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Comment: Mitochondrial genes and cancer

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As a result of an experimental confluence between carcinogenesis and oxidative phosphorylation, we published in 1971 'A Unitary Hypothesis for Carcinogenesis' [(1971) J. Antibiot. Tokyo 24, 405–417]. According to this hypothesis, damaged mitochondria release mitochondrial genetic material which like that from an oncogenic virus could enter the nuclear genome. Our original hypothesis and its justification cover the hypothesis recently presented by Dr C. Richter [(1988) FEBS Lett. 241, 1–5].

Mitochondrial DNA; Carcinogenesis

During the 1970s we reported [1–13] that many metabolites of carcinogens, and in some instances the carcinogen itself, interfered with the mitochondrial process of oxidative phosphorylation. The carcinogens, the metabolites, and certain related compounds, covered a wide range of structures (e.g. polynuclear hydrocarbons, hydroxyquinones, arylamides, arsenate, ...). The effects on oxidative phosphorylation were diverse (e.g. respiratory inhibitors, uncoupling agents, inhibitors of respiratory linked phosphorylation, ...). Because of this experimental confluence between carcinogenicity and oxidative phosphorylation, we presented a unitary hypothesis for carcinogenesis [1] which was stated in the abstract as follows, "...when mitochondria were damaged genetic material could be released from the mitochondria. The released genetic material could behave like an oncogenic virus and enter the nuclear genome." This hypothesis was not restricted to chemical carcinogenesis, but included any means of damaging the mitochondria.

In 1971 when this hypothesis was published [1] it had been unpopular for some time [14,15] to link carcinogenesis to either an impairment of respiration, or to damage of the mitochondria, as suggested by Warburg [16] many years previously. It should be noted, however, that Woods and Burk [17] had proposed in 1965 that an alteration in mitochondrial genetic material was associated with cancer. Our hypothesis involved what today is called, mobile genetic units and insertional mutagenesis [18]. Two important reviews, the first [19] dealing with mitochondrial bioenergetics and cancer, and the second [20] dealing with the transfer of mitochondrial genes to the nucleus, drew significant attention to our unitary hypothesis for carcinogenesis. In addition, an aim of the first review [19] was to 'stimulate additional research and funding for this important but rather neglected area'.

A good hypothesis should lead to otherwise unanticipated investigations [5]. Thus, we reported [21] that mitochondrial DNA and nuclear DNA from normal rat liver, have a common sequence. This was an unexpected observation at the time when it was made and suggested that rat mitochondrial DNA-like sequences in the nuclear genome could not only be relevant to transformation but also to evolution, development, aging and pathological conditions.

Recently Dr Christoph Richter [22] published the hypothesis, 'Do mitochondrial DNA fragments promote cancer and aging'. What Dr Richter pro-

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posed, has already been presented as our original unitary hypothesis for carcinogenesis [1] and in our later publications [2–13,21]. Dr Richter did not mention the originality of our unitary hypothesis for carcinogenesis even though he cited the above two important reviews [19,20] which gave prominence to our publications and our hypothesis and which were germane to his article.

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