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Towards patient stratification and treatment in the autoimmune disease lupus erythematosus using a systems pharmacology approach

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ABSTRACT

Drug development in Systemic Lupus Erythematosus (SLE) has been hindered by poor translation from successful preclinical experiments to clinical efficacy. This lack of success has been attributed to the high heterogeneity of SLE patients and to the lack of understanding of disease physiopathology. Modelling approaches could be useful for supporting the identification of targets, biomarkers and patient subpopulations with differential response to drugs. However, the use of traditional quantitative models based on differential equations is not justifiable in a sparse data situation. Boolean networks models are less demanding on the required data to be implemented and can provide insights into the dynamics of biological networks. This methodology allows the integration of all the available knowledge into a single framework to evaluate the behavior of the system under different conditions and test hypotheses about unknown aspects of the disease. In this proof-of-concept study, we explored the potential of a systems pharmacology model based on Boolean networks to support drug development in SLE. We focused the analysis on the antigen presentation by the antigen presenting cells (APC) to the T-cells to evaluate the scope of this methodology in a medium size network before full implementation of the whole SLE pathway. The heterogeneity of SLE patients was replicated using this methodology simulating subjects with distinct pathway alterations. A perturbation analysis of the network coupled with clustering analysis showed potential to identify drug targets, optimal combinatorial regimens and subpopulations of responders and non-responders to drug treatment. We propose this approach as a first step towards the development of more quantitative platforms to address the current challenges in drug development for complex diseases.

1. Introduction

Systemic Lupus Erythematosus (SLE) is a chronic multiorgan relapsing-remitting autoimmune disease which is characterized by the production of autoantibodies that can affect the majority of organs (Mohan and Putterman, 2015). These autoantigens are suspected to be products of defective apoptosis, necrosis or NETosis (formation of Neutrophil Extracellular Traps [NETs]) of the body cells (Podolska et al., 2015) and can be classified according their molecular structure (Rahman and Isenberg, 2008) (Table 1). The incidence of SLE is about 1 to 10 per 100,000 person-years and the prevalence 20 to 70 per 100,000 people. SLE cases have been reported in all continents but the incidence and prevalence in people of African or Asian background are approximately 2 to 3 times higher than in white populations, being more frequent among women than men (90% or more of patients are women). The 5-year survival rate among SLE patients has shifted from 50% in 1950 to 90% after the 1970s, but the 15 to 20 years survival rate is still approximately 80% (Pons-Estel et al., 2010). Among the factors that have been associated with the development of SLE are genetic, epigenetic, environmental, hormonal, and immunoregulatory among others (Tsokos, 2011), but the underlying mechanisms of the disease remain largely unknown.

SLE is a complex disease involving different signaling pathways and is characterized by a high clinical heterogeneity among patients. Currently, a patient has to exhibit at least four out of eleven symptoms to be diagnosed with SLE. Symptoms include malar rash, photosensitivity, kidney disorder, blood disorder, abnormal antinuclear antibodies among others (Tsokos, 2011). This gives an idea about the magnitude of different possible combinations of clinical manifestations in SLE. Additionally, more than 40 genes have been reported as predisposing to SLE. It is expected that SLE patients with different genetic backgrounds

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Table 1
Type of autoantigens in SLE and definition.

Type	Autoantigen	Definition
DNA antigens	dsDNA	Double-stranded DNA
	Nucleosomes	Fundamental subunit of chromatin
Non-DNA antigens	Ro	Ribonucleoprotein complex
	La	RNA-binding protein
	Sm	Nuclear particles consisting of several different polypeptides
	NMDA receptor	*N*-methyl-D-aspartate receptor
	Phospholipids	A lipid with one or more phosphate groups attached to it
	α-Actinin	Cytoskeletal actin-binding protein and a member of the spectrin superfamily
	C1q	Subunit of the *C*1 complement component

or different autoantigens will show different molecular alterations in their immune response. It seems reasonable to think that the pharmacological treatment of SLE should be personalized and probably should target more than one signaling pathway. Yet, current approaches follow the standard paradigm testing single drug hitting single specific targets while clinical trials have also been characterized by the lack of patient stratification prior to the studies.

The standard treatment for SLE consists of nonsteroidal anti-inflammatory drugs (NSAIDs), antimalarials, glucocorticoids, cytotoxic agents and immunosuppressive agents (Bernknopf et al., 2011; Merrill, 2012; Tsokos, 2011). To date, only one monoclonal antibody (belimumab) has been approved by the FDA for SLE, which is used for mild to moderate SLE disease, in patients who do not present active lupus nephritis or central nervous system disease (Belmont, 2013). SLE treatment attempts to prevent and treat flares and reduce organ damage or other associated problems. SLE therapy depends on the symptoms and the tissue damage experienced by the patient. Several laboratories have investigated different compounds targeting different components of the immune response; several are still in development phases while others have not shown therapeutic success. Most of these research compounds have exhibited promising results in the preclinical development but this has not been translated into effective drugs for the treatment of SLE. Currently, treatment of SLE is far from optimal and requires new paradigms in drug development, speeding selection and validation of active compounds and most promising drug combinations.

At the moment, there are no computational tools capable of evaluating the effect of a drug in a "SLE like" system; target validation/invalidation have been made through costly empirical experiments and modelling has been limited to description of drug Pharmacokinetics (PK) and modest attempts to link SLE severity scores to drug exposure (Budu-Grajdeanu et al., 2010; Chen et al., 2015). In the last years, systems pharmacology has emerged as a new translational tool to study complex biological systems (Bai et al., 2014; Geerts et al., 2015; Goryanin and Goryachev, 2011; Lu et al., 2014; Palmér et al., 2014; van der Graaf and Benson, 2011; Wang et al., 2015; Younesi et al., 2015), with the aim of integrating information from different sources into a system level model that can be used for different purposes during the whole drug development pipeline, including target identification and validation/invalidation, patient stratification, biomarker identification, dosing selection, identification of sources of variability and prediction of toxicity and adverse effects (Ait-Oudhia et al., 2013; Bai et al., 2014; Benson et al., 2013; Birtwistle et al., 2013; Chudasama et al., 2015; Geerts et al., 2013; Gulati et al., 2014; Klinke, 2015; Wajima et al., 2009). Due to the heterogeneity in SLE patients and the complexity of the disease, a systems pharmacology approach can support the drug development chain by identifying different patient subpopulations according to their molecular alterations and thus, predict the variability in the progression of the disease, allowing the design of individualized drug therapies with high likelihood of success.

In this work we propose a systems pharmacology model for the study of SLE pathogenesis and therapeutics that can be expanded or

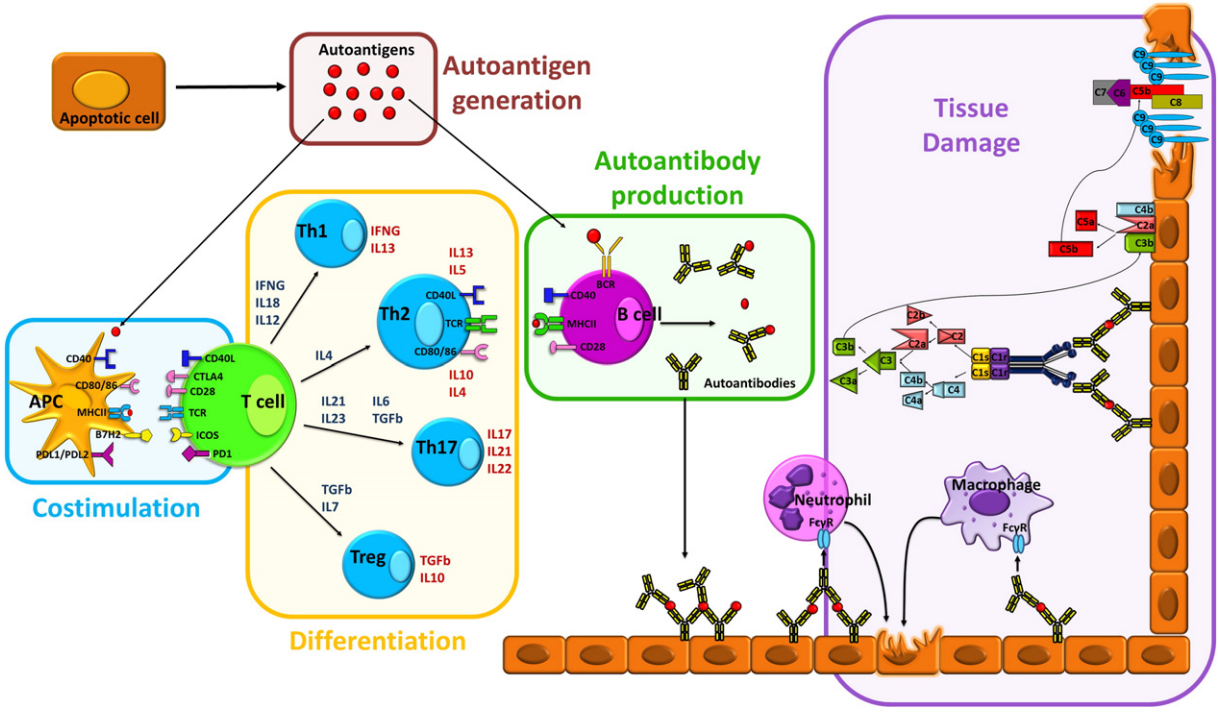

Fig. 1. Assumed physiopathology of SLE. For an unknown reason the body recognizes normal endogenous molecules as antigens, triggering an immune response. These autoantigens are recognized by the receptor of the antigen presenting cell (CD4+ type), processed and then expressed by the MHCII molecule which presents the autoantigen to the Th0 cell. APC molecules interact with their respective ligands on Th0 cell which triggers intracellular signals that will result in activation of Th0 cell. Once activated, depending on the cytokine environment and costimulation signals, it can differentiate into Th1, Th2, Th17, Treg or Tfh. Th2 cells interact with B cells which after maturation produce autoantibodies against these autoantigens. Subsequently, the immune complement and several macrophages and neutrophils recognize these autoantibodies attached to the autoantigens leading to a coordinated attack against tissues expressing those autoantigens causing tissue injury and damage.