Cytokine & Growth Factor Reviews 31 (2016) 1–15

Contents lists available at ScienceDirect

Cytokine & Growth Factor Reviews

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

Survey

STAT3 signaling in immunity

Emily J. Hillmer[a,1], Huiyuan Zhang[a,1], Haiyan S. Li[a,1], Stephanie S. Watowich[a,b,*]

[a] Department of Immunology, The University of Texas MD Anderson Cancer Center, Houston, TX 77030, USA
[b] The University of Texas Graduate School of Biomedical Sciences, Houston, TX 77030, USA

ARTICLE INFO

Article history:
Received 29 April 2016
Accepted 6 May 2016
Available online 9 May 2016

Keywords:
STAT3
Cytokines
Immune system
Inflammation

ABSTRACT

The transcriptional regulator STAT3 has key roles in vertebrate development and mature tissue function including control of inflammation and immunity. Mutations in human *STAT3* associate with diseases such as immunodeficiency, autoimmunity and cancer. Strikingly, however, either hyperactivation or inactivation of STAT3 results in human disease, indicating tightly regulated STAT3 function is central to health. Here, we attempt to summarize information on the numerous and distinct biological actions of STAT3, and highlight recent discoveries, with a specific focus on STAT3 function in the immune and hematopoietic systems. Our goal is to spur investigation on mechanisms by which aberrant STAT3 function drives human disease and novel approaches that might be used to modulate disease outcome.

Contents

Abbreviations: APRF, acute phase response factor; BAC, bacterial artificial chromosome; bHLH, basic helix loop-helix; Breg, B regulatory cells; CDP, common DC progenitor; CLP, common lymphoid progenitor; CMP, common myeloid progenitor; CTLs, cytotoxic $CD8^+$ T lymphocytes; DAMPs, damage-associated molecular patterns; eIF2a, eukaryotic translation initiation factor 2a; EIF2AK2/PKR, eIF2a kinase 2/protein kinase R; ES cells, embryonic stem cells; DC, dendritic cell; Flt3, Fms-related tyrosine kinase 3; Flt3L, Flt3 ligand; G-CSF, granulocyte colony-stimulating factor; G-CSFR, G-CSF receptor; GAS, IFN-γ-activated sequence element; GOF, gain-of-function; GMP, granulocyte-monocyte progenitor; GVHD, graft-versus-host disease; HIES, hyper IgE syndrome; IFN, interferon; IL, interleukin; IL-6, interleukin-6; IL-7, interleukin-7; IL-7R, IL-7 receptor; IL-23, interleukin-23; IL-23R, IL-23 receptor; IgE, immunoglobulin E; IgG, immunoglobulin G; Id2, inhibitor of differentiation 2; KIR, kinase-inhibitory region; LOF, loss-of-function; MAPK, mitogen-activated protein kinase; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; NK, natural killer cell; PAMPs, pathogen-associated molecular patterns; pDCs, plasmactyoid dendritic cells; PD-L1, programmed death ligand-1; PGE2, prostaglandin E2; PI3K, phosphoinositol 3-kinase; RANK, receptor activator of NF-κB; RORα, retinoic acid receptor-related orphan receptor alpha; RORγ, retinoic acid receptor-related orphan receptor gamma; ROS, reactive oxygen species; SH2, Src homology 2; SNPs, single nucleotide polymorphisms; STAT, signal transducers and activators of transcription; *STAT3* AD-HIES, HIES associated with *STAT3* mutation; $Stat3^{f/f}$, $Stat3^{flox/flox}$; TCR, T cell receptor; Tfh, T follicular helper; Th1, $CD4^+$ T helper 1 lymphocytes; Th17, IL-17-producing $CD4^+$ T lymphocytes; TLRs, Toll-like receptors; Tregs, regulatory T lymphocytes; uSTAT3, unphosphorylated STAT3.

* Corresponding author at: Department of Immunology, The University of Texas MD Anderson Cancer Center, Houston, TX 77030, USA.
E-mail address: swatowic@mdanderson.org (S.S. Watowich).
[1] Denotes equal contribution by these authors.

http://dx.doi.org/10.1016/j.cytogfr.2016.05.001
1359-6101/

1. Introduction

1.1. STAT3 discovery, structure and transcriptional function

STAT3 was discovered over 20 years ago as a component of the interleukin-6- (IL-6) activated acute phase response factor (APRF) complex [1–3], which has a crucial role in stimulating expression of innate immune mediators in liver. This discovery led to rapid identification of STAT3 as a member of the STAT (Signal Transducers and Activators of Transcription) family, based on size similarity, antigenic and structural relatedness, as well as comparable DNA binding activity, to the interferon (IFN)-responsive STAT proteins. Subsequent work identified 7 members of the STAT protein family in mammals [3–6]. Activation of STAT3 is elicited by numerous cytokines and growth factors, including cytokines utilizing the IL-6 signal-transducing receptor chain gp130 (e.g., IL-6, oncostatin M, interleukin-11) or homodimeric cytokine receptors (e.g., granulocyte colony-stimulating factor, G-CSF), as well as growth factors that act through protein tyrosine kinase receptors (e.g., epidermal growth factor) [2,3,7,8]. Moreover, STAT3 mediates important signal transduction cascades elicited by intracellular proteins such as activated Ras or tyrosine kinase oncoproteins (e.g., Src) [9–14]. Many early studies foreshadowed the multiple and distinct biological roles for STAT3 that are appreciated today. Accordingly, interest in STAT3 has risen substantially since its discovery, as judged by a survey of STAT3-immune system-related publications (Fig. 1).

The primary amino acid sequence of STAT3 revealed a conserved Src homology 2 (SH2) domain and a C-terminal tyrosine residue (Y705 in mice) that becomes phosphorylated by Jak kinases upon cytokine stimulation, protein tyrosine kinase receptor signaling or intracellular protein tyrosine kinase activation [5,9]. STAT3 forms homodimers by reciprocal SH2 domain-phosphotyrosine interactions between 2 monomers; this was identified as a key activating mechanism leading to stimulation of STAT3 transcriptional function. STAT3 also undergoes serine phosphorylation at position 727 (S727), a modification that enhances transcriptional activity [15–18]. STAT3 DNA association is mediated by a central DNA-binding region (Fig. 2), while protein: protein association domains located at the STAT3 N- and C-terminal regions are also involved in transcriptional regulation. Numerous approaches including sequence comparisons, mutational analyses, biochemical and structural studies of STAT3 and other family members led to these important discoveries [19–31]. Further posttranslational modifications such as acetylation and methylation have been implicated more recently in STAT3 transcriptional function [32–35]. Moreover, STAT3 can be activated constitutively by engineered introduction of cysteine residues, which drive cytokine-independent dimerization, rendering oncogenic activity [36]. Several excellent reviews summarize the discovery of STATs and the intense work to characterize their signaling mechanisms and functions in the early days of the field [37–42].

More recently, unphosphorylated STAT3 (uSTAT3) has been recognized as an important transcriptional regulator [43–45]. In the unphosphorylated state, uSTAT3 binds similar DNA sites as tyrosine-phosphorylated and dimerized STAT3 (e.g., IFN-γ-activated sequence (GAS) elements), yet uSTAT3 works in collaboration with transcriptional regulators such as NF-κB to control a cadre of genes not normally affected by tyrosine-phosphorylated STAT3 [34,44,46]. STAT3 also induces its own gene expression via a STAT3-*Stat3* positive autoregulatory loop [47]. Thus, STAT3 homodimers activated by cytokine or growth factor receptors, as well as intracellular protein tyrosine kinases, have potential to

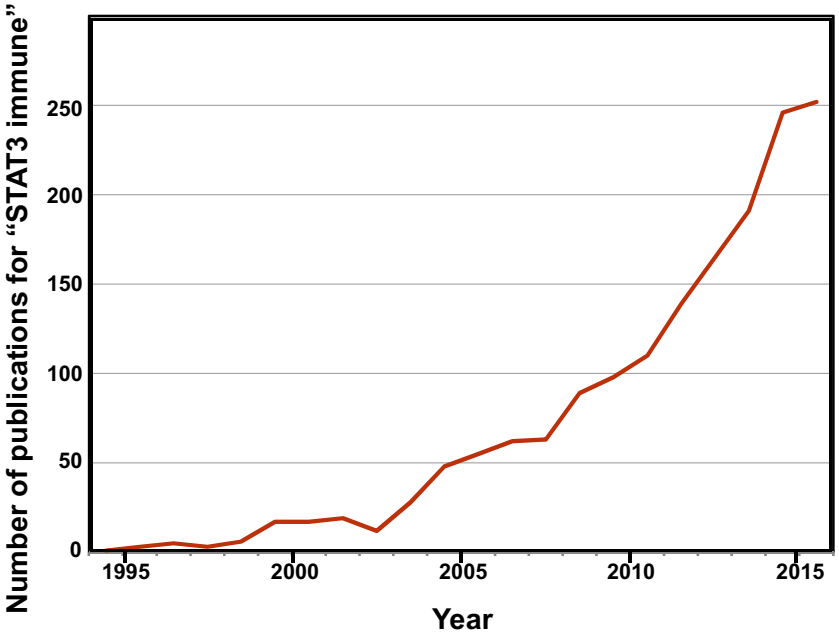

Fig. 1. STAT3-immune publication numbers. The number of publications listed in PubMed with the query "STAT3 immune" is shown for each year between 1994 and 2015.