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Under control: The innate immunity of fish from the inhibitors' perspective

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ABSTRACT

The innate immune response involves a concerted network of induced gene products, preformed immune effectors, biochemical signalling cascades and specialised cells. However, the multifaceted activation of these defensive measures can derail or overshoot and, if left unchecked, overwhelm the host. A plenty of regulatory devices therefore mediate the fragile equilibrium between pathogen defence and pathophysiological manifestations. Over the past decade in particular, an almost complete set of teleostean sequences orthologous to mammalian immunoregulatory factors has been identified in various fish species, which prove the remarkable conservation of innate immune-control concepts among vertebrates. This review will present the current knowledge on more than 50 teleostean regulatory factors (plus additional fish-specific paralogs) that are of paramount importance for controlling the clotting cascade, the complement system, pattern-recognition pathways and cytokine-signalling networks. A special focus lies on those immunoregulatory features that have emerged as potential biomarker genes in transcriptome-wide research studies. Moreover, we report on the latest progress in elucidating control elements that act directly with immune-gene-encoding nucleic acids, such as transcription factors, hormone receptors and micro- and long noncoding RNAs. Investigations into the function of teleostean inhibitory factors are still mainly based on gene-expression profiling or overexpression studies. However, in support of structural and *in-vitro* analyses, evidence from *in-vivo* trials is also available and revealed many biochemical details on piscine immune regulation. The presence of multiple gene copies in fish adds a degree of complexity, as it is so far hardly understood if they might play distinct roles during inflammation. The present review addresses this and other open questions that should be tackled by fish immunologists in future.

1. Introduction

Inflammation is the complex physiological response of multicellular organisms to counter injuries. These breaches in host barriers may occur from traumata or cellular stress and are generally accompanied by the ingress of bacteria or viruses. Immediately after the perception of both exogenous (pathogenic) and endogenous danger signals, inflammatory responses are mounted according to a fixed succession of definite stages that have been well investigated for decades [1]. The first specialised cells that appear at the pathogen-attack site are in large part granulocytes recruited through a complex network of chemokines. As further leucocyte populations including macrophages and lymphocytes become involved by and by, the initiation phase is superseded by the maintenance phase leading up to the elimination of the pathogenic invaders while ensuring the least possible injury of the host. Eventually, the inflammation is resolved, cellular and tissue debris are cleared up and healing processes restore homeostasis. In case that inflammation spreads across the entire organism, pronounced acute phase activation and fever may characterise such a systemic immune response.

The inflammatory process sparks off a series of strong and disruptive defence mechanisms and the host has to take appropriate countermeasures balancing the beneficial and adverse effects of

Abbreviations: ACTH, adrenocorticotropic hormone; AP1, activator protein 1; A2M, alpha-2-macroglobulin; CCP, complement-control protein; CD, cluster of differentiation; CF, complement factor; CPN1, carboxypeptidase N1; CRH, corticotropin-releasing hormone; G protein, guanine nucleotide-binding protein; GPI, glycosylphosphatidylinositol; GR, glucocorticoid receptor; Ig, immunoglobulin; IL1R, interleukin-1 receptor; IκB, inhibitor of NF-κB proteins; IFN, interferon; IRF, interferon-regulatory factor; JAK, Janus kinase; LPS, lipopolysaccharide; LY86, lymphocyte antigen 86; MAC, membrane-attack complex; MAP, mitogen-activated protein; MASP, mannan-binding lectin-associated serine protease; MBL, mannan-binding lectin; MH, major histocompatibility; MYD88, myeloid differentiation primary response gene/protein 88; NF-κB, nuclear factor 'kappa-light-chain-enhancer' of activated B cells; NLRP3, NLR family, pyrin domain-containing protein 3; miRNA, micro-ribonucleic acid; PAMP, pathogen-associated molecular pattern; PIAS, protein inhibitor of activated STAT; PGRP, peptidoglycan-recognition protein; RIPK2, receptor-interacting protein kinase 2; SERPIN, serine-protease inhibitor; TANK, TRAF family member-associated NF-κB activator; TGFB1, transforming growth factor beta-1; TICAM, TIR-containing adaptor molecule; SOCS, suppressor of cytokine signalling; STAT, signal transducer and activator of transcription; TIR, toll/interleukin-1 receptor/resistance; TNF, tumor necrosis factor alpha; TNFAIP3, tumor necrosis factor, alpha-induced protein 3; TLR, toll-like receptor; TRAF, TNF receptor-associated factor

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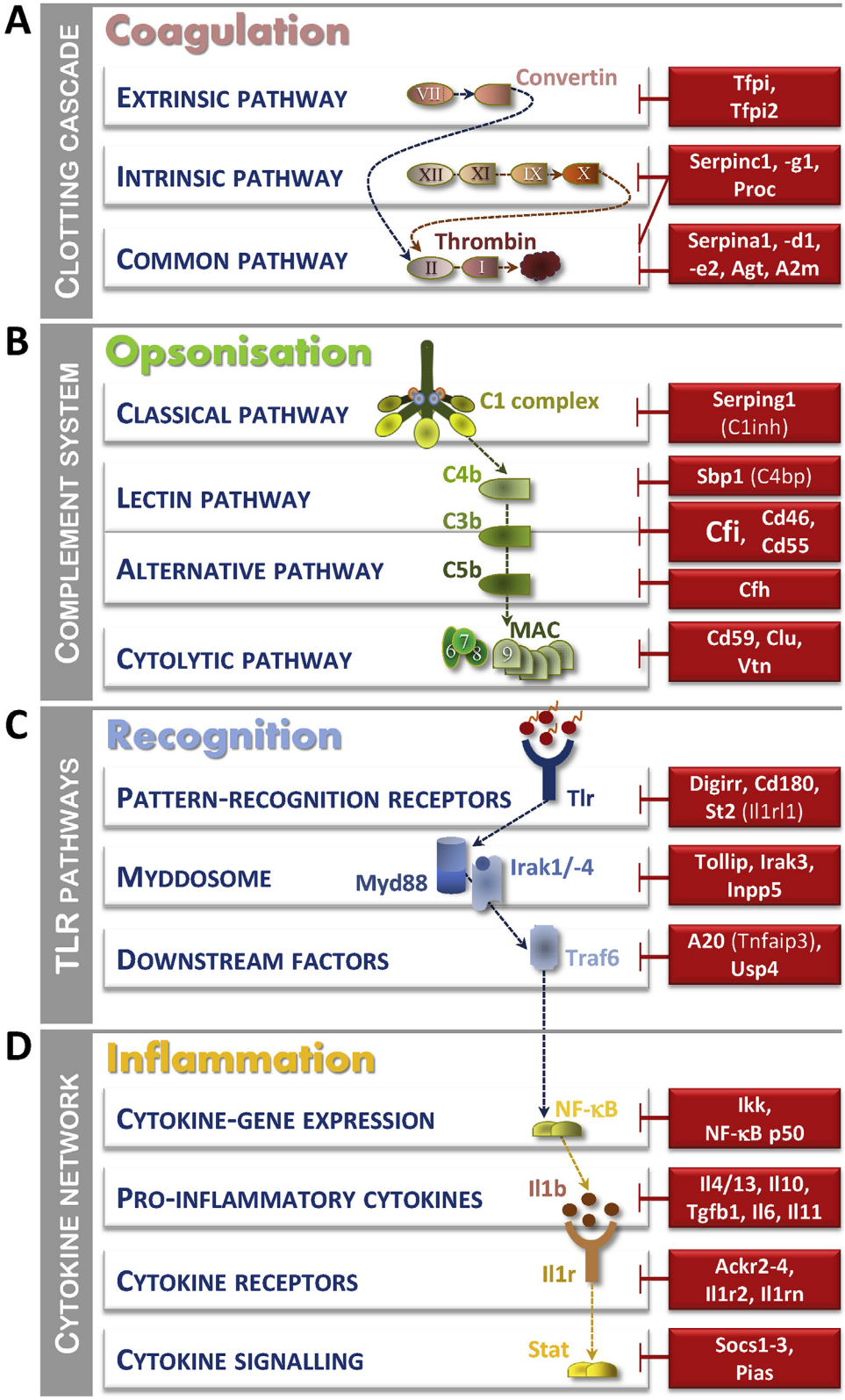

Fig. 1. Teleostean innate immune pathways are checked at multiple levels to sustain homeostasis. (**A**) Coagulation, (**B**) opsonisation of bacteria and (**C**) their detection through pattern-recognition receptors as well as (**D**) cytokine-mediated inflammation are the elementary cornerstones of innate immunity. Negatively regulating molecules (framed in red boxes) control the respective pathways at multiple points to prevent thrombosis, hyperactive immune alerting, improper immune activation and self-destruction. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)