Directing cellular differentiation using biophysical cues on multifunctional biomaterial platforms for neural and osteochondral applications

PhD thesis of Asish Kumar Panda

Societal relevance

World health organization (WHO) has recognized multiple degenerative diseases as the leading cause of mortality, globally. The drugs-based clinical treatment of chronic degenerative diseases such as multiple sclerosis, Parkinson's disease, arthritis, muscular dystrophy, etc., has been accomplished with limited success. In this perspective, "stem cell-based regenerative engineering" provides a new treatment option to repair and regenerate the damaged tissue or organ. Stem cells are the unspecialsed cells, which can be transformed into specialized cells, such as nerve/brain cells (neurons, glial cells), bone cells (osteoblasts), cartilage cells (chondrocytes), fat cells (adipocytes), etc. This process is known as "stem cell differentiation." Stem cells have the unique capability to replicate themselves (self-renewal) unless they are provided with specific external factors (i.e., biochemical and biophysical). The external factors such as biochemical agents and biophysical signals can be artificially regulated to direct the differentiation process to obtain functionally specialized cells to regenerate damaged tissues.

Among various biophysical signals, the efficacy of electrical stimulation, substrate stiffness, and conductivity have been demonstrated to direct stem cell differentiation. In the present thesis, cellular differentiation has been regulated using biophysical signals on multifunctional biomaterials. The multifunctional biomaterials provide a 'smart' platform to deliver biophysical cues to direct stem cell differentiation. The electrical stimulation on conducting polymer (polyvinylidene difluoride, PVDF reinforced with multiwall carbon nanotubes) guided the stem cells towards neuron-like and glial-like cells. The strategy to differentiate stem cells towards functional neurons has future implications in stem cell therapy to treat neurodegenerative diseases. Also, the conducting polymeric biomaterials, developed in the

present dissertation, can be further developed into an artificial nerve conduit and nerve patch to repair the damaged nerve tissues.

To address the osteoarthritis-related clinical challenges, bone and cartilage mimicking polymer composites have been developed in this thesis. The electrical stimulation on a bone-mimicking polymeric platform (PVDF reinforced with Barium Titanate) induced the differentiation of stem cells towards bone-like cells. The continuous electrical signal generated higher stresses in stem cells, while the non-continuous alternative electrical signal exhibited differentiation without causing cellular stress. The bone-mimicking PVDF composite has the potential to be used as an acetabular liner in total-hip-joint replacement. The electrical stimulation technology can be translated to induce a faster bone healing with an upregulated ability of osseointegration of synthetic polymer implant.

Furthermore, a novel hybrid bilayer composite with elastically stiff and compliant (soft) polymeric matrices has been fabricated to mimic the osteochondral tissue (interfacial tissue of bone and cartilage). The upregulated activity of bone cells on the elastically stiff layer and maturation of cartilage cells on the elastically compliant layer demonstrates the efficacy of the bilayer construct to repair the osteochondral defect. The modulated osteochondral functionalities on the elastically stiff and compliant substrate also revealed the role of substrate stiffness to direct cellular differentiation.

Taken together, the present thesis conclusively establishes the efficacy of external biophysical signals to direct cellular differentiation using multifunctional biomaterial platforms for neural and osteochondral regeneration