

# Bilirubin: An Endogenous Inducer of Nrf2 Pathway and Its Possible Application in Therapy



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## Commentary

It has been asked, why convert-in a step that consumes energy-biliverdin a non-toxic easily excretable waste product, into bilirubin, that is unexcretable, neurotoxic, and has to be further metabolized for dispose? These two pages opinion focus on the possible effects of bilirubin on an important cyto-protective pathway named Nrf2 antioxidant signaling. In animals, the end product of oxidative degradation of heme results in a yellow pigment named un-conjugated bilirubin (UCB) that has a significant importance role during physiological and pathological conditions. UCB once produced is transferred into liver and then conjugated with glucuronic acid by the enzyme UGT1A1. UCB is responsible for neonatal jaundice that occurs in most newborn during the first week of life [1,2]. However, UCB is a potential neurotoxic and in very few cases, such as Crigler Najjar syndrome type I in which the activity of UGT1A1 is completely absent; UCB leads to neurotoxicity or kernicterus [3].

UCB plays a major role as a significant antioxidant at physiological levels, although we are still far from a complete understanding of this phenomenon. The antioxidant ability of UCB arises from a popular explanation of redox consuming cycling mechanism that act between the conversions of UCB in biliverdin. Several in vitro studies support the "direct" antioxidant properties of UCB [2,4]. Support for an in vivo antioxidant capacity of bilirubin is mainly "indirect evidences". The modest elevations of the plasma UCB in neonates are suggested by acting as a direct potent antioxidant [5]. Similarly, in Gilbert syndrome, the mild hyperbilirubinemia is negatively related to the risk of different diseases associated with oxidative stress such as atherosclerosis and cancer [6,7]. Gilbert syndrome is a very common chronic, mild hyperbilirubinemia (total serum bilirubin around 5mg/dl), mainly due to a recessive insertional mutation in TATAA box of UGT1A1 gene. Such mutations resulting in a reduced UGT1A1-activity to about 30% of normal [8]. UCB

also possess antioxidant properties in Gunn rat (animal model of Crigler Najjar syndrome type I) [9]. In a recent study, mice have been treated with UCB and showed anti-obesity and anti-diabetic effects. UCB reduces cholesterol, improve insulin resistance and glucose tolerance and authors suggest UCB treatment or use of partial UGT1A1 inhibitors as a possible therapeutic approach to treat metabolic disorders [10].

Since UCB induced cyto-toxicity is specific for certain types of neurons (e.g., Purkinje) and occurred at a very high level of UCB, it is suggested that organs that possess resistance to UCB toxicity such as liver benefit from the "direct" antioxidant properties of UCB, based on the popular model of Baranano et al. [4]. However, further investigations are needed to clarify this direct antioxidant properties of bilirubin, since another more recent study demonstrated a limited role for bilirubin-biliverdin redox cycle in the cellular antioxidant protection [11]. We reported the indirect effects of UCB toward the activation of the master regulator of the endogenous antioxidant system called Nrf2 pathway [12]. Nrf2 transcription factor is tethered within the cytosol by inhibitory partner called Keap-1. Once activated, Nrf2 undergo a conformational change resulting in a translocation of Nrf2 to nucleus and binds to antioxidant response element (ARE), an enhancer sequence presents in the promoter of a wide array of cyto-protective genes. Nrf2 regulates plethora of genes called "Nrf2 gene battery" include genes involved in glutathione homeostasis, NADPH utilization, heme-oxygenase I and quinone oxidoreductase 1 signaling, sulfonyl-transferases, peroxiredoxine, thioredoxine, superoxide dismutase 1, catalase, ABC efflux transporters and many others [13-16].

The coordinated induction of Nrf2 target genes represents a potential therapeutic strategy to overcome several diseases [17]. Interestingly, a novel strategy for reducing oxidative stress-

associated diseases *in vivo* (cardio vascular disease, cancer, and inflammatory syndromes) was suggested by increasing serum UCB level [7,18]. Our previous interesting results [12] in line with another study [19] demonstrated Nrf2 pathway activation by hyperbilirubinemia, indicating that UCB is a potential endogenous compound that activate Nrf2 pathway. This may represent a positive response to the pro-oxidant concentration of UCB in the organs that are able to tolerate UCB toxicity such as liver, by activating cellular antioxidant system through Nrf2 and providing cell protection against toxic insults. It could be possible that the whole cyto-protection effects under elevated hyperbilirubinemia are mainly related to the activation of Nrf2 pathway. According to this hypothesis, it will be interesting to study Nrf2 pathway activation in animals and subjects with hyperbilirubinemia especially in Gilbert syndrome and its possible application in therapy as a potent inducer for Nrf2 signaling. Further studies are needed to confirm or confute this hypothesis

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