CENP-F, Cancer, and the Heart

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Abstract

Centromere protein F (CENP-F) is a large, multifunctional protein with demonstrated roles in mitosis and interphase through interactions with the microtubule network. In this focused review of CENP-F function, we will provide an overview of protein function in various model systems. In addition, we will highlight what is known about CENP-F control of heart development as well as development of other organ systems in specific species. Next, we will describe what is known about CENP-F and adult cardiac disease, which you will see is very limited. Finally, we will present our current hypothesis on the relationship between CENP-F, heart disease, and its juxtaposition with cancer. Our overall goal is to provide our colleagues a platform for further debate and discussion on the present understanding of CENP-F function in the cardiovascular system.

ABBREVIATIONS

CENP-F: Centromere Protein-F

CENP-F PROTEIN FUNCTION

Centromere protein F (CENP-F) is a complex protein whose role in the body and in disease has yet to be fully elucidated. CENP-F encodes a protein that associates with the centromere-kinetochore complex [20]. It is a component of the nuclear matrix during interphase, specifically phase G2, where it subsequently associates with the kinetochore and maintains this association until early anaphase. In anaphase, CENP-F localizes to the spindle middle, and in telophase it localizes to the intracellular bridge, before it is thought to be degraded [10,11]. Studies of the localization of CENP-F suggest it may play a role in mitosis, particularly in chromosome separation. Additionally, CENP-F has demonstrated and varied functions during interphase [13]. These functions include but are not restricted to maintenance of overall cell shape, trafficking of intracellular vesicles, regulation of cell adhesion proteins, and governance of persistent cell migration [16]. CENP-F directly binds tubulin through domains in its N- and C-termini [6,14] and is a critical regulator of the microtubule network [16]. Feng et al. [6], have shown that CENP-F binds the kinetochore in the same N-terminal domain seen to bind microtubules. In addition, a predicted coiled/coil domain within amino acids 930-1619 of CENP-F interacts with centrosomal protein HOOK2 [13] and vesicular proteins synaptin 4 [18] and SNAP 25 [19] further demonstrating the functional complexity of this protein. In a recent report from our laboratory, we show that loss of CENP-F has major impact on the microtubule network structure and basic cell functions dependent on microtubule activity was disrupted [16]. While significant progress has been made of identifying functional domains within CENP-F, it is clear that further work exploring domains throughout the protein is needed. With the recent impact of genomics and proteomics on the underlying basis of disease and developmental abnormalities, this need may be amplified. In this brief review, we will summarize what is known about CENP-F in malformations in development and its potential role in cancer.

CENP-F AND DEVELOPMENT

Disruption of CENP-F function has been reported in mouse, human and zebrafish development [4,23]. With global knockout of CENP-F in the mouse, disruption of heart development has been observed [4]. In this study, the heart was observed to be smaller in overall size with a reported decrease in mitotic activity in cardiac myocytes. Interestingly, the size of the heart was smaller but the overall structure of the heart chambers, values, vascular outlets, and epicardial/endocardial organization was generally maintained. Importantly, all knockout mice developed a dilated cardiomyopathy in post-natal life which amplified in adulthood. Further detailed analysis of other organ systems is needed in this species. A recent report by Waters et al., demonstrated that a specific mutation in CENP-F caused numerous and severe malformations in the developing human [23]. Severe defects in brain and central nervous system formation was reported along with craniofacial and renal malformations. These studies demonstrate the board impact CENP-F has in the developing embryo. Waters et al., further analyzed CENP-F function in the zebrafish embryo and showed that loss of function resulted in ciliopathies effecting axis patterning, brain and kidneys. Another report from Filges et al., very recently documented that mutation of the CENP-F gene in both exons 12 and 20 caused Strømsme syndrome which is characterized by microcephaly, microphthalmia and jejunal atresia [8]. Taken together, these studies demonstrate the importance of CENP-F regulation of proper cardiovascular development and in the generation of other organ systems. It is also obvious that further and more...
extensive analysis of CENP-F function development in various species by diverse laboratory groups is needed.

CENP-F, CANCER AND THE HEART

Many chemotherapy drugs are considered cardiotoxic because they weaken heart muscle [9]. Indeed, the relationship between cancer and chemotherapeutic induction of cardiomyopathy is not well understood but, at the same time, is a pervasive and devastating problem for the human population. It is of interest to note that many chemotherapeutic drugs either directly attack or indirectly affect the microtubule network [3,7]. This chemotherapeutic “strategy” is largely aimed at slowing or disrupting mitosis in cancerous cells by disabling the microtubule component of the mitotic structure, although clinical success is also attributed to interphase effects [7]. Indeed, use of paclitaxel which directly attacks the microtubule network, is known to produce cardiomyopathies when used individually or in concert with other chemotherapeutics [5,9]. A major negative and off-target consequence of chemotherapeutic treatments is the induction of cardiac disease including dilated cardiomyopathy [17,21,24]. Given that embryonic loss of CENP-F function leads to dilated cardiomyopathy and that CENP-F is a powerful regulator of the microtubule network, exploration of the relationship between CENP-F, cancer, and heart disease needs to be investigated. Our underlying hypothesis or premise is that a “first hit” on the microtubule network of cardiac myocytes such as mutation of CENP-F may put the heart at risk for a “second hit” from a chemotherapeutic. Exploring whether chemotherapeutics directly attacking microtubules put an individual with this genetic risk at higher risk than treatment with chemotherapeutics that do not directly attack the microtubule would be of interest. Additionally, the potential influence of other microtubule components in the generation of chemotherapeutically-induced cardiomyopathy needs to be explored.

Various studies show a relationship between CENP-F and cancer, specifically breast cancer [1], prostate cancer [25], nasopharyngeal carcinoma [2] and esophageal squamous cell carcinoma [12]. In each case, CENP-F is not diagnostic of these cancers, but rather prognostic, meaning that the way in which CENP-F is expressed in these patients predicts poor outcomes. For example, up-regulation of the CENP-F gene is most predictive of poor prognosis in human breast cancer [15]. There may be a connection, therefore, between treatment for CENP-F related cancers and heart disease. CENP-F may have important treatment implications and may be helpful in determining strategies for anti-cancer therapies, many of which may have an effect on the heart.

CONCLUSIONS

Work from many laboratories has demonstrated the importance of CENP-F in mitosis and interphase cellular actions. Disruption of CENP-F in development leads to numerous deleterious effects on organogenesis including the cardiovascular system in humans and other model systems. While it is abundantly clear that differential expression of CENP-F is associated with various cancers, the relationship between the expression of CENP-F and other microtubule-associated proteins, cancer outcomes, and heart disease needs to be explored in depth.

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