC1 possibly playing an important role in the adverse effects induced with quinolone antibiotic treatment.

2. Supporting evidence

2.1. Chondrotoxicity

In the clinic, the arthropathic effects induced by quinolones have led to the antibiotics being contraindicated in children and adolescents. Quinolone-induced chondrotoxicity causes histopathological changes in articular cartilage. Studies of the mechanisms of quinolone-induced arthropathy have mainly involved juvenile animals such as rabbits, rats and canines (Burkhardt et al., 1992; Goto et al., 2008; Sheng et al., 2007), and the exact mechanisms are still unclear. However, the progress of chondrocyte differentiation in humans greatly differs from that in other mammals, so the conditions required for maintaining human chondrocytes might differ from those for other mammals (Shen et al., 1997).

DEC1 was first identified and cloned from human embryo chondrocytes. It is highly expressed in developing chondrocytes but not in dedifferentiated cells in humans, and the differentiation of human embryo chondrocytes was markedly induced by the forced expression of DEC1; for example, insulin can induce chondrogenic differentiation by increasing the transcription of *DEC1* (Shen et al., 2002). Further studies verified that this bHLH transcription factor plays an important role in the regulation of human chondrocyte differentiation probably through the cAMP pathway (Shen et al., 2001). This research suggested that DEC1 is a chondrocyte-related gene and has an important function in chondrogenesis and maintaining healthy cartilage in humans.

The differentiation and maturation of chondrocytes involves a series of events such as proliferation, matrix formation, maturation, hypertrophy and calcification (Chen et al., 1995; Schmid et al., 1991). A proper expression of several chondrocyte-specific genes such as aggrecan, collagen type II, and collagen type X is essential for the differentiation and maturation of chondrocytes (Kergosien et al., 1998). Quinolones induce cavitations in the articular cartilage of juvenile but not adult animals by inhibiting the synthesis of proteoglycans and collagen in chondrocytes and the matrix, thereby leading to severe damage of articular cartilage, including arthralgia, joint swelling, arthropathy, and arthritis (Burkhardt et al., 1992). Overexpression of DEC1 in mesenchymal cells and prehypertrophic growth-plate chondrocytes induced the early mRNA expression of chondrogenic markers such as collagen II and proteoglycans, as well as cartilage matrix accumulation, and increased alkaline phosphatase activity and mineralization; these cells then become hypertrophic and synthesized collagen X (Shen et al., 2001, 2002). Studies of primary human chondrocytes concluded that DEC1 plays a vital role in chondrogenesis and maintaining healthy cartilage. DEC1 was the first transcription factor determined in a human model system to promote chondrogenic differentiation both at the early and terminal stages (Shen et al., 2002). Thus, quinolones may exert chondrotoxicity by regulating the expression of the chondrocyte differentiation-related gene DEC1. Altering the expression of DEC1 might be a therapy to control the chondrotoxicity.

2.2. Neurotoxicity

The central nervous system is a vital target of quinolone-mediated neurotoxicity. Quinolones can cause neurological and psychiatric adverse effects, including tremor, confusion, anxiety, insomnia, agitation and even psychosis (Iannini, 2007).

Many transcription factors containing the bHLH domain take part in neurogenesis and neuroregulation. As a bHLH protein, DEC1 has an important role in neuronal differentiation and “adaptive” changes in the neural system (Rossner et al., 1997; Boudjelal et al., 1997). In pheochromocytoma PC12 cells and rat cerebral cortex tissue, DEC1 expression can be induced immediately by nerve growth factor and kalnic acid, respectively (Rossner et al., 1997). In embryonal carcinoma P19 cells, overexpression of DEC1 induced by retinoic acid inhibits mesodermal differentiation but promotes neuronal differentiation (Boudjelal et al., 1997). As a new transcriptional modulator of brain-derived neurotrophic factor gene, DEC1 can alter neuronal excitability (Jiang et al., 2008), and as a clock gene, it may influence bipolar disorder susceptibility and dysfunctional circadian rhythm (Shi et al., 2008). *In vivo* and *in vitro* studies of the mammalian central nervous system both showed that DEC1 is involved in the determination of progenitor cells, regulation of neuronal differentiation, adaptation to environment stimuli, and maintenance of physiological functions. Thus, DEC1 may take part in neurotoxicity caused by quinolones.

2.3. Phototoxicity

Phototoxicity is another major side effect induced by quinolone antibiotics, but the molecular mechanism has not been elucidated. In photosensitivity reactions, normal harmless doses of visible and UV light can lead to DNA damage, cell death, and acute inflammatory response. Reactive oxygen species (ROS) induced by quinolones during photolysis cause photodynamic DNA strand-breaking activity and lead to inflammation, which suggests that ROS are involved in the pathogenesis of the phototoxicity (Umezawa et al., 1997).

As a clock-related gene, DEC1 exhibits a circadian rhythm expression pattern, with the light–dark cycle induced by light (Honma et al., 2002; Nakashima et al., 2008). DEC1 is also a photosensitive gene. It is involved in the UV signal transduction pathway and might lead to skin cancer. UV radiation induces the expression

of hypoxia inducible factor 1 alpha and vascular endothelial growth factor via the epidermal growth factor receptor/phosphoinositide 3-kinase/DEC1 signaling pathway (Li et al., 2006). However, DEC1 plays an important protective role in the defense against oxidative damage caused by ROS in podocytes (Bek et al., 2003) and muscle cells (Vercherat et al., 2009). Thus, DEC1 contributes to maintaining cell integrity against oxidative stress-mediated damage and may have an important function in the phototoxicity induced by quinolones through ROS.

2.4. Dysglycemia

The maintenance of normal blood glucose concentration mainly depends on the proper secretion of insulin and the right conditions of its target organs such as liver, muscle and adipose tissues. Hypoglycemia and hyperglycemia induced by quinolones have been reported occasionally. Gatifloxacin was one of the quinolones most frequently linked to disturbed blood sugar levels (Zvonar, 2006). Although the mechanism of gatifloxacin-induced dysglycemia is unknown, *in vitro* studies have revealed that certain quinolone antimicrobials can lower serum glucose levels by stimulating insulin release in pancreatic B cells (Yip and Lee, 2006).

DEC1 was found to be a transcription factor implicated in cell metabolism by inhibiting adipogenesis and repressing gluconeogenesis through regulating key enzymes (Yun et al., 2002; Yamada et al., 2005b). Glucose could induce DEC1 mRNA expression, subsequently inhibit the expression of fatty acid synthase and liver pyruvate kinase, and thus take part in regulating lipogenesis in rat hepatocytes (Iizuka and Horikawa, 2008). In mice, fasting and re-feeding modulated the circadian rhythms of DEC1 in peripheral tissues; this phenomenon suggested that the expression of DEC1 was closely linked with the metabolic activity of these tissues (Kawamoto et al., 2006). Liver X receptor (LXR) plays an important role in the regulation of the expression of genes involved in the metabolism of lipids and carbohydrates (Baranowski, 2008). In liver, the ligand-dependent LXR binds to the promoter of *DEC1* to regulate the transcription of the downstream genes involved in hepatic metabolism (Noshiro et al., 2009). Research in rat hepatocytes showed that DEC1 transcription could be induced by high levels of insulin via the phosphoinositide 3-kinase pathway (Yamada et al., 2003). As an important target gene of insulin, DEC1 is involved in the regulation of gene transcription mediated by insulin and the process of inflammation in human skeletal muscle *in vivo* (Rome et al., 2009). Therefore, DEC1 is a major physiological regulator maintaining the metabolism and energy balance and might be a necessary factor in dysglycemia induced by quinolones.

3. Conclusion

DEC1 might be involved in the generation and regulation of the side effects induced by quinolones. DEC1 expression disturbed by quinolones might disrupt the equilibrium of protein–protein interactions in the affected cells and subsequently lead to biological disorder. Investigation of the molecular details of the toxicity may help overcome the shortcomings of quinolones and reveal new, useful therapy functions besides the antimicrobial effects. Meanwhile, knowledge of the protective mechanisms of DEC1 may provide insight into new therapeutic strategies in tumors and metabolic and immunological disease.

Conflicts of interest statement

The authors declare that they have no competing interests.

Acknowledgements

This work was supported by grants from the “Spring City Scholars” construction project of Jinan City (Q2-06), the key projects of Science and Technology of Jinan City (No. 200807027), and the Youth Science and Technology star project of Jinan City (No. 20080210).

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