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Research review paper

Cell-interactive 3D-scaffold; advances and applications

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ABSTRACT

Culturing cells *ex vivo* that differentiate and maintain *in vivo* characteristics holds great promise not only for the pragmatic revelations of cell function but also in tissue engineering and regenerative medicine. Lack of *de-novo* extra-cellular matrix (ECM) milieu, which plays a crucial role in generating physical and chemical signals besides providing structural support is attributed to be the major hurdle in normal cell growth *in vitro*. Hence, to comprehend the outcome of cell biology research in clinical context, it is important that the cell culture based models should incorporate both the three dimensional (3D) organization and multi cellular complexity of an organ while allowing experimental interventions in a desirable manner. This calls for the development of ECM-mimicking 3D scaffold, which can be integrated with relevant ECM cues to offer cell interactive versatility for different medical and non-medical applications. Present review discusses the status of ECM mimicking for 3D cell culture and its diverse implications.

Contents

"Snatched from a life of obscurity and installed in contemporary glass and plastic palaces, cells are in danger of becoming Pygmalion's protégés. Housed in more traditional residences constructed of water and collagen instead of plastic or glass, do cells lead primitive, less cultured lives?" Tom Elsdale and Jonathan Bard (J. Cell. Biol. 54, 1972, 626–637).

1. Introduction

Conventional cell culture provides unnatural conditions with only 2D space for growing cells that leads to the development of physiologically compromised cells (Schmeichel and Bissell, 2003). The said unnatural conditions created in the laboratory are exemplified by flat and rigid plastic/glass surface and culture medium that is supplemented with fetal wound fluid (fetal bovine serum or FBS). Tissue/cells in the body on the contrary, grow in three dimensions surrounded by extra-cellular matrix (ECM) and other cells bathed in

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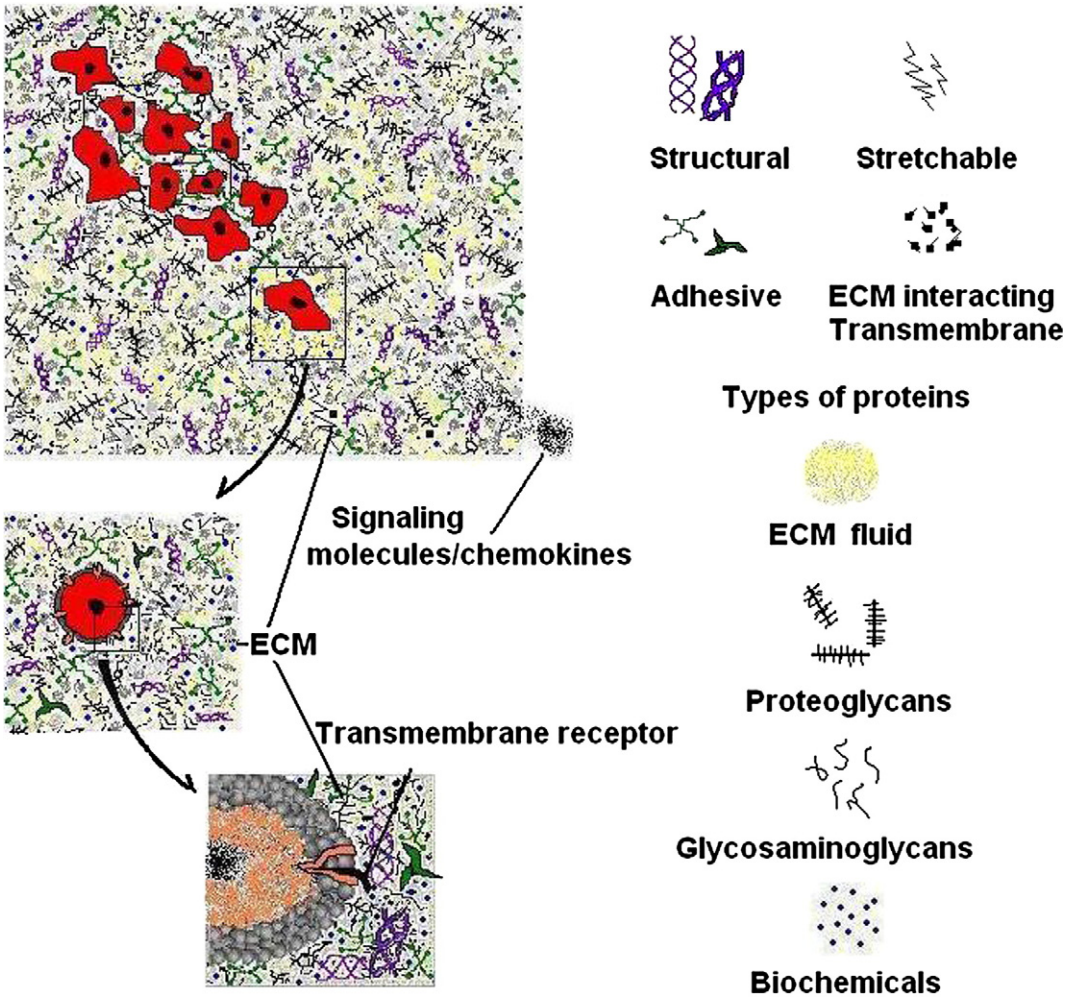

Fig. 1. Cells surrounded by extra cellular matrix (a schematic view).

blood plasma or tissue fluid. Blood serum unlike plasma consists of several factors that trigger fibroblast multiplication and divert tissue homeostasis from normal differentiated functions to a typical wound healing response. Consequently fibroblast subpopulation multiplies quickly to outnumber other specialized functional population like epithelial cells leading to impairment of specialized tissue functions. Though in conventional cell culture various growth factors and other important constituents are supplied in media, yet in absence of natural matrix like environment where many such proteins are present in bound state, the normal growth and differentiation is mislaid. In natural ambience ECM provides physicochemical stimuli and makes available water and ions to the tissue, which exists as an aggregate of different cell-types. ECM also plays an important role in regulating the morphology, development, migration and metabolic functions of the cells besides providing anchorage and mechanical scaffolding for tissue renewal. Constituted by a highly vibrant but complicated network of secreted macromolecules, ECM imparts resilience for the stresses of movement and gravity and maintains the structural integrity of the body tissues. Through cell surface receptors ECM is dynamically integrated with the intracellular signaling molecules and pathways that regulate gene expression and ascertain the cell phenotype [Fig. 1]. Since each tissue differs both morphologically and physiologically, their ECMs, which are the outcome of their continuous, integrated, bi-directional interaction also differ considerably. Fibrous proteins like collagen and fibrin, intra-fibrillar proteoglycans and other adhesive proteins like fibronectin and laminin are some of the major ECM components. Recent findings further endorse the direct influence of ECM microenvironment on cell lineage specification. The phenotype of originated cell is observed to be extremely sensitive to the tissue level elasticity and the soft matrices that mimic the brain are found to be neurogenic whereas stiffer matrices that mimic muscle are myogenic and comparatively rigid matrices that mimic collagenous bone prove to be osteogenic (Engler et al., 2006). Culturing cells that differentiate and maintain *in vivo* cell behavior is thus, not possible by conventional flat surface methods and require an ECM mimicking 3D environment. Existing knowledge however permits only partial and qualitative duplication of ECM which could be by 1) adding speculative amounts of known ECM components to culture media; 2) using media supplements known to stimulate cells for secreting ECM; 3) growing cells on pre-culture beds; 4) using tissue explants e.g. matrigel and 5) creating biomaterial tailored with ECM biomaterial. The first two approaches do not provide the semi-rigid structural availability of ECM inducers as found *in vivo* whereas the third and fourth deal with undefined ECM components. It is the final approach where a biomaterial can be integrated with appropriately chosen, well-defined ECM components.

Here we discuss the adaptation of vital ECM components and ECM mimicking biomaterial as scaffold for 3D cell culture and its anticipated consequence on fundamental and applied research areas.

2. Hydrogels as cell interactive 3D scaffold/ECM substitute

Importance of 3D microenvironment and its use in the development of physiologically relevant tissue models was acknowledged and