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Hypothesis of mitochondrial oncogenesis as the trigger of normal cells to cancer cells

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ABSTRACT

The Warburg Effect showed that energy metabolism of cancer cells was similar to prokaryotic cells, which were different from normal eucaryotic cells. The Endosymbiotic Theory offered a plausible explanation that the eucaryotic cells were evolved from prokaryotic cells, by which host cells (ancient prokaryotic cells) had ingested mitochondria (ancient aerobic bacteria), which depended on oxidative phosphorylation rather than glycolysis for generating energy. The alteration of energy metabolism might mean that the survival style of cancer cells were the re-evolution from eucaryotic cells to prokaryotic cells. But how this alteration happened was still unknown. This hypothesis tries to explain how mitochondria take part in the re-evolution from normal cell to cancer cell.

Introduction

The Endosymbiotic Theory offered an explanation for the evolution of eukaryotic cells from prokaryotic cells. The Grossgebauer's Hypothesis proposed that based on cytoarchitecture, cancer cells were re-developed from eukaryotic cells and Warburg Effect showed that the most important feature of cancer cells was that the energy metabolism of cancer cells was similar to that of ancestor prokaryotic cells which generated energy through glycolysis rather than through oxidative phosphorylation. This feature could be basically confirmed that the cancer cells were retrograded from eucaryotic cells to prokaryotic cells in their survival style. However, above theories did not answer which cells could become cancer cells. The fact was that all kinds of cancer cells originated from mitotic cells and none of cancer cells originated from terminal differentiation cells. This hypothesis tries to give a speculation about how cancer cells originate from mitotic cells and how mitochondria trigger the transformation from normal cells to cancer cells in their carcinogenesis process.

The Endosymbiotic Theory and re-evolution

The Endosymbiotic Theory was proposed by Lynn Margulis in the 1960's. This hypothesis suggested that aerobic bacteria (ancient mitochondria) were ingested by anaerobic bacteria (ancient prokaryotic cells) and transferred most of their DNA to the nucleus of anaerobic bacteria; they both had a survival advantage as long as they continued their partnership. The aerobic bacteria would have handled the toxic oxygen for the anaerobic bacteria, and the anaerobic bacteria would ingested food and protected the aerobic "symbiote" [1,2]. The theory gave good explanation for the many similarities between prokaryotic cells and the organelles of eukaryotic cells, and offered a plausible explanation for the evolution of eukaryotes. According to the Endosymbiotic Theory, the reason for evolution was that the ancient organisms were forced to adapt to the concentration of oxygen risen in the atmosphere and shield themselves [3]. In light of Endosymbiotic Theory and based on the replicative ability of cancer cells similar to the proliferation of prokaryotic cells, Klaus Grossgebauer firstly proposed the Prokaryote Hypothesis of Oncogenesis that a re-evolution of eucaryotic to procaryotic cells led to cancer [4,5]. As has been stated, the stress for survival was the actuating force to make anaerobic prokaryote develop into eukaryotes, but which elements induced oxidative phosphorylation eukaryotic cells into transform glycolysis cancer cells remained unknown. The clue to the answer might be found in the process of mitochondria evolution in their host cells.

Mitochondria (aerobic bacteria) evolved in their host cells (ancestor prokaryotic cells)

At first the ancient aerobic bacteria (ancestor mitochondria) had been ingested by ancient anaerobic bacteria (ancestor prokaryotic cells) in the ancient time, the ancient aerobic bacteria (ancestor mitochondria) were still self-replicative organelles [6] and had to evolve to fit new environment. Instead of the oxygen-enriched

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environment, the ancestor mitochondria, isolated by membrane of ancestor prokaryotic cell, were in hypoxia environment after they got in ancestor prokaryotic cell. The last consequence of the evolution could be in two parts:

(1) Ancestor mitochondria had to up-regulate oxidative phosphorylation to fit into the new hypoxia environment, otherwise, if mitochondria down-regulated oxidative phosphorylation, combine of the two organisms was nonsense for ancestor prokaryotic cells. For ancestor mitochondria, only those that consumed more oxygen and pyroracemic acid could survive and become modern mitochondria. The increased oxidative phosphorylation was fixed by the related mitochondrial DNA(mtDNA) mutation. The evolution process of the mitochondrial metabolism must be accompanied by more active electron transport and produce more metabolic products, such as water, adenosine triphosphate (ATP) and reactive oxygen species (ROS). For the above reasons, the ancestor intrinsic mitochondrial membrane, as the place for the oxidative phosphorylation position had gradually proliferate and fold in order to adsorb more oxidative phosphorylation enzymes and more substrate for metabolism. So, more effective membrane channels, enough voltage gradient and concentration gradient between the ancestor intrinsic mitochondrial membrane (mitochondrial inner membrane) were built for more oxygen, pyroracemic acid, ATP and ROS to get into or out of the mitochondrial inner membrane. The enough ATP permeating from mitochondria into cytoplasm inhibited the glycolysis of ancestor anaerobic bacteria (host cells), and primary glycolysis genes of ancestor anaerobic bacteria such as HIF-1α, c-Myc, and Akt were forced to down-regulate by the negative feedback mechanism.
(2) In line with the traditional view about the life of bacteria, the aerobic bacteria (ancestor mitochondria) and ancient anaerobic bacteria (ancestor prokaryotic cells) were immortal cells before aerobic symbiote formed. Although aerobic bacteria could utilize and tolerate oxygen in the ancient time, they might be damaged by oxygen and its metabolites because they had to consume more oxygen than they needed in aerobic symbiote. The studies showed that ROS could injure mitochondria [7]. One of the accumulative oxidative injuries caused by ROS was that it made the inner mitochondrial membrane age (mitochondrial membrane oxidation) [8]. While mitochondria replicate and divide, daughter mitochondria that inherited the more aged inner mitochondrial membrane in the "mother mitochondria" progressively exhibited their decline in its energy metabolism capacity with their increasing mitochondrial membrane oxidation time. The mitochondrial membrane oxidation underlies the apoptosis of mitochondriu and the progressively aged mitochondria gradually increased their inner mitochondrial membrane permeabilization, which contributed to cell death [9]. Meanwhile, cytochrome *c* was released into the cytoplasm from mitochondria and engaged a vicious cycle [10]. The result is that modern mitochondria and host cells became mortal cells. Under physiological conditions, mitochondrial reduplication and programmed death were in a dynamic equilibrium in cytoplasm, so were host cells in their biological entities.

From the trace of mitochondrial evolution in their host cells, the following conclusions can be made: ① The hypoxia environment drove mitochondria to develop and the survival stress was the cause of the mitochondrial development. ② Accumulative oxidative injury induced the mitochondria and their host cell programmed death. ③ The mitochondrial function was the crucial biological action for influencing the metabolic style of host cell.

The Warburg Effect and subsequent effects

Under physiological conditions, most normal eukaryotic cells use more energy-efficient oxidative phosphorylation as the main route to generate ATP. But Warburg observed that cancer cells performed energy metabolism in a way that was different from normal adult cells–cancer cells obtained energy through glycolysis rather than oxidative phosphorylation. So he originated the hypothesis that the cause of cancer was primarily the defect in energy metabolism [11,12]. Many cancer cells had been proved to actively use the glycolytic pathway for ATP generation, even in the presence of oxygen. Some studies showed that cancer mitochondria were structurally and functionally abnormal and incapable of generating normal levels of energy [12,13]. That means not only defective mitochondria but also other mechanisms were involved in up-regulating glycolysis. For example, several molecules in cancer cells, including HIF-1α, c-Myc, and Akt, had been suggested to play important roles in promoting glycolysis and thus might be involved in "metabolic reprogramming" in the cancer cells [14,15]. Recent studies suggested that oncogenic transformation by the K-ras oncogene might also significantly alter the cellular metabolism, including the suppression of mitochondrial respiration [16] and the increasing generation of reactive oxygen species [17]. The Warburg Effect was not only a consequence that normal cells re-evolved into cancer cells, but also the basis of biological characteristics, for example, the resistance to chemotherapy resulted in large part from the enhanced aerobic fermentation of the tumor cells [18]. Our hypothesis tries to explain the process of normal cells turning into cancer cells from the Endosymbiotic Theory, Prokaryote Hypothesis of Oncogenesis and Warburg Effect.

New hypothesis

Our hypothesis was based on the fact that cancer cells were derived from proliferative potential cells (mitotic cells) [19,20] and never derived from terminal differentiation cells [21–23]. Our hypothesis suggests that all terminal differentiation cells are capable of being programmed to inhibit all genes replication and only proliferative potential cells are capable of being programmed to activate all genes proliferation by long time natural selection.

① Mitochondrial DNA might be more susceptible to mutation than nucleus DNA [24]. This might be due either to its supercoiler structure [25] or the paucity of the repair mechanism for Mitochondrial DNA [26]. Another contributing factor might be the relatively constant exposure of mtDNA to free radicals produced by the respiratory chain [27]. Mitochondrial mutations were divided into two parts: the accumulative oxidative injury mutation and the carcinogen mutation. Besides cancer cells, mitochondrial mutations were also reported in normal subjects, especially those with advanced age, which were called the accumulative oxidative injury mutation. For example, the A189G age-associated mutation was found only in older individuals and prevalent in ragged red fibers in muscle [28]. The accumulative oxidative injury mutations were proposed to happen gradually and its impact on their host cells was limited. This mutation was not able to induce carcinogenesis of host cells [29]. Besides, the mtDNA mutation had been observed in many types of human cancer and had been found present in both the non-coding region and the coding region of the mtDNA. These mtDNA mutations happening in cancer cells could be called carcinogen mutations. For example, the A3243G mutation was found in a colon cancer sample [30]. The carcinogen mutations were proposed to happen suddenly and their impact on host cells