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Coenzyme Q in Cancer Therapy

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Abstract: The presentation is a brief review of the oxidative damage mechanism of carcinogenesis, the anti-oxidative properties of Coenzyme Q (CoQ) and the expectation of CoQ applying to cancer treatment. The oxidative damage to DNA, lipid and protein has been suggested to contribute to initiation and progression of carcinogenesis. Nevertheless CoQ, known as the electron carrier in mitochondrial respiratory chain, has shown potent anti-oxidative activity, which is more efficient than vitamin E by about four mechanisms. Though few researches have been reported on the pharmacology of CoQ on cancer or tumor, CoQ deficiency in human or animals bearing tumor has been long observed and CoQ administration has shown a benefit for cancer patients. But more researches should be launched to explore the relationship between CoQ and cancers, especially the dynamic relation and to illustrate the anti-carcinogenesis mechanism of CoQ in order to enable a wider application of CoQ to cancer therapeutics.

Key words: Oxidative damage, anti-oxidation, coenzyme Q, carcinogenesis

Oxidative Damage and Cancer

Cancer is the number one killer in diverse diseases and is significant in human mortality. WHO reported that each year over nine million cancer cases occurred and five million persons died of cancer, which would soar up to twenty million and ten million by 2020, respectively. How does cancer occur? Accompanying with oxidative phosphorylation and ATP's production, Reactive Oxygen Species (ROS) including free radical come into being. ROS is any species capable of independent existence that contains one or more unpaired electrons. In the presence of metal ions, ROS may cause an oxidative damage by reacting with macromolecules including proteins, lipids and DNA in the cells (Halliwell and Gutterage, 1989a; Halliwell, 1991), which is called as oxidative stress. Oxidative damage has been suggested to contribute to the initiation and progression of carcinogenesis (Halliwell and Gutterage, 1989b) and causes of oxidative stress including transition metals (e.g., iron and copper), ultraviolet radiation, inflammation, some chemicals or drugs (e.g., carbon tetrachloride) are all associated with carcinogenesis or tumor biology (Halliwell and Gutterage, 1989a).

Since free radicals are usually generated near membranes, lipid is the first target of free radicals and lipid peroxidation is the first reaction to occur. It has been reported that products of lipid peroxidation may cause DNA damage (Halliwell and Gutterage, 1989b; Esterbauer, 1990; Marinari *et al.*, 1984). Lipid hydroperoxides may directly induce DNA chain breaking (Marinari *et al.*, 1984) and lipid peroxyl and alkoxy radicals may cause base oxidation in DNA (Cochrane, 1991). Peroxide and hydroperoxides have also demonstrated tumor promoting activity *in vivo* (Park, 1992). It is known that the epoxy derivative of 4-hydroxynonenal (HNE) has a tumor causing activity (Chung *et al.*, 1993; Sodom, 1991; Wang *et al.*, 1996). Reaction of MDA with DNA is a hot subject, which has drawn considerable attention because of its mutagenicity. An endogenous MDA-

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deoxyguanosine adduct that has been implicated in the induction of G to T transversions was detected by mass spectrometry in healthy human liver (Imlay *et al.*, 1988).

Protein oxidation usually occurs at certain amino acid residues of a particular protein. Reactive oxygen radicals react with amino residues in proteins and give rise to produce of carbonyl products, changing protein structure or converting sulphhydryl (thiol) groups of proteins into disulfide groups (Butterfield *et al.*, 1998; Dean *et al.*, 1997). Peroxynitrite generated after the reaction between superoxide radicals and nitric oxide damages protein by binding nitro groups with protein tyrosine residues to form nitrotyrosine (Kaur and Halliwell, 1994; Halliwell, 1997). Oxidation of cellular proteins might result in the inactivity of anti-oxidative enzymes and especially DNA repair enzymes.

DNA is another major object targeted by free radicals. Oxidative damage of DNA could result in strand breaks, base modifications and DNA-protein cross-links. H_2O_2 is known to cause DNA breaks in intact cells and purified DNA (Imlay *et al.*, 1988; Baker and He, 1991). Though there are a variety of modified DNA bases produced by free radical reactions, only the modifications of C-8 position of guanine has been studied in many aspects because of the sensitivity detection method of 8-oxoguanine (8-oxoG) by high performance liquid chromatography and the electrochemical detector developed in 1986 (Baker and He, 1991). It has been revealed that C-8 position of guanine is hydroxylated to produce 8-oxoGs. This hydroxylation completely changes the stereographic charge mapping of the molecule to allow guanine to pair adenine as well as guanine to pair cytosine. Accordingly, 8-oxoG induces G:C to T:A transversions in DNA replication (Kuchino *et al.*, 1987; Shibutani *et al.*, 1991), which appears to be important in carcinogenesis and tumor biology.

In fact, oxidative stress has been founded in human or animals bearing diversity cancer or tumor (Gibanananda *et al.*, 2000; Ilker *et al.*, 2003). In plasma or cancer tissue, reactive oxygen species (e.g., superoxide anion, hydrogen peroxide and hydroxyl radical) and products of lipid peroxidation and protein oxidation increase, while the activities of some antioxidant enzymes activity decrease.

Under normal physiological conditions oxidation and anti-oxidation are in equilibrium. Changes in this balance in favor of free radical formation would result in oxidative stress (Rizzo *et al.*, 1992). Anti-oxidants are enzymes and nonenzymatic agents that eliminate ROS or prevent their formation. Antioxidant enzymes include superoxide dismutase and various peroxidases such as glutathione peroxidase, catalase, thioredoxin reductase and peroxiredoxin (Holmgren and Bjornstedt, 1995; Wood *et al.*, 2003); vitamins C and E, carotenoids, glutathione, α -lipoic acid, flavinoids, the reduced form of CoQ (CoQH₂) are recognized as nonenzymatic agents of anti-oxidative activities. Antioxidants have been used as radioprotectors, antimutagens and anticarcinogens (Ames and Gold, 1990). Vitamin E (α -tocopherol) is a biological lipid antioxidant that prevents the formation of free radicals from lipid peroxidation and has proved an antimutagen or anticarcinogen in *Salmonella tester* strains (Tavan *et al.*, 1997) as well as in human leucocytes *in vitro* (Bolkenius, 1991). Of note here is the fact that the anti-oxidative activity of CoQ is more efficient than Vitamin E (Frei *et al.*, 1990; Shi *et al.*, 1999), implying that CoQ might be used as antimutagen or anticarcinogen.

What Is Coenzyme Q?

In 1957, CoQ was first isolated and purified from beef hearts by Fred Crane. Now, CoQ has been found in all cells, tissues and membranes (Dallner and Sindelar, 2000). For animals and humans, CoQ distributes in subcellular organelles, blood plasma and serum lipoproteins. Its molecular formula is shown in Fig. 1 CoQ consists of a quinonoid head group attached to a long, hydrophobic tail of 5-carbon isoprene units numbering from 6 to 12 in different species (Battino *et al.*, 1990) (e.g., 6, 8, 9, 10 in *Saccharomyces cerevisiae*, *Escherichia coli*, rodent, human, respectively). *In vivo*, the quinonoid head mainly exists alternately in three different redox states: ubiquinone, the fully oxidized form; ubisemiquinone (\bullet QH), the partially reduced form, also a free radical; and ubiquinol (CoQH₂), the fully reduced form (Turrens *et al.*, 1985; Kozlov *et al.*, 1998). CoQ plays multiple functional roles in living cells in many aspects. Among those functions, three have been well

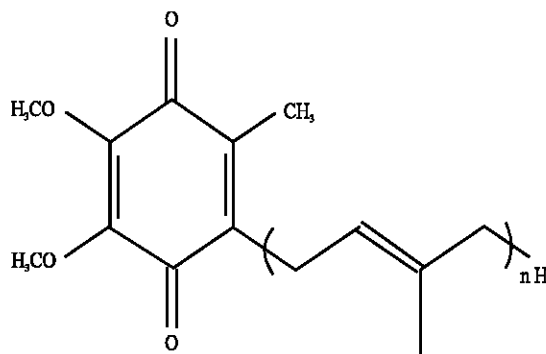


Fig. 1: Structure of ubiquinone, n=6,7,....,12

characterized. First, as an endogenous enzyme cofactor, CoQ is an essential component of the mitochondrial respiratory chain and adenosine triphosphate (ATP) production, carrying electrons from complexes I or II to complex III (Ernster and Dallner, 1995). Second, CoQ functions as pro-oxidant. Superoxide radicals are generated during the redox process associated with •QH formation, which accounts for the major part of superoxide anion and hydrogen peroxide physiologically generated in the mitochondria (James *et al.*, 2004). Third, as the only endogenous lipophilic antioxidant, ubiquinol exerts strong anti-oxidant power on plasma and cellular membranes (e.g. scavenging reactive oxygen species or lipid radicals and regenerating α -tocopherol from α -tocopheroxyl radical) (Crane, 2001; Hargreaves, 2003; Genova *et al.*, 2003). Anthony and Hayden (2004) supposed on the base of these three roles that CoQ could regulate gene expression and metabolism.

The Anti-oxidation and Pro-oxidation of Coenzyme Q

Literature on the anti-oxidation of CoQ is exhaustive. Ubiquinol is a potent antioxidant and its anti-oxidative activity is much stronger than that of α -tocopherol (a-T) (Frei *et al.*, 1990). When phosphatidylcholine liposomes are oxidized by a water-soluble radical initiator in the presence of ascorbate, a-T and CoQ, the antioxidants are consumed in the order: Ascorbate-CoQ-a-T (Shi *et al.*, 1999); while with a lipidsoluble radical initiator, the order is CoQ-ascorbate-a-T. It has been reported that ubiquinol inhibits lipid peroxidation *in vitro* using submitochondrial particles (Mellors and Tappel, 1966; Takayanagi *et al.*, 1980). Simultaneously ubiquinone appears workable for anti-oxidation even without appropriate reducing systems (Tomasetti *et al.*, 1999). It is now well established that CoQ prevents lipid peroxidation in most subcellular membranes (Ernster and Dallner, 1995) and acts as antioxidant also in the circulation (Romagnoli *et al.*, 1994; Alleva *et al.*, 1995). Investigations suggested that the endogenous content of CoQ might prevent membrane proteins and DNA from oxidative damage mediated by lipid peroxidation (Forsmark, *et al.*, 1995; Forsmark and Ernster, 1994). DNA oxidation measured by 8-oxoG formation in rat liver mitochondria and DNA strand breaks in human lymphocytes are also prevented by CoQ administration *in vitro* or *in vivo* (Tomasetti *et al.*, 1999; Atroschi *et al.*, 1997; Tomasetti *et al.*, 2001). CoQ supplementation increases CoQ homologues in tissues and their mitochondria, decreases selectively protein oxidative damage and increases anti-oxidative potential in rat (Kwong *et al.*, 2002). CoQ prevents the hydrazine- and chloramphenicol-induced changes in the membrane potential of mitochondria and decreased ROS generation rate in mitochondria. Furthermore, CoQ accelerates the repair of damage induced by chloramphenicol in mitochondrial structure and functions (Teranishi *et al.*, 1999). Various studies have reported the beneficial effects of CoQ supplementation in animal experimentation (Rauscher *et al.*, 2001; Kwong *et al.*, 2002) or human therapy on different diseases related to oxidation damage (Geromel *et al.*, 2002; Hodgson *et al.*, 2002).

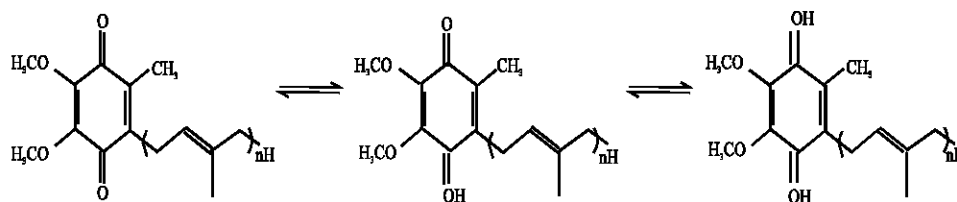


Fig. 2: The redox process of CoQ

CoQ *in vivo* undergoes the redox process shown in Fig. 2. Ubiquinone is reduced by ubiquinone reductases first to \bullet QH and then to ubiquinol, each step with an additional electron and an additional proton (Rich and Harper, 1990). Because cells have effective systems to reduce ubiquinone at all intracellular locations, CoQ mainly exists as ubiquinol and the ratio of ubiquinol and ubiquinone varies from one tissue to another (Aberg *et al.*, 1992). The cellular pool of ubiquinol in some tissues was reported to be elevated following the external administration of ubiquinone in order to increase the antioxidant capacity (Crane *et al.*, 1984). Various NADH-dehydrogenases associated with cell membranes are supposed to transform ubiquinone to ubiquinol (Kishi *et al.*, 1999). Although the antioxidant activity of CoQ in systems is mainly attributed to ubiquinol, the role of ubiquinone should not be neglected. According to reported researches, the probable mechanisms of CoQ as an anti-oxidant could be as the follows: (1) ubiquinol (CoQH_2) prevents the initiation and/or propagation of free radical chain reaction. CoQH_2 acts by affecting the initiation process and preventing the formation of lipid peroxyl radicals (LOO) (Ernster and Forsmark, 1993) by reaction (i). It is also possible that CoQH_2 eliminated LOO directly by reactions (ii) and (iii) where a CoQH_2 molecule scavenges two free radicals eventually.



(2) CoQ spares and regenerates α -tocopherol. It is established that CoQH_2 regenerates α -tocopherol from α -tocopheroxyl radical. In reactions (iv) and (v) α -tocopherol was transferred to α -tocopheroxyl radical by reacting with lipid radical and in reaction (vi) CoQH_2 reacts with α -tocopheroxyl radical to produce α -tocopherol. When coexisting with α -tocopherol, it is CoQH_2 that is first oxidized by radical initiator, which thus spares α -tocopherol (Shi *et al.*, 1999). This sparing effect of CoQH_2 on α -tocopherol has also been observed in low-density lipoprotein (LDL) (Stocker *et al.*, 1991; Thomas *et al.*, 1995). Vitamin E level does not decrease, but CoQH_2 is oxidized to ubiquinone at an early stage in the oxidation of human plasma (Yamamoto *et al.*, 1991). CoQ administration enhanced α -tocopherol level in mitochondria (Kagan *et al.*, 1990; Maguire *et al.*, 1992; Stoyanovsky *et al.*, 1995) However, it is evident that the antioxidant function of CoQH_2 is not dependent on the presence of α -tocopherol. An investigation suggested that submitochondria particles containing CoQ were protected against lipid peroxidation even in the absence of α -tocopherol (Forsmark *et al.*, 1991).



(3) CoQ is a cofactor for uncoupling protein (UCP) function of performing anti-oxidative activity. UCP, situated in the inner mitochondria membrane, transfers H^+ from the outside to the inside of the mitochondria. UCP could be involved in suppressing the generation of oxygen radicals. Recently

Echtay *et al.* (2000, 2001) testified that CoQ was an obligatory cofactor for UCP function by using bacterial overexpressed UCPI, -2 and -3 in liposomes. (4) CoQ stabilizes membrane structure so as to block the propagation reaction in phospholipid bilayer (Landi *et al.*, 1987). The mechanism suggests that such antioxidant activity is related to the localization of ubiquinone within the lipid bilayer, where CoQ prevents autocatalytic free radical reaction by stacking among phospholipid molecules and keeping the quinone ring in the nonpolar phase (Fato *et al.*, 1986). In fact, fluorescence studies have demonstrated that ubiquinone homologues possess a strong ordering effect on the lipid bilayer, which is much higher than that produced by ubiquinol (Jemola *et al.*, 1996). The ordering effect decreases the rate of free radicals leaking from mitochondria in the cell when they consume oxygen to generate adenosine triphosphate.

On the other hand, CoQ plays key roles in physiology as pro-oxidant. During the redox process associated with CoQ semiquinone formation as shown in Fig. 2 and Reaction ii, superoxide radicals are generated. Some superoxide radicals are converted to hydrogen peroxide (H_2O_2) by superoxide dismutase. More should not be re-visited here. But it should be emphasized that the pro-oxidative activity of CoQ is not evil because intact mitochondria produces only a small amount of H_2O_2 , and this the very low level of H_2O_2 is crucial to both cell function and the role of H_2O_2 as a second messenger molecule (Gille and Nohl, 2000; St- Pierre *et al.*, 2002).

It is emphasized that CoQ pro-oxidant and anti-oxidant roles are not mutually exclusive (Anthony and Hayden, 2004), but essential to cells. On the one hand, the action of CoQ leads to the cellular bioenergy modulation through superoxide formation and the synthesis of the mitogen H_2O_2 , which is accompanied by the formation of ROS and the damage of some lipid, protein and DNA. On the other hand, as an anti-oxidant, CoQ contributes to alleviating the oxidative damage derived from ROS.

Coenzyme Q and Cancer

CoQ has certain relation with the occurrence and development of cancer or tumor even though researches on this subject have not been bountiful. CoQ in tissue or plasm is decreased in subjects with cancer (Kozlov *et al.*, 1998; Quiles *et al.*, 1994). For breast cancer patients, the following conditions were observed: CoQ concentrations in tumor tissues significantly decreased compared with the surrounding normal tissues; higher MDA levels were observed in tumor tissues than noncancerous tissues; The activities of MnSOD, total SOD, GSH-Px and catalase in tumor tissues significantly increased compared with the controls. These findings may support that reactive oxygen species increased in malignant cells and caused overexpression of antioxidant enzymes and the consumption of CoQ. Increased antioxidant activities may be related to the susceptibility of cells to carcinogenic agents and the response of tumor cells to the chemotherapeutic agents. Hyperplastic noduli is the first stage during development of chemically induced hepatocellular cancer in rat and during this stage the amount of CoQ increases (Olsson *et al.*, 1991, 1995). Interestingly, the level of CoQ in the mitochondria is stable and the change of CoQ concentrations is attributed to the extra-mitochondrial compartments. During the first stage of the disease, there is increasing oxidative stress, which has been suggested to induce an adaptive response, resulting in the cell protecting itself by raising the concentrations of antioxidants (Droge, 2002). Upon progression of the disease, manifest cancer develops and the amount of CoQ decreases to only 40% in human and 76% in rat (Eggen *et al.*, 1989).

Because of the reasons presented above and CoQ preventing lipid, protein and DNA from oxidation damage, CoQ is considered to be feasible to treat cancer. Several small studies have shown a benefit for people with breast or prostate cancer. There are a number of reports on the use of CoQ10 in the treatment of cancer, specially breast cancer (Lockwood *et al.*, 1994; 1995).

Additionally, Other findings have indicated that CoQ boosts the immune system (Folkers *et al.*, 1993), possibly helping to limit the spread of cancerous tissue. Karl Folkers published that complete biochemistry relating to biosyntheses of CoQ and the DNA bases was a rationale for the therapy of cancer with CoQ (Folkers, 1996).

Conclusions

Attributed to its anti-oxidative activity and other intrinsic functions, CoQ has shown promise for cancer. Nevertheless, researches on pharmacology of CoQ on cancer are so rare that the anti-cancer mechanisms of CoQ and the dynamic relation between CoQ concentration in tissue or plasma and carcinogenesis are still unclear. More researches should be lunched to explore the anti-carcinogenesis properties and the mechanisms in order to enable CoQ to benefit human health widely.

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