Identifying Nuclear Membrane Proteins that Facilitate Chromosomal Mechanotransduction

(Technical Paper)

The Technological Momentum of Cosmetic Procedures

(STS Paper)

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On my honor as a University Student, I have neither given nor received unauthorized aid on this assignment as defined by the Honor Guidelines for Thesis-Related Assignments

General Overview

Only a few centuries ago, heroin was prescribed for asthma, morphine was used to quiet crying babies, and bloodletting was a common procedure for a variety of illnesses and injuries (Greenstone, 2010; Walsh, 1923). Today, these 'treatments' seem both outdated and taboo due to increased understanding both within the medical profession and among the general public. This increased knowledge along with the rise in medical technology has led to treatments, procedures, and diagnostics that have changed how society views health and medicine. Both the proposed technical and sociotechnical topics utilize and investigate the rise of such technologies for medical practices.

The proposed technical topic is aimed at elucidating the mechanisms involved in Idiopathic Pulmonary Fibrosis (IPF), an interstitial lung disease characterized by progressive scarring and reduced functionality of lung tissue. While it is known that force-induced, protein signaling pathways lead to scar formation, the specific proteins involved in these pathways are unknown. By finding upstream targets, this project will attempt to delineate specific proteins involved in these fibrotic pathways in order to find upstream targets to target and stop its pathogenesis.

The proposed sociotechnical project investigates the motivating factors behind elective, cosmetic surgery and whether it is a valuable treatment option for patients. With the recent spike in popularity of cosmetic enhancement in the past two decades, a disconnect has been created between its popularity and its measures of value for patients. For example, although cosmetic procedures have been supported to improve self esteem in mentally stable patients, these studies are limited and not standardized (Dreher et al., 2016). Additionally, cosmetic procedures have been shown to worsen Body Dysmorphic Disorder (BDD) symptoms, yet there are only weak diagnostic measures in determining a patient's suitability for cosmetic enhancement. Many times these patients will go under-the-knife unnoticed. To illustrate, "in a survey of 265 members of the American Society for Aesthetic Plastic Surgery, 84% of plastic surgeons reported that they had unknowingly operated on patients with BDD" (Joseph et al., 2016). Through this sociotechnical investigation, I hope to examine the rising popularity of cosmetic procedures, address the ethically-questionable diagnostic and postoperative tests, and analyze sources for improvement in its application.

Summary of Idiopathic Pulmonary Fibrosis and Network Modeling

Introduction

Upon injury, tissues begin the wound healing process. Rather than regaining functionality, many times the tissue is remodeled as a scar leading to tissue fibrosis. In the case of Idiopathic Pulmonary Fibrosis (IPF), the interstitial region between the vasculature and alveoli is progressively damaged and scarred. With the loss of healthy pulmonary tissue, the functionality of the lungs is compromised. IPF is the most severe among a family of interstitial lung diseases. There is only a median 3.8 year survival rate for IPF, highlighting the need for better treatments and therapies (Olson, Gifford, Inase, Pérez, & Suda, 2018).

The current therapeutic and treatment methods fail to effectively treat IPF. While double-lung transplants are a viable treatment option, IPF patients have the highest mortality rates on the waiting list among patients with indications for lung transplantation (George, Arnaoutakis, & Shah, 2011). Additionally, lung transplants have the lowest survival rate, 54.4%

after five years, of all solid organ transplants (George et al., 2011). These issues with lung transplants have given momentum to pharmaceutical treatments for IPF. There are two Food and Drug Administration approved treatments, Nintedanib and Pirfendione. Nintedanib inhibits tyrosine kinases which are proteins involved in expression of profibrotic mediators including vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), and fibroblast growth factor (FGF) (Rivera-Ortega, Hayton, Blaikley, Leonard, & Chaudhuri, 2018). Pirfenidone inhibits the small molecules like VEGF, procollagen I and FGF- blocking the functions of these factors thereby reducing fibrotic activity (Margaritopoulos, Vasarmidi, & Antoniou, 2016).

While both Nintedanib and Pirfenidone slow down the progressive fibrosis, they do not fully stop it. These drugs are important, however, in that they have given momentum to studying profibrotic mediators as targets for fibrotic development. As mentioned earlier, tissue damage has been shown to initiate the wound healing process (Kotton & Morrisey, 2014). The wound healing process includes hemostasis, inflammation, proliferation, and scar remodeling. Due to the low regenerative capacity of pulmonary tissue, fibrotic remodeling results, in which mechanical integrity is maintained at the expense of functionality (Kotton & Morrisey, 2014). As pulmonary tissue becomes more fibrotic, the stress experienced as a result of myofibroblast contraction increases (Hinz, 2012). These stresses are of particular interest in fibrotic development. It is well known that force-induced mechanisms are involved at each step of the wound healing progress, and that these mechanisms lead to fibrotic remodeling.

Taking Advantage of Mechanotransduction

The conversion of force to biochemical signals is referred to as mechanotransduction (Duscher et al., 2014). This signal transduction pathway has recently been implicated as a potential target for IPF treatment. The force initiates a response through extracellular (ECM) proteins like fibrinogen and fibronectin that are bound to integrins. Integrins are transmembrane proteins that connect to these ECM proteins on one end and cytoskeletal actin on the other end. The intracellular binding to cytoskeletal proteins is accomplished through cross-linking proteins. This interwoven network creates the mechanical connection that allows for force transduction. Continuing down the pathway, cytoskeletal proteins have recently been shown to connect to the linker of nucleoskeleton and cytoskeleton (LINC) complex (Belaadi, Millon-Frémillon, Aureille, & Guilluy, 2018; Wang et al., 2018). After this complex, proteins that are still-to-be elucidated reach chromatin and DNA, serving as transcription factors for gene expression of profibrotic activity.

While there has been recent discovery of proteins and complexes like the LINC complex, there are still missing pieces in the protein puzzle of the mechanosignaling pathway (Belaadi et al., 2018; Wang et al., 2018). Utilizing *in situ* and *in vitro* methods, this capstone project aims to both predict and validate proteins that are involved in mechanotransduction and fibrosis.

Creating the Network

I will be working with Allison Horenberg, under the supervision of Dr. Thomas Barker and Dr. Chiuan-Ren Yeh, to predict and validate proteins involved in the mechanosignaling pathway. All experimental and computational work is split jointly between Ms. Horenberg and myself. Approximately 10 hours per week for each of us are dedicated to the in-laboratory experiments discussed below. An overview of the technical project timeline is shown in Figure 1.

Figure 1: Gantt chart of proposed timeline for predicting and elucidating proteins involved in the mechanosignaling pathway.

Cytoscape will first be used to visualize predicted novel proteins. As an open source software, Cytoscape creates biomolecular reaction networks based off of already known protein interactions (Su, Morris, Demchak, & Bader, 2014). This software is especially useful in large-scale networks like the mechanosignaling pathway because there are a plethora of potential interactions between proteins. Although the proteins present after force induction can be found through *in vitro* proteomics data, it is difficult to determine how they are spatiotemporally relevant in the pathway without an analysis of gene expression and direct protein interactions.This high-throughput screening of interactions will allow us to more efficiently and accurately predict proteins involved in the network.

In order to determine the proteins specifically involved in the mechanosignaling pathway, a magnetic precipitation technique is used, in which force is induced by a magnetic force on fibronectin coated beads. This application of force induces the mechanosignaling pathway and formation of protein complexes and connections that will ideally mimic the early response caused by force applied to pulmonary tissue *in vivo.* Following cell lysis, only the proteins involved in the mechanosignaling pathway will remain for analysis. Previously, magnetic precipitation has been used to extract protein from egg whites and for experiments in which the proteins of interest are already known (Cao, Zhang, He, Chen, & Zhang, 2014). The current project novelly applies magnetic precipitation towards studying mechanotransduction, and it is being used to extract unknown proteins. Two controls are used in this experiment- force negative and negative controls. No magnetic force is applied for the negative control and the beads are added with the lysis buffer to account for potential background interactions. The force negative control tests for the presence of proteins that may natural bind in the presence of the magnetic beads. These controls are important to ensure that the candidate proteins were upregulated in the force-induced, mechanosignaling pathway. The proteins isolated from these experiments have been subject to high performance liquid chromatography to initiate the search for the novel proteins through a high-throughput method.

Other *in vitro* methods will be used to identify and validate the identity of such proteins. Western blotting will test for the presence of specific proteins by molecular weight. Using a marker well with respective molecular weights serves as comparison for both the expected molecular weights and expression levels of proteins found in the experimental and control groups. Immunofluorescence imaging will confirm the localization of the proteins of interest by visualizing fluorescent immunoglobulin staining through confocal microscopy. If proteins are localized to their respective cellular compartments, further interaction analysis can be performed.

A proximity ligation assay (PLA) will be used to confirm the interactions of these proteins within a 40 nanometer range (Bagchi, Fredriksson, & Wallén-Mackenzie, 2015). Successful PLA experiments will drive the future steps toward defining the mechano-signaling pathway and confirming direct and indirect interactions between proteins isolated through force mechanotransduction.

By predicting proteins *in situ* via computational methods and validating through *in vitro* studies, the technical project aims to identify novel proteins involved in the mechanosignaling pathway to elucidate the mechanisms involved in fibrotic development. The identified proteins have potential to support the development of an upstream curative therapeutic that could halt the progression of IPF.

Overview of Cosmetic Surgery and its Technological Momentum

Introduction

With over 21 million surgical and minimally invasive procedures in 2015, cosmetic surgery has become a common procedure and a booming business throughout the world; the U.S. alone contributed 15.9 million of these procedures (Higgins & Wysong, 2017). However, cosmetic surgery is a problematic option for people with mental illnesses like Body Dysmorphic Disorder (BDD). Additionally, there is no standardized model to determine whether certain cosmetic surgeries improve quality of life (Dreher et al., 2016). Through looking at the technological momentum of cosmetic procedures, my sociotechnical paper will investigate ethics in cosmetic surgery and potential sources for improvement.

Rise of Plastic Surgery

The French surgeon Desault first coined the term “plastique’ for plastic surgery in 1798, as derived from the Greek word “Plastikos” meaning to mold tissue (Chandra, Agarwal, & Agarwal, 2016). However, plastic surgery, or the reconstruction and repair of tissue, has been documented since 600 BCE- one of the earliest being a Hindu surgeon rebuilding a nose from a piece of the patient’s cheek (Donohoe, 2006). Rhinoplasties were common by 1000 BC due to noses being slashed off from war or severe deformities like syphilis’ characteristic ‘saddle-nose.’ Modern plastic surgery arose after World War II due to the combination of economic prosperity and a large volume of injured veterans (Davis, 1946).

The World War I and II eras were also the introduction of elective, cosmetic surgery. The first cosmetic rhinoplasty was performed in 1923 and the first public facelift in 1931. In Japan, people had similar focuses in cosmetic enhancement post- WWII and prostitutes began directly injecting industrial silicone into their breasts- this proved ultimately unsuccessful and resulted in gangene around the injection site (Peters & Fornasier, 2009). Modern breast augmentation surgery was introduced later in 1961 with the introduction of safer silicone implants (Schiff et al., 2014). If plastic surgery has been around for so long, why has there been this recent jump in people getting cosmetic surgeries like the 231% spike in minimally invasive procedures between 1997 and 2009 (Schiff et al., 2014)?

Stakeholders, Physical Artifacts, and Non-physical Artifacts

The stakeholders involved are doctors, patients, and medical technology developers. In the United States, there is a rigorous medical education required for surgeons. However, it is important to note that there is a difference between a plastic surgeon and cosmetic surgeons. Not all cosmetic surgeons have to be board-certified plastic surgeons. With over 65 percent of cosmetic procedures non-surgical- like Botox, lip injections, and fillers as examples- there are more opportunities and a larger market for non-board certified plastic surgeons such as dermatologists to perform such procedures (Atiyeh, Rubeiz, & Hayek, 2008).

The number of people electing for cosmetic surgery are increasing annually (Schiff et al., 2014). According to a 2017 census study, 92% of people seeking cosmetic surgery were women with 49% between the ages of 40-54 years old. The racial distribution of cosmetic surgery patients was 70.3% caucasian, 10.9% hispanic, 9.1% african american, and 6.3% asian american. The top five surgical cosmetic procedures were breast augmentation, liposuction, rhinoplasty, eyelid surgery, and tummy tuck. The top five nonsurgical cosmetic procedures were Botox, soft tissue fillers, chemical peels, laser hair removal, and microdermabrasion ("2017 Plastic Surgery Statistics Report," 2017).

With over 16.5 billion dollars spent on cosmetic procedures in 2018 alone, the field also provides a market for global cosmetic surgery vendors (Ross, 2019). Computational methods, pharmacologic/biologic drug development, and medical device technologies are all being researched and developed. Computer-aided design allows for detailed planning and imagery for cosmetic surgeries. To illustrate, CT-acquired data can be used to virtually reconstruct the area of interest. With certain software, cosmetic surgeons can preoperatively plan the surgery and show patients the results even before the surgery is performed. Amira, iPlan, and ImageJ are among such software (Markiewicz & Bell, 2011). Pharmaceutical companies also have a large stake in cosmetic surgery with drugs and products making up a billion dollar industry. In 2017 alone, the popular neurotoxin Botulinum toxin (Botox) generated 2.2 billion dollars in revenue (Ramsey, 2019). Lastly, the medical devices used in cosmetic surgery can range from general equipment to those geared for cosmetic enhancement like body-contouring technologies (Markiewicz & Bell, 2011). The physical artifacts pertinent to the stakeholders are the biotechnological and medical products. The non-physical artifacts are societal norms and ideals that have pushed the public towards these elective procedures. In conjunction with one another, these artifacts both resulted in the development and rapid growth of cosmetic surgery.

Technological Momentum in Cosmetic Surgery

This rise in cosmetic surgery will be analyzed under the lens of technological momentum. As Dr. Thomas Hughes notes, technological momentum is located in between the more rigid theories of social constructivism and technological determinism (Hughes, 1969). Where social constructivists argue that human factors govern technology, technological determinists argue that technology governs human factors (M.R. Smith, 1994). In contrast, technological momentum is a combination of both, positing that the origins of innovation are governed by social influences but are eventually overridden as technology gains momentum. To summarize, Hughes writes that as a technological system gains momentum, it becomes, “less shaped by and more the shaper of its environment (Hughes, 1969).”

As mentioned previously, cosmetic surgical procedures have been documented since the 19th century, with records of rhinoplasties, skin flap surgeries, and face lifts (Denkler & Hudson, 2015). Plastic surgery has much more extensive roots, dating back to 600 BCE (Donohoe, 2006). Societal factors dominated early development such as economic prosperity post World War II and the rising media influence from television. In recent years, the technology used in cosmetic surgery has found itself ingrained in society, especially with the advent of noninvasive procedures. Continuing technological innovation and development in cosmetic surgery is progressively shaping both the economic market among cosmetic surgical vendors, as well as beauty standards and normalization of body modifications among the general public.

Critics of technological momentum would be of the earlier-mentioned, more rigid theories: social construction and technological determinism. Proponents of social construction of technology (SCOT) theory might argue that these technologies have developed due to social factors and fit the needs of society. It would be important to look at, for example, how Botox is used across different cultures. Determinists might argue that technology has shaped the social values that have normalized and increased the number of annual cosmetic procedures.

Research Question and Methods

Cosmetic procedures are on the rise. I would like to analyze how sociotechnical factors have led to the momentum in cosmetic procedures and popularity, and whether these procedures are valuable for the public.

I will use the wicked problem framework to research the factors that have led to this normalization of cosmetic procedures in popular culture in the United States and how to better understand its value (Elia & Margherita, 2018). As shown in the Gantt chart, the timeline will be: problem identification and concept, problem analysis and study, problem synthesis and modeling, solution proposal and definition, solution prototyping and testing, solutions implementation, and solution maintenance.

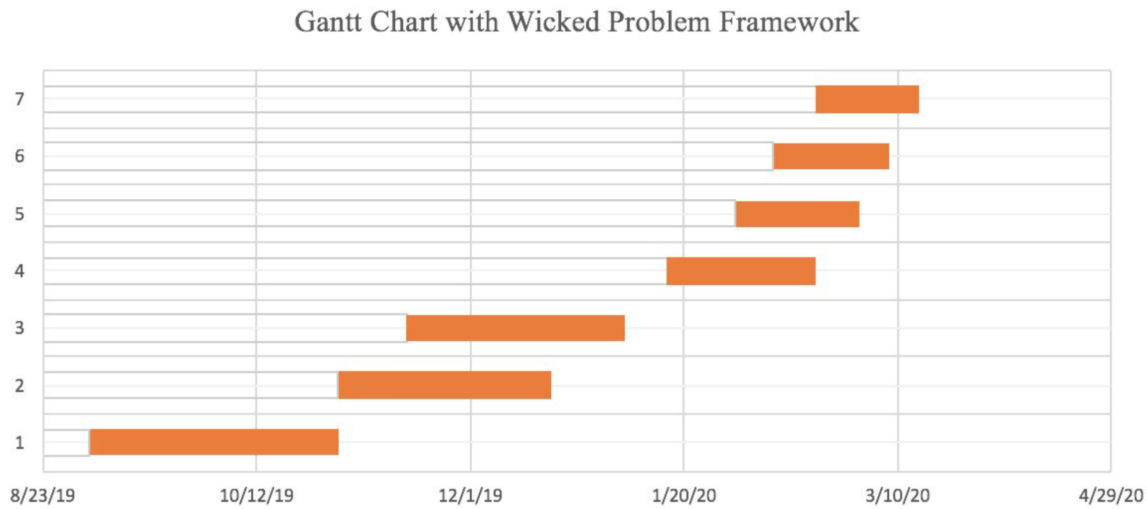

Table 1: Gantt chart for proposed research framework: 1) Problem identification and framework, 2) Problem analysis and study, 3) Problem synthesis and modeling, 4) Solution proposal and definition, 5) Solution prototyping and testing, 6) Solution implementation, 7) Solution maintenance

(1) Problem identification and concept was already completed through developing the Prospectus and framework through which I will analyze the rise in cosmetic procedures. (2) Problem analysis and study will be conducted through elucidating both the identity and hierarchy of all stakeholders and artifacts. (3) Problem synthesis and modeling will involve creating an interaction network between the previously identified stakeholders and artifacts, and how they relate to the momentum of cosmetic procedures. (4) Solution proposal and definition will be completed through idea generation and analysis of ideas through quantitative metrics comparison. (5) Solutions prototyping and testing will be conducted through simulating application of proposed solution. (6) Solution implementation will be conducted through finding

a larger scale application for proposed solution. (7) Solution maintenance will be completed through creating measures for long term success of proposed solution.

Conclusion

With continuously emerging technologies and treatments, the medical field is developing at a rapid rate. Diseases and illnesses once thought incurable are no longer the death sentences they were. My technical project aims to create a similar narrative for Idiopathic Pulmonary Fibrosis by elucidating and targeting novel proteins in the mechanosignaling pathway for therapies to stop fibrotic development. This development also warrants ethical analysis of its application in different fields. Cosmetic surgery is of particular interest due to its growing popularity and use. I aim to analyze its value and ethics in terms of treating patients with body image issues. Both my technical and sociotechnical topics aim to better understand, use, and analyze medicine for the general welfare.

Prospectus Sources

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