Cytokine & Growth Factor Reviews xxx (2015) xxx–xxx

Contents lists available at ScienceDirect

Cytokine & Growth Factor Reviews

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

Survey

Dynamic aberrant NF-κB spurs tumorigenesis: A new model encompassing the microenvironment

Spiros A. Vlahopoulos [a,*], Osman Cen [b], Nina Hengen [c], James Agan [b], Maria Moschovi [a], Elena Critselis [a], Maria Adamaki [a], Flora Bacopoulou [a], John A. Copland [d], Istvan Boldogh [e], Michael Karin [f], George P. Chrousos [a]

[a] First Department of Pediatrics, University of Athens, Horemeio Research Laboratory, Athens, Greece
[b] Department of Microbiology and Immunology, Feinberg School of Medicine, Northwestern University, United States
[c] Bernard J. Dunn School of Pharmacy, Shenandoah University, United States
[d] Mayo Clinic Comprehensive Cancer Center, Department of Cancer Biology, United States
[e] Department of Microbiology and Immunology, School of Medicine, University of Texas Medical Branch at Galveston, United States
[f] Department of Pharmacology, University of California, San Diego, United States

ARTICLE INFO

Article history:
Received 3 June 2015
Accepted 15 June 2015

Keywords:
Immunity
Inflammation
Homeostasis
Cancer
Nuclear Factor kappa B

ABSTRACT

Recently it was discovered that a transient activation of transcription factor NF-κB can give cells properties essential for invasiveness and cancer initiating potential. In contrast, most oncogenes to date were characterized on the basis of mutations or by their constitutive overexpression. Study of NF-κB actually leads to a far more dynamic perspective on cancer: tumors caused by diverse oncogenes apparently evolve into cancer after loss of feedback regulation for NF-κB. This event alters the cellular phenotype and the expression of hormonal mediators, modifying signals between diverse cell types in a tissue. The result is a disruption of stem cell hierarchy in the tissue, and pervasive changes in the microenvironment and immune response to the malignant cells.

Contents

* Corresponding author. Tel.: +30 6977441008.
E-mail address: v_spiros@hotmail.com (S.A. Vlahopoulos).

http://dx.doi.org/10.1016/j.cytogfr.2015.06.001
1359-6101/

1. Introduction

The role of transcription factor Nuclear Factor kappa B (“NF-κB”) in cell physiology has been reviewed extensively, and excellent articles describe mutations on genes that encode for NF-κB regulators in lymphoid malignancy [1]. Such mutations are relatively rare in solid tumors [2]. Lineages that give rise to solid tumors normally restrict their growth to generate solid tissue – this restriction can be overcome by NF-κB in carcinogenesis [3]. However, in recent years, study models for adenocarcinoma show oncogenes acting through NF-κB to cause cancer [1,4,5]. We selected a few of these models to present key changes in cell signaling to highlight the common theme. Lastly, we use leukemia as a model for metabolic homeostasis. Cell lineages giving rise to leukemia differ from adenocarcinoma in that they possess a natural capacity to initiate rapid clonal growth and migration.

NF-κB is a dimer of proteins with Rel homology domain at the N-terminus (e.g., RelA/p65, RelB, NF-κB1/p50, NF-κB2/p52), which forms a complex the Ikappa B protein (IκB) that restricts NF-κB from entering the nucleus (Table 1). IκB can be inducibly or constitutively degraded, depending on the signaling context [1]. In many cell types a dimer of RelA with p50 regulates NF-κB target genes, including other Rel domain proteins. We focus on RelA as a paradigm for NF-κB effects in study systems discussed here unless otherwise specified.

NF-κB activation can proceed through the canonical pathway, or the non-canonical pathway [6]. In canonical signaling, IκB protein restricts the Rel dimer. The protein kinase complex IKK, which interacts with a variety of proteins (Supporting Table S1) can phosphorylate IκB; after phosphorylation, the proteasome degrades IκB [7,8], enabling a rapid nuclear entry of Rel proteins, where, depending upon their posttranslational modifications, they activate or repress specific groups of target genes [9]. “Noncanonical” signaling takes place when the restricting protein is p100. p100 processing gives rise to the protein p52, which forms a dimer with RelB [6]. During cell stress, other proteins, such as tumor suppressor p53, can restrict RelA from entering the mitochondria [10]. Multiple proteins thereby ensure a tight regulation of NF-κB activity. Under conditions of high expression of the RelA protein, or mutations of enzymes that modify RelA function, some cell types escape feedback regulation of NF-κB activity, as we discuss in Section 5.2. We focus on proteins that show why feedback control of NF-κB activity is critical in shaping the microenvironment in malignancy, including cell phenotypes, immune response, and material exchange within a niche.

2. NF-κB subunit RelA is modified to control multiple signal transduction pathways

NF-κB regulates cell differentiation and its inflammatory responses [1]. What makes NF-κB unique is the fact that it is activated in response to diverse changes in the host tissue, and has the capacity to alter the state of the host tissue and of multiple components of the immune system profoundly. Signals that modulate RelA (Fig. 1A) activity affect stability, tertiary structure, and specific combination of charged and hydrophobic residues exposed on RelA, and determine:

1. Whether RelA associates specifically with nuclear, mitochondrial, or cytoplasmic proteins.
2. The gene promoters or enhancers RelA associates, modulating transcriptional activity.

RelA interacts with a number of key regulatory proteins, such as nuclear hormone receptors, either by direct physical association, or through competition for coactivators and corepressors [11]. In this way steroid hormones and inflammatory cytokines regulate one another. Several growth factors, or cytokines, binding to their transmembrane receptors, as well as cell stress, elicit intracellular signal cascades that activate distinct Rel proteins, depending on the cell type [12,13]. Recipient cells, in turn, respond by integrating those signals and expressing adhesion molecules, enzymes, and

Table 1
Identities of representative isoforms of the proteins referred herein, according to the National Center of Biotechnology Information (NCBI) and the Online Mendelian Inheritance in Man catalog (OMIM) that outlines the current consensus for the biological role of each entry.

Protein name	NCBI (Entrez Gene ID)	OMIM entry
AKT1	207	164730
AMPK	5562	602739
AR	367	313700
Bcl-2	596	151430
Bfl1	597	601056
Calpain1/mu I	823	114220
Calpain2/m II	824	114230
CCL2	6347	158105
CCL20	6364	601960
CCL5	6352	187011
ccnd1 (cyclin D1)	595	168461
CD11b	3684	120980
CD8	925	186910
CD44	960	107269
COX2	5743	600262
CSF3	1440	138970
CXCL1	2919	155730
CXCL10	3627	147310
ER	2099	133430
Fascin-1	6624	602689
Foxp3	50943	300292
GATA3	2625	131320
GRα	2908	138040
Hexokinase 2	3099	601125
HIF1	3091	603348
HMG-CoA reductase	3156	142910
IFNα	3439	147660
IFNβ	3456	147640
IFNγ	3458	147570
IκBα	4792	164008
IKK1	1147	600664
IKK2	3551	603258
IL-10	3586	124092
IL-12A	3592	161560
IL-12B	3593	161561
IL-1β	3553	147720
IL-2	3558	147680
IL-23A	51561	605580
IL-6	3569	147620
IL-8	3576	146930
JAK2	3717	147796
Mcl-1	4170	159552
MMP2	4313	120360
MMP9	4318	120361
Myc	4609	190080
Nanog	79923	607937
NFκB1 (p50)	4790	164011
NFκB2	4791	164012
P53	7157	191170
PFKB3	5209	605319
Proteasome subunit A1	5682	602854
Proteasome subunit C5	5705	601681
Ras (KRAS1)	3845	190070
Rb (Rb1)	5925	614041
Rel	5966	164910
RelA	5970	164014
RelB	5971	604758
Src	6714	190090
STAT3	6774	102582
Tert (telomerase)	7015	187270
TGFβ	7040	190180
TLR3	7098	603029
TNF	7124	191160
VEGF	7422	192240

Please cite this article in press as: Vlahopoulos SA, et al. Dynamic aberrant NF-κB spurs tumorigenesis: A new model encompassing the microenvironment. Cytokine Growth Factor Rev (2015), http://dx.doi.org/10.1016/j.cytogfr.2015.06.001