DESMOSOMAL CADHERINS BEATING UNDER TENSION

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EXECUTIVE SUMMARY

A seminal event in the history of life on Earth is the transition from single-celled organisms to multicellular life, which required the ability to form strong yet dynamic cell–cell contacts. Among the many classes of molecules that fulfill this role, the cadherin superfamily of cell adhesion proteins is one of the most prominent. Two members of the classical cadherin family, desmoglein (DSG) and desmocollin (DSC), form the robust cell–cell contacts known as the desmosomes, which provide mechanical strength to skin epithelial and cardiac tissues in the face of constant stress, normal stretching, and which protect them from cuts and abrasions. Using the molecular dynamics engine NAMD on Blue Waters, the PI was able to perform simulations on an atomistic model of the desmosome. These simulations provided insight into how this essential cellular junction may function and respond to forces, both in its wild type form and with the addition of disease-causing mutations.

RESEARCH CHALLENGE

Skin epithelial and cardiac tissues are subject to constant stress. The skin epithelium must withstand stretching and shearing forces as well as abrasions, while cardiac tissue must remain viable despite continuous contraction and expansion. To maintain the integrity of these tissues, the cells that comprise them have developed strong and mechanically robust contacts with one another, including the more apical adherens junction and the more basally situated desmosome. The desmosome is found in skin epithelial and cardiac tissues and is formed through interactions of the desmosomal proteins DSG and DSC. However, the stoichiometry and three-dimensional arrangement of these proteins in the junction remain largely unknown.

The architecture of the adherens junction is believed to be a well-ordered array of molecules, forming a zipperlike pattern in which both *trans*-interactions (those formed from opposite cells through the strand-swap mechanism) and *cis*-interactions (those between molecules from the same cell) are present in the mature lattice [1]. The molecular arrangement in three-dimensional space has been more difficult to identify in desmosomes, however. While it is known that both DSG and DSC are required for the formation of the mature desmosome [2,3], the stoichiometric relationship between DSG and DSC and the arrangement of molecules in the junction is a question that remains to be decisively answered. Models from cryo-electron tomographic imaging and those based on the structure of E-cadherin lattices have been suggested, however, and with the deposition of high-resolution crystal structures of DSG and DSC, further information can be extracted from these models [4–7].

Lattices of DSG and DSC, constructed based on the crystallographic lattice of C-cadherin, offer insight into how these proteins may be arranged in the desmosome and how their interactions contribute to desmosome function. In addition, these models can offer molecular explanations for skin epithelial and cardiac diseases. Several missense mutations known to cause cardiomyopathies have been mapped to the extracellular domain of DSG and DSC, suggesting their adhesive or mechanical properties are compromised. However, the molecular mechanism underlying this often fatal disease remains unknown. Simulations on these models offer a unique ability to bridge the gap between genetics and cell biology, and this power is leveraged in these simulations to propose a model of desmosomal dysfunction in arrythmogenic cardiomyopathy.

METHODS & CODES

Models were constructed using high-resolution crystal structures of DSG and DSC [1,7]. Lattices for the desmosome were assembled based on the crystallographic lattices present in the solution of classical cadherins and contain four DSG and four DSC molecules. This was done both in a "polarized" fashion, with all DSG on one side and all DSC on the other. To replicate the physiological conditions located in the extracellular space in which the desmosome is found, models were solvated in explicit water and ions. Models were constructed using VMD (Visual Molecular Dynamics) [8] and simulated using NAMD [9], both of which are developed at the University of Illinois at Urbana–Champaign. In addition to the wild-type systems, two separate systems were built by introducing mutations to the DSG molecules in the lattice, both of which cause the inherited and often fatal disease arrythmogenic cardiomyopathy. All systems consist of approximately 1.8 million atoms.

RESULTS & IMPACT

The wild-type lattice was simulated in equilibrium for 20 nanoseconds (ns), and was subsequently subjected to stretching steered molecular dynamics simulations at 10, 1, and 0.1 nanometer (nm)/ns. Additionally, creep tests were performed in which a constant force was applied to one face of the lattice with the other held fixed, allowing the viscoelastic behavior of the junction to be studied. The resultant elastic response and mechanical properties of the complexes were analyzed, providing a glimpse of how these essential cellular junctions may respond to force *in vivo*. Such modeling and simulation efforts offer unique insights into how these molecules may arrange physiologically and may guide future experimental efforts. Simulations have revealed the formation of *cis*-contacts that persist throughout equilibrium and stretching, suggesting a possible lateral contact that may have relevance in desmosome function. Creep tests revealed differing viscoelastic behavior in these proteins in the lattice as opposed to individual dimers. In particular, the damping coefficient for each individual protomer was increased when it was tested in the lattice compared to the dimer alone, suggesting the lattice acts as a shock absorber to distribute force across the junction. This property would be vital to maintain desmosomal integrity as it is subjected to very rapid and often violent perturbations.

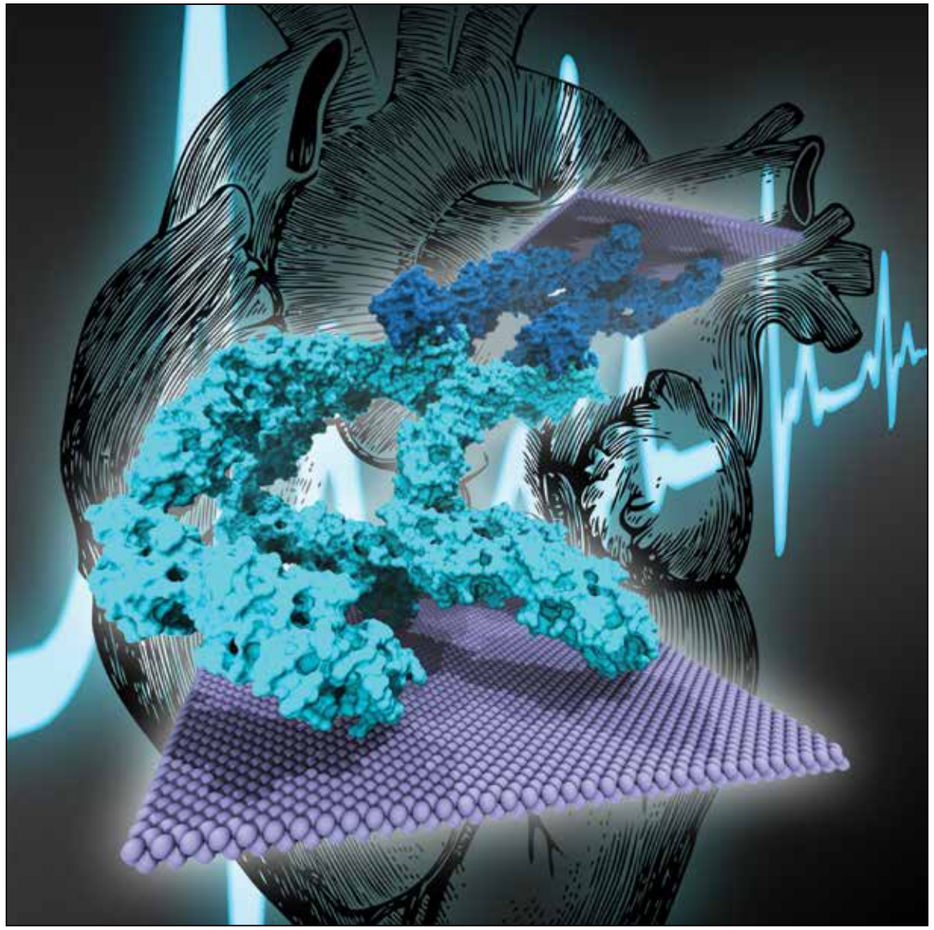

Figure 1: The desmosome represented by the extracellular domains of four molecules of DSG (cyan) and four molecules of DSC (blue; 1.8 million atom system). The system shown is of a polar arrangement of molecules. The membrane planes are shown in pale blue.

WHY BLUE WATERS

Atomistic simulations as large as those performed on these models of the desmosome, which are composed of up to 1.8 million atoms, require significant computational resources. Such simulations need a fast networked and massively parallel system such as Blue Waters. With the slowest stretching speed, at 0.1 nm/ns, the PI was able to sample hundreds of nanoseconds, a timescale that would be unfeasible for such a large system without the capabilities provided by Blue Waters.