Available online at www.sciencedirect.com

ScienceDirect

Physics of Life Reviews 17 (2016) 61–85

PHYSICS of LIFE reviews

www.elsevier.com/locate/plrev

Review

Towards a unified approach in the modeling of fibrosis: A review with research perspectives

Martine Ben Amar [a,b], Carlo Bianca [a,b,*]

[a] *Laboratoire de Physique Statistique, Ecole Normale Supérieure, PSL Research University, Université Paris Diderot Sorbonne Paris-Cité, Sorbonne Universités UPMC Univ Paris 06, CNRS, 24 rue Lhomond, 75005 Paris, France*

[b] *Institut Universitaire de Cancérologie, Faculté de médecine, Université Pierre et Marie Curie-Paris 6, 91 Bd de l'Hôpital, 75013 Paris, France*

Received 29 March 2016; accepted 29 March 2016

Available online 6 April 2016

Communicated by J. Fontanari

Abstract

Pathological fibrosis is the result of a failure in the wound healing process. The comprehension and the related modeling of the different mechanisms that trigger fibrosis are a challenge of many researchers that work in the field of medicine and biology. The modern scientific analysis of a phenomenon generally consists of three major approaches: theoretical, experimental, and computational. Different theoretical tools coming from mathematics and physics have been proposed for the modeling of the physiological and pathological fibrosis. However a complete framework is missing and the development of a general theory is required. This review aims at finding a unified approach in the modeling of fibrosis diseases that takes into account the different phenomena occurring at each level: molecular, cellular and tissue. Specifically by means of a critical analysis of the different models that have been proposed in the mathematical, computational and physical biology, from molecular to tissue scales, a multiscale approach is proposed, an approach that has been strongly recommended by top level biologists in the past decades.

Keywords: Complexity; Wound healing; Therapeutics; Multiscale; ODE and PDE; Kinetic theory; Agents

1. Introduction and motivations of the review

The modeling of complex phenomena in physics and life sciences systems is a hot theme of the last and this century. The complex phenomena emerging in physical/biological systems is the consequence of nonlinear interactions occurring among the elementary elements that constitute the system, e.g. molecules, cells, tissues, animals, humans, see the book [1]. The comprehension and the related modeling of the different mechanisms that have as result a physical/biological phenomenon is a challenge of many researchers that work in the field of the applied sciences. The great interest comes from the fact that emerging phenomena in complex system are not obvious from the analysis of the

* Corresponding author.
E-mail addresses: benamar@lps.ens.fr (M. Ben Amar), bianca@lps.ens.fr (C. Bianca).

http://dx.doi.org/10.1016/j.plrev.2016.03.005
1571-0645/

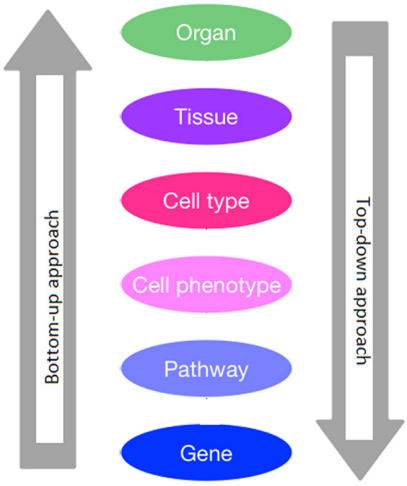

Fig. 1. The top-down and bottom-up approaches for a biological system.

properties of the individual parts, indeed these phenomena are consequence of nonlinear collective interactions, see, among others, [2–4].

The modern scientific analysis of a phenomenon generally consists of three major approaches: theoretical, experimental, and computational. In particular, various biological systems have been considered by researchers that work in the field of the mathematical, computational and physical biology, e.g. tumor growth under the immune system surveillance [5–7], soft tissues growth [8–14], and recently fibroproliferative disorders such as the pathological fibrosis, see the review paper [15] and references cited therein.

Recently the different mechanisms that trigger physiological and pathological fibrosis have gained much attention. Fibrosis is the result of a failure in the wound healing process characterized by the formation of excess fibrous connective tissue in an organ or tissue. Different organs and tissues can be affected by fibrosis, e.g. lungs (idiopathic pulmonary fibrosis, cystic fibrosis), liver (cirrhosis), heart (post-myocardial infarction, endomyocardial fibrosis/hypereosinophilic syndrome), kidney (renal fibrosis), brain, skin (scleroderma, nephrogenic systemic fibrosis), joints (arthrofibrosis), bone marrow (myelofibrosis). In particular the organs, in the fibrotic process, become stiff and cannot perform correctly functions essential to life and health, leading to organ failure and death. The fibrotic progression is characterized by the development of fibro-proliferative wound healing. This type of abnormal healing can be regarded as pathologically excessive responses to wounding in terms of cells profiles and their inflammatory growth factor mediators. The mechanisms which are responsible of fibrosis and its disease comprise many phenomena occurring at different scales, among others, atomic, molecular (nucleotides, DNA helix), organelle (chromatine, cell nucleous), cellular and tissue scales. In particular molecular scale is devoted to the dynamics of genes, the cellular scale deals with the cell-cell interactions (epithelial and endothelial cells, platelets, fibroblasts/myofibroblasts, inflammatory cells such as macrophages, neutrophils), and the tissue scale is concerned with the dynamics of tissue including invasion, angiogenesis, morphology and shape.

The major causes of fibrosis include tissue damage (postoperative, burns, liver cirrhosis), infections and autoimmune diseases, foreign material (silicone implants, e.g., silicone mammary implants, gastric banding), spontaneous (Dupuytren's contracture, Peyronie's disease), tumors (tumor stroma, fibroma). Biological insight into the pathogenesis, progression and possible regression of fibrosis is lacking and many issues are still open. Different theoretical tools coming from computational, mathematical and physical biology have been proposed for the modeling of physiological and pathological fibrosis. However a complete framework that takes into account the different mechanisms occurring at different scales is missing and the development of a general theoretical framework is required. Specifically the fibrosis-modeling methods present in the literature can be grouped into two main approaches (see Fig. 1):

– Top-down approach. The system is broken down to gain insight into its compositional subsystems. In this approach an overview of the system is formulated, specifying but not detailing any first-level subsystems. Each subsystem is then refined in yet greater detail, sometimes in many additional subsystem levels, until the entire