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Cancer cell mechanics with altered cytoskeletal behavior and substrate effects: A 3D finite element modeling study

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ABSTRACT

A robust computational model of a cancer cell is presented using finite element modeling. The model accurately captures nuances of the various components of the cellular substructure. The role of degradation of cytoskeleton on overall elastic properties of the cancer cell is reported. The motivation for degraded cancer cellular substructure, the cytoskeleton is the observation that the innate mechanics of cytoskeleton is disrupted by various anti-cancer drugs as therapeutic treatments for the destruction of the cancer tumors. We report a significant influence on the degradation of the cytoskeleton on the mechanics of cancer cell. Further, a simulations based study is reported where we evaluate mechanical properties of the cancer cell attached to a variety of substrates. The loading of the cancer cell is less influenced by nature of the substrate, but low modulus substrates such as osteoblasts and hydrogels indicate a significant change in unloading behavior and also the plastic deformation. Overall, softer substrates such as osteoblasts and other bone cells result in a much altered unloading response as well as significant plastic deformation. These substrates are relevant to metastasis wherein certain type of cancers such as prostate and breast cancer cells migrate to the bone and colonize through mesenchymal to epithelial transition. The modeling study presented here is an important first step in the development of strong predictive methodologies for cancer progression.

1. Introduction

Extensive recent studies in the theoretical, computational and experimental evaluation of the mechanical behavior of cellular systems and their relationship to health and disease have been reported. These present an extraordinary opportunity to develop novel detection capabilities for diseases such as cancer and malaria (Suresh, 2007a; Dao et al., 2005; Suresh, 2006; Yallapu et al., 2015). Qualitative and quantitative or semi-quantitative relationships between structure-mechanics-function and disease (Suresh, 2007a; Suresh, 2007b) are explored showing great promise in understanding the connections between underlying cellular and molecular scale mechanisms and disease progression, providing the possibility of novel diagnostic tools and intervention technologies. Cellular shapes and mechanisms of cellular interactions with extracellular environments influence important cellular processes such as proliferation, differentiation, and apoptosis (Keren et al., 2008; McBeath et al., 2004; Zemel et al., 2010; Huang and Ingber, 2000). In particular, the cytoskeleton plays an important role in the cellular response to external stimuli (Fletcher and Mullins, 2010). Microtubules, intermediate filaments, and actin filaments are important structural components of the cytoskeleton. These components are also intimately engaged in biological processes. Actin filaments form the basis of filopodial protrusions and support the leading edge in cells which are important for cell motility and are associated with cellular shape changes (Fletcher and Mullins, 2010). The role of intermediate filaments is primarily structural. The diameters of these are in between those of microtubules and actin filaments. Structural details of these components are described in the work of Suresh (2007a). The elastic properties of cancer cells in *in vitro* studies indicate a much lower value of elastic modulus than healthy cells (Suresh, 2007b). These experiments done using AFM force curves analysis are in agreement with tests done on biopsies of tissue from cancer patients (Cross et al., 2007).Inherently motivated by their potential rewards in enhancing cancer detection, these studies, primarily through AFM force curves have initiated a new era in the possibilities of novel methods of cancer detection and also the characterization of cancer subtypes (Zeng et al., 2016). The anticancer drug and moiety discoveries are also benefitting from their evaluation of anticancer effects of these moieties on cancer cells (Zhao et al., 2013; Saab et al., 2013) The relationship between metastasis and mechanical compliance remains rather unclear (Bastatas et al., 2012).

Extracellular biochemical signals translate to mechanical forces in

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living tissues and cells are constantly faced with a variety of mechanical loading conditions. The interactions of cells with the extracellular components influences cellular morphology resulting in changes to cellular structure (Ingber and Tensegrity, 2003). Cellular components have been known to contribute to cellular mechanics. In particular, the cytoskeleton plays a key role in cell mechanics, function, differentiation, locomotion, etc. (Suresh, 2007a; Suresh 2007b; Fife et al., 2014; McKayed and Simpson 2013). The cytoskeleton is an important structural member contributing to mechanics of cell. The cytoskeleton is often described as the response unit responsible for altering cellular mechanical behavior in response to events of extracellular nature and undergoes remodeling through a systematic remodeling of molecular characteristics of the cytoskeleton. Hence, cytoskeleton disruption is often targeted by drugs (Jordan and Wilson, 1998; Haga et al., 2000; Rotsch and Radmacher, 2000). The changes to cytoskeleton are often captured as changes to genes through gene expression studies (Janmey, 1998). Two of the cytoskeleton filaments. microtubules and actin filaments, participate in important cellular functions such as cell division, cell signaling, and motility. These are often considered the most important contributors to the elastic response of the cell (Sato et al., 1990; Wang, 1998; Tseng and Wirtz, 2001). Reorganization of these filaments is often the targeting activity of anti-cancer drugs (TerHaar et al., 1997; Jonnalagadda et al., 1997; Kowalski et al., 1997). In light of this fact, several recent studies have attempted to build computational models of human cells incorporating various elements of cellular substructure and its properties (Barreto et al., 2013; Xue et al., 2015). Computational studies using finite element modeling have been used to model a single cell (Barreto et al., 2013; Vaziri and Gopinath, 2008; Mijailovich et al., 2002; Viens and Brodland, 2007). These studies often investigate the role of external mechanical stimuli. Membrane thickness, cytoskeletal density, and extent of loading is varied parametrically. Biological behaviors such as cellular ageing are also investigated through the finite element models (Xue et al., 2015). Many of the finite element models built for the cells are simplistic and make large approximations of cellular substructures and properties (Fallqvist et al., 2016).Recent studies also dissect the specific contribution of some of the individual cytoskeletal components such as actin and vimentin intermediate filaments (Gladilin et al., 2014). Experimental evidence indicates that the quantitative contribution of these elements to elastic behavior of the cell is often cell type dependent (Grady et al., 2016) which further increases the complexity of evaluation of cell mechanics during disease progression.

Thus this work attempts to include the various evaluations of mechanical properties of cancer cellular substructure from literature into the development of a robust finite element model that accurately captures nuances of the various components of the cellular substructure. In addition, the mechanical behavior of cells is often influenced by the substrate and hence an evaluation of mechanics of cancer cell on various substrates is also attempted. In particular, during cancer metastasis (Hanahan and Weinberg, 2011) cells migrate to environments remote to the original location, such as breast cancer cells migrating to the bone. Hence mechanics of cancer cells during this stage of metastasis is influenced by their behavior on osteoblastic cells. Similarly, recent attempts at developing cancer tumor models in vitro using 3D scaffolds (Katti et al., 2016; Adjei and Blanka, 2015; Subia et al., 2015; Zhu et al., 2015) suggest a need for evaluating the mechanical behavior of cancer cells on nanocomposite biomaterials. Nanoindentation experiments are important tools to evaluate cell mechanics. In this work, the results of simulations of nanoindentation on cancer cell using flat tip nanoindentor to evaluate the effect of cytoskeletal degradation and substrate stiffness on the force displacement behavior of the cell are described.

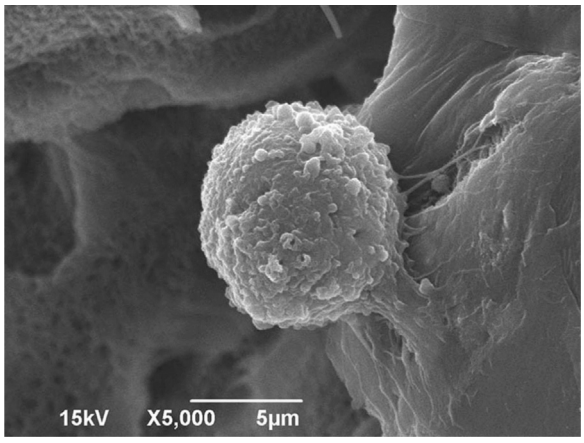

Fig. 1. Scanning electron micrograph of breast cancer cell seeded on the nanoclay-hydroxyapatite-PCL composite scaffold.

2. Materials and methods

2.1. Cancer cell model construction

A three dimensional finite element model of a cell having dimensions similar to that of breast cancer cells observed in the laboratory (Fig. 1) is constructed. The 5 μm diameter cell consists of all major components identified as contributing to the mechanics and cell conformation including the cytoskeleton (actin filaments, intermediate filaments, and microtubules), cytoplasm, cell membrane, and nucleus (Fig. 2). The three dimensional geometry of the cell membrane, cytoplasm and nucleus are created in Solid Works™ software and exported to finite element pre-processing software MSC/Mentat™. The geometry of the cytoskeleton elements is created in the Mentat software. Since the cytoskeleton plays a critical role in defining the shape of the cell, the actin filaments and the intermediate filaments have circular conformations and symmetric to mimic the initial 3D spherical shape of the cell. The microtubules are hollow tube strut like structures having a diameter of 25 nm and wall thickness of 7 nm emerging from the cytoskeleton surrounding the nucleus and extending through the cytoplasm to the cytoplasm-cell membrane interface. The microtubules are connected to the other cytoskeletal subunits that prevent buckling and allow for the microtubules to carry relatively larger compressive forces. The intermediate filaments play a tension bearing role. The intermediate filaments, having a diameter of 10 nm form a ring around the nucleus and extend to the cytoplasm-cell membrane interface and support the plasma membrane. At the cytoplasm-cell membrane interface, the intermediate filaments have a circular conformation to mimic

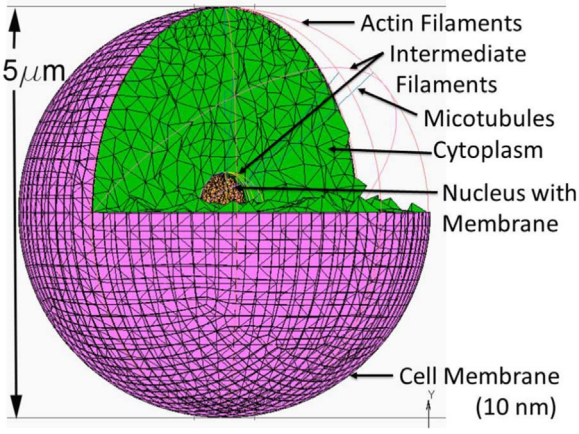

Fig. 2. 3D Finite element model of the 5-micron diameter spherical cancer cell. The cutout shows the various components of the cell.