Biochemical Pharmacology 92 (2014) 184–191

Contents lists available at ScienceDirect

Biochemical Pharmacology

journal homepage: www.elsevier.com/locate/biochempharm

Commentary

Therapeutic targeting of the inflammome

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ARTICLE INFO

Article history:
Received 16 July 2014
Accepted 27 August 2014
Available online 6 September 2014

Keywords:
Inflammation
Anti-inflammatory agents

ABSTRACT

Inflammatory responses can vary depending on a myriad of factors including: (1) the initiating stimulus or trigger, (2) the cell types involved in the response, and (3) the specific effector cytokine–chemokine milieus produced. The compilation of these and other factors in a given mechanistic context is sometimes referred to as the "inflammome". Humans and other higher-order mammals have evolved (over time) several discrete inflammomes to counter the effects of pathogens. However, when these inflammomes are induced inappropriately, they drive the development of chronic inflammatory diseases. The vast majority of biological anti-inflammatory treatments currently being developed are focused on the *post hoc* inhibition of downstream effectors by anti-cytokine monoclonal antibodies and receptor antagonists. This prevailing "end-point treatment" has even directed a new disease classification paradigm, namely a cytokine-based disease classification, as opposed to a traditional diagnosis based on a particular tissue or organ system dysfunction. Although this approach has a number of advantages, it omits the processes that led to the generation of the inflammatory effectors in the first place. In this review, we will expand the cytokine-based disease taxonomy into an inflammome-based taxonomy that includes interventions that subvert *a priori* cytokine development and can complement *post hoc* inhibition.

1. Introduction

Inflammation, to use a timeworn axiom, is a double-edged sword. Under normal physiological circumstances, it operates as an integral component of a defense system that the human body utilizes to ward off the incursion of foreign pathogens [1]. However, if inappropriately directed or poorly regulated, inflammation can lead to significant morbidity and mortality [2]. It is truly a unique circumstance within physiology that one of the greatest assets for developing Darwinian fitness can abruptly become one of the most significant contributors to tissue dysfunction, destruction, and disease.

Although the mechanisms by which inflammation develops have become more complex and efficient over evolutionary time, there are only but a handful of molecular signaling pathways and professional immune cell types that drive inflammatory processes [3]. Nevertheless, the term inflammation is used very broadly, particularly as it is portrayed to the general public. This oversimplification has contributed to the stagnation in therapeutic options for patients suffering from "inflammatory" diseases, until the advent of cytokine-specific biologicals in the 1990s [4,5]. In reality, inflammation can vary depending on a myriad of factors including: (1) the initiating stimulus or trigger (e.g. pathogenic infection, cell injury, molecular mimicry, or inappropriate responses to a self-antigen), (2) the cell types, receptors, and signaling pathways involved, (3) the generation of specific effector cytokine and chemokine milieus, (4) temporality of the response (e.g. acute vs. chronic, or early vs. late phase), and (5) the type of pathology that results (e.g. systemic vs. local, tissue destruction vs. tissue repair). The compilation of these factors in a given mechanistic context is the "inflammome" [6].

Humans and other higher-order mammals have, over evolutionary time, developed several discrete inflammomes designed to counter specific types of pathogens (Fig. 1). However, when these inflammomes are induced inappropriately, they drive the development of distinctive disease-causing effector molecules that have become the basis of many new interventional therapies [7]. The vast majority of biological anti-inflammatory treatments currently being developed are focused on the *post hoc*, direct inhibition of downstream effectors by anti-cytokine monoclonal antibodies or

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http://dx.doi.org/10.1016/j.bcp.2014.08.027
0006-2952/

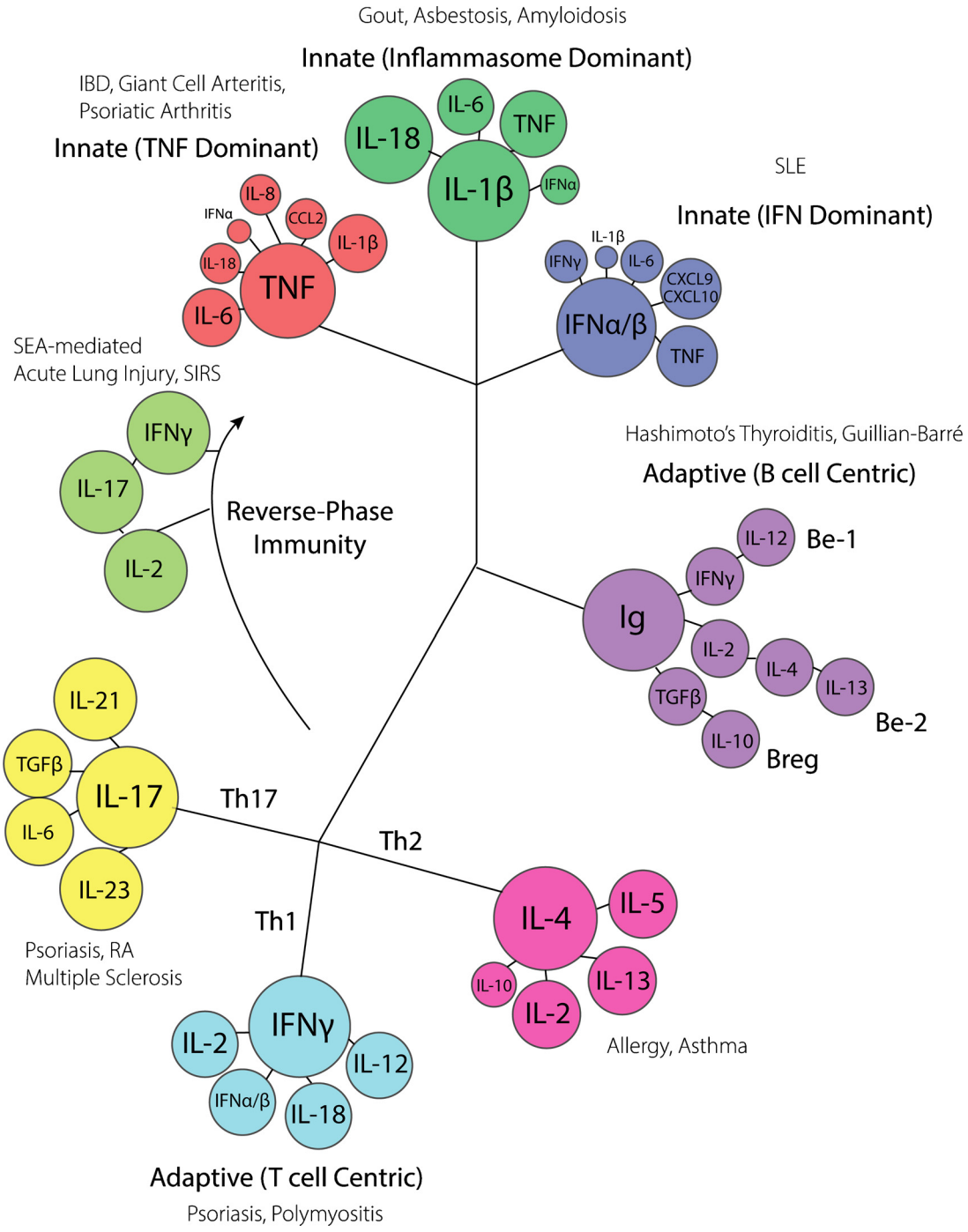

Fig. 1. An inflammome-based disease taxonomy. A schematic representation of the cytokine networks established by the host's major inflammomes; the size of each circle pictorially represents the relative abundance of a given cytokine within its respective inflammome. Human diseases associated with each inflammome are listed in non-bold script.

receptor antagonists. This prevailing predilection for "end-point treatment" has even directed a new approach to disease classification, namely a cytokine-based disease taxonomy [8], as opposed to a traditional diagnosis based on a particular tissue or organ system dysfunction. Although this approach can be beneficial for categorizing inflammatory diseases, it omits the underlying processes that led to the generation of these effectors in the first place. In this review, we will focus on delineating not only the pathogenic sequelae of inflammation-driving effector cytokines, but also the distinct inflammomes that lead to their synthesis. Through this, we discuss the benefits of expanding the present cytokine-based disease taxonomy into an inflammome-based disease taxonomy, while directing the focus of future therapeutic development toward those interventions that subvert *a priori* cytokine development, in addition to their *post hoc* inhibition.

2. The major inflammomes

2.1. Innate (TNF dominant)

The innate immune response is composed of different cell types that respond to diverse endogenous or exogenous signals and mediate distinct downstream effects within minutes to hours of