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Prospects of Acellular Organ Scaffolds for Drug Discovery

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Abstract : Drug toxicity often goes undetected until clinical trials, the most expensive and dangerous phase of drug development. Both human cell culture and animal studies have limitations that cannot be overcome by improvements in drug testing protocols. Tissue engineering is an emerging alternative approach to creating models of human malignant tumors for experimental oncology, personalized medicine, and drug discovery studies. This new generation of bioengineered tumors provides an opportunity to control and explore the role of every component of the model system including cell populations, supportive scaffolds, and signaling molecules. An area that could greatly benefit from these models is cancer research. Recent advances in tissue engineering demonstrated that decellularized tissue is an excellent scaffold for tissue engineering. Decellularization of donor organs such as heart, liver, and lung can provide an acellular, naturally occurring three-dimensional biologic scaffold material that can then be seeded with selected cell populations. Preliminary studies in animal models have provided encouraging results for the proof of concept. Decellularized Organs preserve organ microenvironment, which is critical for cancer metastasis. Utilizing 3D tumor models results greater proximity of cell culture morphological characteristics in a model to its in vivo counterpart, allows more accurate simulation of the processes within a functioning tumor and its pathogenesis. 3D models allow study of migration processes and cell proliferation with higher reliability as well. Moreover, cancer cells in a 3D model bear closer resemblance to living conditions in terms of gene expression, cell surface receptor expression, and signaling. 2D cell monolayers do not provide the geometrical and mechanical cues of tissues in vivo and are, therefore, not suitable to accurately predict the responses of living organisms. 3D models can provide several levels of complexity from simple monocultures of cancer cell lines in liquid environment comprised of oxygen and nutrient gradients and cell-cell interaction to more advanced models, which include co-culturing with other cell types, such as endothelial and immune cells. Following this reasoning, spheroids cultivated from one or multiple patient-derived cell lines can be utilized to seed the matrix rather than monolayer cells. This approach furthers the progress towards personalized medicine. As an initial step to create a new ex vivo tissue engineered model of a cancer tumor, optimized protocols have been designed to obtain organ-specific acellular matrices and evaluate their potential as tissue engineered scaffolds for cultures of normal and tumor cells. Decellularized biomatrix was prepared from animals' kidneys, urethra, lungs, heart, and liver by two decellularization methods: perfusion in a bioreactor system and immersion-agitation on an orbital shaker with the use of various detergents (SDS, Triton X-100) in different concentrations and freezing. Acellular scaffolds and tissue engineered constructs have been characterized and compared using morphological methods. Models using decellularized matrix have certain advantages, such as maintaining native extracellular matrix properties and biomimetic microenvironment for cancer cells; compatibility with multiple cell types for cell culture and drug screening; utilization to culture patient-derived cells in vitro to evaluate different anticancer therapeutics for developing personalized medicines.

Keywords : 3D models, decellularization, drug discovery, drug toxicity, scaffolds, spheroids, tissue engineering
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