

Commentary

Why is Cardiac Cancer Rare: Contractility by Epigenetic Regulations?

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Cancer is one of the most common disease and known to have a lethal risk. The most common cancers worldwide in 2012 were diagnosed in lung, breast, intestines, prostate, stomach, liver, cervix, esophagus and bladder, respectively [1]. In theory, carcinogenesis can occur in each organ/tissue of the living organism. However, heart cancer likely appears the rarest cancer seen in a vital organ and even has a low incidence in people with heart problems as reported that only 9% of those people who had open-heart surgery showed malignant cardiac tumor [2]. Besides, heart cancer is not the only, such paraganglioma and retinoblastoma are also the rare cancers. Their existence/incidence can be rather reasonable, whereas life ends immediately when heart fails.

Researchers have revealed the oldest case of cancer in a skeleton from 1200 B.C [3]. However, the people of those times were probably not aware of cancer. After thousands of years, we are able to have lots of understandings on cancer progress. Nonetheless there is not a certain therapy for cancer developed yet. Cancer was earlier thought to be induced by the genetic mutations only. The missing part of puzzle has recently been added: Epigenetics. The term of "Epigenetics" represents dynamic and reversible biochemical changes within the nucleic acids and chromatin proteins that involve in normal processes of life. Abnormalities in DNA methylation can associate with cancer formation since DNA methylation at genomic and/or gene specific scale has been detected to alter in gastric [4], prostate [5], ovarian [6], leukemia [7], lymphoma [8], pancreatic [9], lung [10], liver [11], colorectal [12], breast [13], esophageal [14], paraganglioma [15], brain [16], skin [17], bladder [18], adrenal [19], anal [20], salivary gland [21], renal [22], cervical [23], oral [24], thymus [25], thyroid [26], retinoblastoma [27], rhabdomyosarcoma [28] and head-neck [29] cancers. These suggest that changes in DNA methylation are highly associated with cancer but one of the questions is whether the changes in DNA methylation are the result or the cause of cancer.

Heart is the organ highly composed of muscle tissue, but it has a unique muscle tissue neither exactly the same with skeletal nor smooth muscle tissues. Skeletal muscle is under control of human activity (by somatic nervous system) but heart and smooth muscles work automatically (by autonomic nervous system), suggesting that heart and organs containing smooth muscle such intestines are regularly exercising by themselves. But heart is clearly emphasized to be the most active organ physically. Each cell in the organs has a level of micromotility by such actin [30,31] and myosin proteins [31], but not each organ itself has an active motility, except heart. Therefore, a possible reason why heart cancer rarely develops can be that heart is the only organ with the highest physical activity by itself in the body, resulting in its automatic and fast refreshment. This can be symbolized by people with physical activities living healthier and even longer than people with low activity [32-34]. Nevertheless this is considerable that heart diseases cannot be tolerated much than chronic diseases of other organs so early and sudden deaths can be resulted from heart failures. This may cause not to estimate the incidence of malignant heart cancer properly.

Heart beats through electrical signaling by cardiac cells having a role in contractility. Common contractile proteins include *e.g.* myosins (Myl), myosin heavy chain proteins (Myh), kinesins, tropomyosins, Ca^{+2} ATPases, troponin and alpha actinin. *Myl2* gene, involved in tight function signaling and contractility, was demethylated in ventricular myocyte derived stem cells [35], suggesting gene specific DNA methylation is supposed to occur in the mature heart. Pattern of Myh

proteins are also differentially found in developmental stage of heart, as *Myh7* gene is expressed in heart during embryogenesis but *Myh6* is expressed after the birth [36]. Zebularine, a demethylating agent, induced embryonic stem cells to be cardiac cells and contractility by increasing the expression of cardiac markers such *Myh7*, *Myl7* and *Myl2* [37]. Inhibition of DNA methylation by a demethylating agent decreased the anomaly of cardiac contractility induced by carcinogen exposure [38], and revoked the decreased contractility in cardiac hypertrophy [39]. Therefore it can be said that gene specific alterations in heart's cytosine methylation can associate with contractility abnormalities.

Gene-specific methylation plays a role during heart development. Genes involved in heart development are actively expressed so that they are demethylated. Disruption in the balance between methylation and demethylation of genes encoding contractility proteins can result in malfunction of contractility that will shortly cause heart arrest. This can indirectly prevent cancer progress of heart. One presumption is related to the genes functioning in contractility of heart which are the key since being highly and automatic contractile, therefore this makes heart different than other organs. Studies point out that some contractility genes are demethylated in development of heart but some is demethylated in adult heart. It suggests that contractility can be immediately failed if methylation patterns of these genes change. This is expectable when there is no contractility; the heart is subject to stop in a short time. This also supports the proposed obstacle to determine the incidence of heart cancer. But, making a conclusion is hard since heart cancer cases are limited. Revealing the pattern of DNA methylation in heart cancer will surely provide a large part of puzzle to understand about carcinogenesis, and give an insight into answer of opposite question how cancer cannot occur.

Conflict of Interests

The author declares no conflict of interests.

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