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**EDITORIAL**

# Atrial myxoma: the cardiac chameleon

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**This editorial refers to 'Atrial myxomas arise from multipotent cardiac stem cells', by M. Scalise *et al.*, doi:10.1093/eurheartj/ehaa156.**

*Stay away from chameleon tendencies. Your heart is not safe from them.*

*Sipho P. Nkosi (paraphrased)*

The same vexing lack of ongoing cellular proliferation in the adult human heart that frustrates those seeking repair via regeneration also makes myocardial tissue notably resistant to oncogenic transformation and tumour formation. Among relatively rare cardiac tumours, the most commonly observed type is myxoma: a generally benign growth often presenting in the left atrium near the septum. The specific cellular origin of atrial myxoma remained obscure other than an association with primitive stromal/connective tissue cells. Of course, defining the underlying cellular aetiology of atrial myxomas would offer much needed insight toward developing therapeutic interventional approaches. A significant step forward in such understanding has now been provided in a report from Scalise *et al.* in this issue of the *European Heart Journal* that establishes the protagonists as multipotent c-kit+ cardiac stem cells (CSCs).[1] This seminal link is important, not only for understanding atrial myxoma causality but also for revealing yet another previously unrecognized biological property of this controversial and often maligned endogenous CSC population.

CSCs were identified as a tissue-resident c-kit+ cell population over a dozen years ago and are one of the most well characterized interstitial cell types in the heart. Numerous studies attributed important biological and functional activities to c-kit+ CSCs including roles in development, postnatal growth, response to injury, contribution to multiple cell lineages, tissue homeostasis, and ageing.[2–4] Dozens of laboratories worldwide have contributed to advancing appreciation of the diverse and complex roles of c-kit+ CSCs in myocardial biology, particularly the Torella and Ellison-Hughes groups[5–9] responsible for the present study. Enduring qualities of endogenous CSCs validated by multiple independent studies include multipotentiality, plasticity, and heterogeneity. These characteristics coupled with proliferative capacity (that declines with age) allow CSCs chameleon-like adaptability to changing environmental conditions, but also render them one of the few resident cardiac cell types exhibiting traits reminiscent of oncogenic transformability described in cancer stem cells.

The atrial myxoma cohort obtained from 23 patients in the present study by Scalise *et al.* is particularly noteworthy considering the rarity of occurrence estimated at only one out of 2 million people annually. This impressive sample collection coupled with detailed phenotypic characterization allowed for robust comparative analyses of constituent myxoma cell populations, which turn out to be comprised predominantly of c-kit+ cells concurrently expressing markers of haematopoietic (CD45), endothelial (CD31), or mast cell (tryptase) origin. However, a fraction of c-kit+ myxoma cells did not express these markers (CD45–, CD31–, tryptase–), suggesting cardiac origin and possible CSC origin. Delving into this putative CSC-related subset revealed distinctive properties including the myxoma-associated cell marker calreticulin in polygonal cells. Closing in on a myxoma stromal precursor cell, additional characteristics of clonogenicity, spherogenicity, expression of stemness markers, and commitment potential to various lineages were assessed *in vitro*. Furthermore, these cells also produce the gelatinous matrix that is particularly abundant in myxomas. Collectively, these features are fundamentally consistent with expectations for myxoma tumour cells and raise the question of their relationship to endogenous CSCs that share many of the superficial phenotypic markers. What distinguishes the 'CSC-like' myxoma-resident population from their brethren that reside within the myocardium? Why did they stray from their normal roles in maintenance of tissue homeostasis and into the realm of cancer stem cells? Clues to answer these questions lie within molecular profiling and bioinformatic analyses.

Profiling of CSCs derived from normal tissue relative to select c-kit+ 'CSC-like' myxoma cells found substantial similarities, sharing ~90% of their transcriptome, consistent with a progenitor–progeny relationship. Yet, significant differences were also present that highlight the orientation of CSCs found within the myxoma toward tumour initiators such as abortive differentiation and proteoglycan hyperproduction. Subsequent assessment of microRNA (miRNA) expression provided further clues to regulatory networks dysregulated in myxomatous transformation, some of which were tested by Scalise *et al.* through selective gain- or loss-of-function

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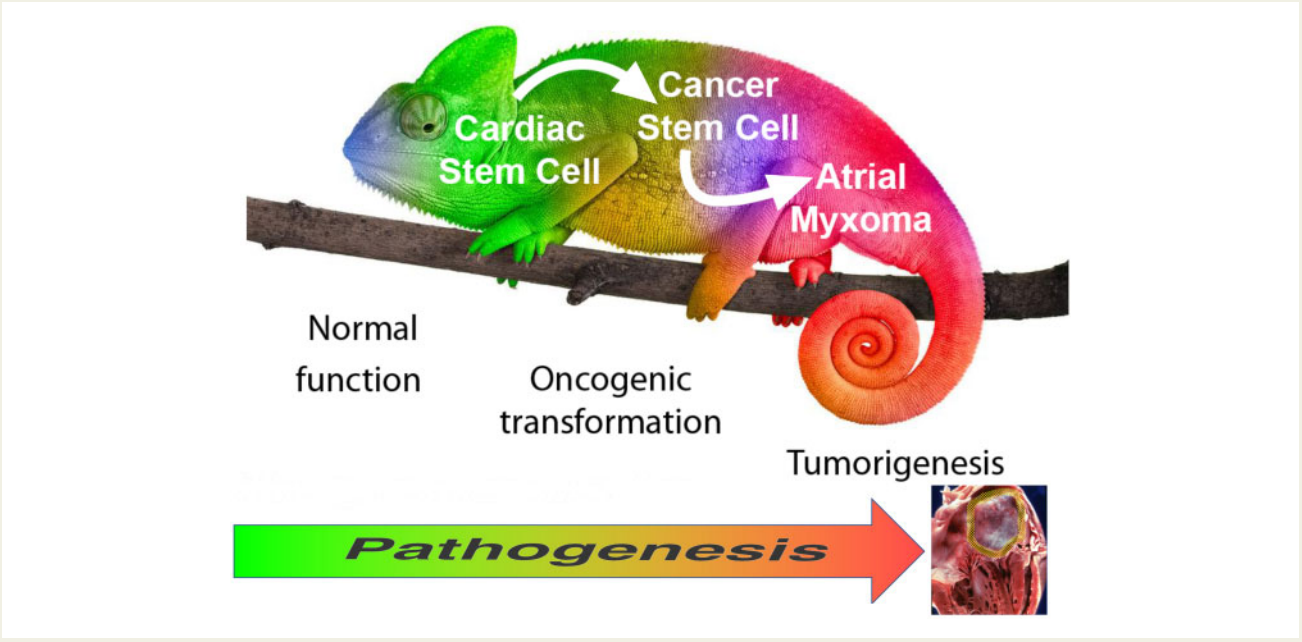


**Take home figure** Cardiac stem cells—chameleons of the heart. The remarkable plasticity of cardiac stem cells is evident from their ability to undergo transformation while retaining many characteristics of their origin. Challenges in characterizing and identifying cardiac stem cells have allowed them to 'hide in plain sight' while undergoing significant changes in biological form and function.

experiments *in vitro*. Two miRNAs highlighted in these experiments are miR-126-3p and miR-335-5p that are responsible for control of the cell cycle and differentiation, with clear implications for how c-kit+ 'CSC-like' myxoma cells could be led astray into tumour promotion by aberrant miRNA reprogramming.

The acid test for cancer promotion is the ability of adoptively transferred cells to form tumours when delivered into a naive recipient host, and this fundamental hallmark of cellular transformation was convincingly demonstrated using the c-kit+ 'CSC-like' myxoma cells compared with cognate normal CSC controls. This elegant *in vivo* demonstration of tumorigenicity required xenogenic transplant of the human cells into an immunocompromised mouse host. The c-kit+ 'CSC-like' myxoma cells derived from three different patient samples were injected into the quadriceps muscle and monitored for 9 months. Clear histological evidence of human myxomas was present in several of the injected mice, with occurrence that titrated with the initial bolus of injected cells. Moreover, tumours were only observed in mice injected with c-kit+ 'CSC-like' myxoma-derived cells and none of the mice receiving normal CSCs developed tumours. With this crucial evidence, the tumour-initiating capabilities of c-kit+ 'CSC-like' myxoma cells and their participation as cancer stem cells giving rise to myxoma tumours are confirmed.

Several important conclusions and implications from the findings of Scalise *et al*. deserve attention and emphasis. (i) These results provide an unassailable demonstration of the cellular origin for atrial myxomas. (ii) Detailed phenotypic and functional characterizations establish a descendant relationship of c-kit+ 'CSC-like' myxoma cells from normal endogenous CSCs. Elucidating what genetic and/or environmental triggers promote conversion from a normal CSC to a cancer stem cell would carry tremendous value for intervening in transformation. (iii) In-depth transcriptome and miRNA profiling provides a molecular mechanism to account for the underlying dysregulation of proliferative and commitment network signalling in c-kit+ 'CSC-like' myxoma cells. (iv) Findings of endogenous CSC biological properties remain consistent with longstanding precedents from the authors[5–7,9] and others,[2,10–12] while also providing insight regarding how the proliferative and commitment potential of CSCs may be influenced via comparative analyses with the closely related c-kit+ 'CSC-like' myxoma cells. (v) Identification of nodal dysregulation in miRNA expression serves as a reference point for future interventional strategies intended to blunt myxoma development and growth. (vi) Heterogeneity of atrial myxoma cellular composition highlights a fundamental area of cancer biology that remains challenging to address when conceptualizing treatments targeted at a spectrum of rapidly adapting and evolving cancer stem cells and their progeny. The normal functional plasticity inherent to CSC biology[13,14] makes this cell population particularly well suited to the role of cancer stem cell. The relative rarity of cardiac tumours such as atrial myxoma is likely to be due to the refractory nature of the heart to proliferative adaptation as a consequence of functional imperatives that do not allow for substantial structural remodelling. Identifying signals regulating induction and arrest of the CSC cell cycle could provide sorely needed insights if such signalling is communicated and shared between various myocardial cell types in service of promoting beneficial repair and remodelling.

Looking toward the future, endogenous c-kit+ CSCs giving rise to c-kit+ cancer stem cells provides compelling new evidence in support of their plasticity and adaptation potential. Therein lies the crux of an ongoing unresolved debate regarding c-kit+ CSC contribution to myocardial homeostasis, response to injury, and repair. Cancer stem cell theory posits that cancer stem cells are closely related to normal stem cells and will share many behaviours and features of

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normal stem cells,[15] consistent with findings presented by Scalise *et al.* Since c-kit+ CSCs possess cancer stem cell potential, then their normal capabilities would include self-renewal and asymmetric division. Thus, c-kit+ CSC progeny presumably contribute to ongoing cellular replacement and renewal that can be leveraged to mediate recovery from pathological damage.[11,12] However, not all c-kit+ CSCs are created equal, but actually comprise a heterogeneous population with profound variability on the single-cell level.[13,14] Furthermore, expression of c-kit alone is insufficient to serve as an arbiter of stem cell status in the heart,[9,10] and the need for selective and specific markers of resident CSCs remains unfulfilled.

CSCs exhibit natural proclivities to blend into their background, adroitly displaying their remarkable chameleon tendencies that have allowed them to hide in plain sight—until now (*Take home figure*). Scalise *et al.* reveal the fundamental contribution of CSCs to atrial myxomas, offering provocative and tantalizing new insights for myocardial biology as well as strategic approaches to translational application. The biological relevance of c-kit+ CSCs should never be dismissed or overlooked, as the health of our hearts depends upon these stealthy myocardial chameleons.

**Conflict of interest:** none declared.

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