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Review Article

An overview of ethical issues in Tissue Engineering

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Abstract:

Emerging technologies like regenerative medicine and tissue engineering try to develop promising methods for a variety of incurable diseases by revolutionizing conventional medical approaches in order to achieve the most effective treatment strategies. Current studies in this field are focused on restoration of functionally active organs mimicking the healthy organ structure and function. The regeneration process of a tissue in laboratory composed of the application of biodegradable architecture as scaffolds, desirable cell types, and appropriate growth factors and signaling molecules potentially aimed for totally restoration of an organ or a tissue. According to the main objective of tissue engineering to regenerate a tissue or an organ, which is finally implanted into the human body, ethical considerations have been raised by the advancement of this relatively novel treatment strategy. Therefore, its ethical concerns and challenges should be scrutinized carefully. In this review, we explain the scope of tissue engineering and its clinical applications, along with highlighting ethical challenges using a comprehensive approach.

Key words: Tissue engineering, ethical issues

Introduction

In recent years, technological change has been led to many public and professional debates from the legitimacy of genetic manipulations to environmental pollution, informed consent in medicine, privacy and confidentiality, and also the safety and desirability of tissue engineering. Given the large and increasing number of these moral discussions, propose to consider the ethical challenges of new technologies and to mention a proper framework to analyze them. In the field of technology and ethics discussion, there are two distinct types of interaction, one focuses on the ethics of technical professionals in order to propose specialized code of ethics. The other one focuses on how could the ethics be extend from its traditional focus on human-human interactions to human- technology interactions with regard to both human and non-human environment. This means that

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we need to mention and address the ethical aspect of a new technology, such as tissue engineering, and having a framework to supply an explicit moral tag on it.

The scope of tissue engineering

Tissue engineering has been emerged as an interdisciplinary field that apply the basis of engineering, biomaterial, molecular cell biology, and regenerative medicine to produce a biocompatible and biodegradable tissue with efficient function *in vivo*. The current use of the term tissue engineering was first used in medicine in 1987. The agreed definition was the application of engineering methods and life science to understand the function and structure-function relationship in the tissue and organs [1]. In early years it was based on the cell and tissue. This artificial construct resemble the properties and functions of natural tissue, which aimed to be replaced. To this end, three key elements including scaffolds, cells, and growth factors are essential for generating a new functional tissue. The dynamic cooperation and signaling pathways between cells, growth factors, and extra cellular matrix (ECM), as *in vivo* scaffold with desirable three-dimensional (3D) architecture of specific tissues, determine the features of each tissue. Due to this concept, mimicking the structure of ECM and applying the inductive biomolecules of each specific tissue with the presence of specific cell types, theoretically should lead to generate a bioactive and functional tissue [2-4].

In this field, biomaterials science and engineering scientists try to design highly biocompatible and biodegradable 3D scaffolds with good mechanical strength mimicking microenvironment of tissue to ensure proper remodeling of the given tissue. Engineered 3D scaffolds using naturally derived materials and/or synthetic polymers supply a network for seeding progenitor cells and proper vascularization as critical factor supplying the nutrient and oxygen, as well as removal of waste materials. Therefore, designed scaffolds are responsible for providing a biodegradable framework for cell growth and deposition of newly produced ECM, until the total regeneration of tissue. The final constituent involved in tissue regeneration includes bioactive signaling molecules and a variety of growth factors. These are necessary for differentiation and development induction of seeded cells on the scaffolds providing a well-structured structure for promoting tissue repair and reconstruction [2, 4].

Despite a large body of studies on the tissue engineering constructs production, there are some issues that should be considered in order to generate optimal tissue engineering substitutes. The complex cross talk between cells and the sophisticated interplay between cells, ECM, and signaling molecules, highlight the need for further efforts to establish fully functional engineered tissues.

Some applications of tissue engineering

In this section we focus on the main applications of tissue engineering and among them we explain skin, bone, and cardiac tissue engineered substitutes.

Skin tissue engineering

One of the most common application of tissue engineering is manufacturing of skin tissue engineered substitutes. There is increasing advancement toward developing clinical application of skin constructs. Today, there is a variety of commercially available skin engineered substitutes in order to specific clinical applications for treatment of burn injuries and wound healing. These products are available in market as three major groups including epidermal, dermal, and epidermal/dermal (composite) substitutes. [5].

A large number of biocompatible biomaterials such as cellulose, collagen, chitosan, polycaprolactone (PCL), poly-ethylene-glycol (PEG) and also the combination of synthetic and natural scaffold named composites are commonly used for skin tissue engineering. Composites show suitable biocompatibility, biodegradability, and acceptable biomechanical strength needed for functional skin tissue. Engineered skin bioconstructs are appropriate candidate for investigation of the wound healing efficacy and the effect of drugs [6].

The development of the concept of modern tissue engineering and its applications to dermal treatment and replacements in conditions such as burn and chronic wounds opened new hopes in this scope. However the aim of this technique should be to replace a truly functional skin with permanent skin-like quality with natural regeneration ability.

Bone tissue engineering

Engineered bone tissue present a potential for clinical applications as suitable substitute for the use of conventional bone grafts. The development of 3D scaffolds mimicking the actual *in vivo* microenvironment and composition of the bone is considered as a promising method to clinical practice as safe substitutes with no risk for disease transmission. The presence of porous scaffold supply an efficient network for diffusion nutrient and oxygen with efficient removal of waste material. 3D scaffolds are typically porous, biocompatible and biodegradable materials that serve to provide suitable microenvironments, mechanical support, physical, and biochemical stimuli for optimal cell growth and function. In order to bone defect repair, 3D porous scaffolds such as hydroxyapatite (HA) as bioceramic scaffolds considered as the most applicable technique, due to their similar composition to bone structure with good osteoconductivity, and high compressive strength. It has been reported that successfully bone constructs come from combinational use of HA with other synthetic polymer including chitosan, alginate, gelatin, and polylactic acid [7-9]. Therefore, it seems one step towards functional bone regeneration with aim of bone defect treatments.

One of the valuable and efficient method of bone tissue engineering is to develop vascularized 3D scaffolds in combination with essential signaling molecules and growth factors such as vascular endothelial growth factor (VEGF), and bone morphogenic proteins (BMPs), according to their angiogenesis and osteogenesis induction in order to manufacture a functional bone as an applicable substitute [8].

Cardiac tissue engineering

Cardiac tissue engendering tries to repair or replace damaged heart muscle tissue to provide functionally engineered constructs. Therefore, producing muscle cells from suitable sources including different types of stem cells like embryonic, mesenchymal, and resident cardiac stem cells, and also induced pluripotent stem cells responsible for producing cardiomyocytes, fibroblasts, neural cells, pacemaker cells, smooth muscle cells and endothelial cells as essential components of a functional tissue in heart.

These cells are then seeded on synthetic or biologically derived matrices as scaffolds for providing the microenvironment for manufacturing functional heart tissue possess mechanical properties closely resembles heart tissue structure and functions. Some common scaffolds use in cardiac engineering contain decellularized whole organs, chitosan, polyoctanediol-co-citrate/ poly L-lactic acid-co-poly-caprolactone (POC/PLCL), poly D, L-lactic-co-glycolic acid (PLGA), combination of PLGA with carbon nanofibers [10-12]. Using these engineered tools could be considered as a promising approach toward cardiac tissue regeneration.

In addition to above mentioned examples of tissue engineering application, other efforts were reported to manufacture other tissues or whole-organ tissue engineering. This field continues to evolve and introduce artificial substitutes for various tissues such as cartilage, liver, lung, vascular tissue and pancreas [9, 13]. Tissue engineering is a highly multidisciplinary field that acquire the knowledge of different fields including biomaterial, engineering, molecular cell biology and regenerative medicine. The main objective of tissue engineering is to regenerate damaged tissues by producing novel set of tissue for manufacturing of functionally active constructs in the body which led to improvement in life quality of worldwide population [14].

The ethical framework

Human agency would be characterized from two aspects, each of them is important for ethical evaluation. Justification an action could be based on the externality of it (what the agent does) and its internality (why he/she is doing it) [15, 16] However, the ethical evaluation of actions must also include a judgment of the means by which we wish to attain our goals. Considering the different domain of tissue engineering and its application, the ethical challenges of the field could be classified based on the phase in development of it. Phase development contain; preclinical research, clinical trials, clinical practice, and advanced clinical application [17]. This means that a wide range of perspectives could possibly address the issue, all of them linked to development and application of tissue engineering. Therefore not only there is a need for ethical analysis of tissue engineering research and therapy, but some aspects of issue are beyond the scope of research ethics and clinical practice. Analogically, the ethical assessment of tissue engineering would be complex. Depending on the applied techniques, the source of the subjects and the intended goal of the intervention would be different ethical concerns [18]. If one wants to arrive a full ethical appraisal of tissue engineering and its possible impact, would choose a comprehensive approach.

Ethical appraisal of Tissue Engineering

The comprehensive model of tissue engineering appraisal should contain different anthropological, socioeconomic, clinical, and research ethics. In this part, we will examine the main ethical issues that will raise from these different perspectives by focusing on its application.

The anthropological ethical challenges of the tissue engineering need to clarify some fundamental reference frames that shape our perception of personhood, the human body and its component, and their values. For instance allogeneic tissue engineering involves the use of biological materials (e.g donated human cells), which influences our interpretation of the meaning of human body and our life cycle and also will shape the modalities for the exchange of human materials and the use of cells. The ability to create viable human tissues *in vitro* is a source of concern that can be reinforcing if particular cells are used, for example animal or embryonic human cells. These concerns are closely linked to the concept of personhood [19, 20].

Furthermore using implants and prosthesis, which enable us to replace damaged organs, also poses ethical issues about the meaning of humanhood. The question in this regard, is can the artificial part cause a challenge in patient's identity? This means that may replacing some organs change the human identity and therefore should not be replace? If the answer is "yes" which organs should be under this limitation? [21]

Furthermore, the possibility of *in vitro* creation of human tissue and altering the life cycle by replacement of the damaged and ageing tissues not only has implication for directly involved individual but also for the society as a whole. This means that if tissue engineering become widely available will also have an influence on the constitution of the general population and therefore have socio-economic effect. As the cells and tissues play an important role in this regard, a growing and global tissue economy will form [22] which in turn shape a transition of tissue donation as an altruistic and gift relationship to a commercial one. In this context, the fundamental reference frame is not the dignity and autonomy, but would be the ownership of the body and marketing.

The development of tissue engineering also has some other social and economic consequences [23]. The two major one of them are; how each individual patient can access to tissue engineering and how this innovative methods may impact the health care system.

The access to the tissue engineering interventions can be assessed from biological perspective and socio-economic perspective. Experiences with organ donation, umbilical cord blood banking, and bone marrow registries indicate that there are large disparities between social, religious and ethnic groups with regard to their willingness to participate in donation and therefore in biological access due to shortage of histocompatible cells, tissues and organs [24]. Therefore, if we do not want to reproduce these disparities, we should anticipate the issue.

On the other hand, the development and application of tissue engineering may also influence the health care system in two aspects: the condition for the application and reimbursement of tissue engineering, and its allocation. Consequently, one of the main questions to be answered is how tissue engineering performs for specific therapies in comparison with existing treatments, in terms of benefits and disadvantages? If the supremacy of tissue engineering established, then based on the number of potential patients, the effect on health care budgets may be considerable. Considering the limited resources and increasing cost of treatments, it would be justified to balance the resource allocation based on defensible criteria [25]. The allocation of tissue engineering to specific patient groups needs that allocating criteria to be established in order to guarantee a fair and equitable access. This means that tissue engineering will add another element to the already complicated debate with regard to the just distribution of appropriate medical care.

The development of tissue engineering with regard to the research ethics in some aspects is as same as other innovative fields and indeed discrete characteristics needs specific attentions. In addition to the general ethical principles of research such as social and scientific value, scientific validity, fair subject selection, risk/benefit assessment, informed consent and independent review [26], some additional elements deserve closer attentions. These domains are: the interest of the donor of cells, the importance and place of animal in clinical trials, the conduct of clinical trials, and the post – trial events.

Donating cells for the use in tissue engineering application necessitates an informed consent procedure that need to address the information which should give to donor and also the information that has to be provided by the donor. This may raise a potential conflict of interest between the donor and future recipient. While the recipient has the right to maximal safety based on as much information linked to the donated cells, the donor has a right to privacy and confidentiality. This shows the great importance of an authentic informed consent process.

The different values of the donated cells, their informational value and material value also should be considered. Genetic data and other information related to the donor's life style justify the donor's interests throughout the entire process of tissue engineering. This issue should be considered when obtaining informed consent of donation. The informed consent process would also have to address the material value of the donated cells, financial and etc. However, unlike the informational value, the material values can be separated entirely from the donor by transferring the property of cells in informed consent form.

In preclinical trial phase of tissue engineering, the use of animals and their role need major considerations. Based on the fact that the animal models cannot fully mimic the complexity of the human environment and the limited applicability of animal trials, invite us to mention the possibility to replace, reduce and refine the use of animals and investigate other possibilities in preclinical research [27]. There is also an important issue in transition from animal research to human investigations that is the transitional distance, [28] which can show the questions that should be answered to affirm the steps for moving from animal models to first in human trials. One of the most important one is "Has enough preclinical data collected from animal models before the researchers conduct further studies in humans? "[29]

The criteria to move from pre-clinical phase to clinical trial and then to therapeutic use are generally well established; however the application of these criteria to tissue engineering is blurred as a result of the continuity that is inherent to tissue engineering. The dynamic interaction of implanted tissue or cell to the body may continue beyond the duration of the trial. Thus, the adverse events or positive and negative secondary outcomes will not necessarily detect. In order to minimize the risk for research participants, the end-point of the trial and post-trial follow-up should be carefully worked out. It should be mentioned that the trials themselves will not comprehensively project the future safety, efficacy and quality of the tissue engineering based therapies. It might be ethically justifiable to think of tissue engineering therapies as "therapies under control" or "technology under investigation" [30].

Beside these additional considerations, the conduct of the clinical trial per se has its challenges such as considering the aim of trial, the risk/benefit balance, the safety of participants, their autonomy and the generalizability of the results. Each of these challenges will have new aspects with regard to tissue engineering [28, 31].

Finally at the post- trial phase and in order to evaluate the long term performance of tissue engineered therapies and to monitor the adverse events, the establishment of a registry could be an ethical necessity. However, the quality of such a registry is largely depend on the amount and kind of the registered data with respect to donors and patient's privacy [32].

Final conclusion

Tissue engineering like any other scientific activity should be valued in proper ethical frameworks. By examining the main ethical challenges of tissue engineering, it is clear that there would be a distinction between ethical issues in the research and development practice itself and ethical issues regarding the implications of developed techniques and biomedical engineering ethics devices for medical practice [33].

Within research and development, there are ethical issues regarding human and animal experimentation and the use of biomaterials, as well as general issues of research ethics. Next to common issues inherent to research practice, tissue engineers have a responsibility to ensure that technologies and techniques which they used, are designed in a manner consistent with and supportive of ethical principles for medical practice as well as the special challenges of the field. These concerns differ from anthropological ones to socio-economic ones.

Confronting these issues need a regulatory system. An established regulatory system in addition to safety and efficacy standards and also policies for fair and just the use of new therapies may guarantee the proper progress of the field. All these require a regulatory structure including local committees, institutional, and national reviewing boards.

Constitutions that play a great role in policy writing, addressing the issues involving the process of tissue engineering, applying in clinical level for therapeutic purposes, in order to protect humanistic values of medicine and science.

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