Post-Transcriptional Control of Cytokine Gene Expression in Health and Disease

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Post-transcriptional control of cytokine gene expression is essential for rapid and transient response to stimuli and external stress. In health, post-transcriptional control is exerted by a number of *trans-acting* RNA-binding proteins and *cis-acting* sequence elements. These elements exist largely in the 3' untranslated region and comprise microRNA targets and notably AU-rich elements, and exert regulated mRNA decay and translation repression. Defects in this control can lead to increased and sustained production of pro-inflammatory mediators contributing to several chronic inflammatory disease and cancer states. This introduction to the Journal's special issue on the topic summarizes, in a non-comprehensive list, the types of RNA-binding protein and their target cytokines, and potential contributions to disease, and presents the highlights of the individual reviews.

IN THE HEALTHY BODY, cellular post-transcriptional control contributes to rapid cytokine gene expression in response to inflammatory or microbial stimuli while allowing a transient reaction to the inducer. If this control becomes aberrant, then extended and overproduction of proinflammatory cytokines and other mediators will exacerbate certain disease conditions (Khabar 2010). The post-transcriptional control of cytokine expression in health is exerted by *trans-acting* RNA-binding proteins and *cis-acting* sequence elements, largely in the 3' untranslated region (3'UTR), comprising microRNA (miRNA) targets and notably AU-rich elements (ARE). The latter have been of the most extensively studied pattern elements and can pose controlled mRNA instability and translation repression in health. In disease, the post-transcriptional control of cytokines is subject to a number of defects that lead to different abnormalities and conditions. Table 1 outlines a noncomprehensive list of these defects, the types of RNA-binding protein and cytokines involved, and their potential contributions to disease. This special review issue offers updated views on the roles of the post-transcriptional control of cytokine expression and was written by the experts who are not only knowledgeable about the key basic mechanisms, but also about the interrelationships with disease processes.

A prominent example of cytokines that is subject to post-transcriptional control is tumor necrosis factor alpha (TNF- α). Because of its involvement in a number of diseases, it is one of the most often studied cytokines, which has led to anti-TNF therapy in recent years (Paulsen and others 2013; Tanaka 2013). Rapid shutoff of TNF- α production after encountering stimuli, such as bacterial endotoxins (lipopolysaccharides), is necessary because of the extreme proinflammatory and cytotoxic action of TNF- α (Kontoyiannis and others

1999). Continued production of TNF- α is a feature observed in chronic inflammatory conditions, such as rheumatoid arthritis. In this review issue, TNF- α has been widely referred to during the discussions on the post-transcriptional regulation of cytokine expression, either because TNF- α gene is a model of post-transcriptional control investigations or as a key modulator in inflammatory response.

An important pathway that has been extensively studied in ARE-mediated control of cytokine expression is the mitogen-activated protein kinase (MAPK). During demand, for example, as in cellular stress and inflammatory insults, MAPK transiently phosphorylates the mRNA decay-promoting protein, tristetraprolin (TTP/*ZFP36*) leading to loss of binding to AREs, and subsequently increases cytokine mRNA stability and translation (Hitti and others 2006; Clement and others 2011). However, in certain chronic disease and cancer conditions, where MAPK is continually activated, this transient activity becomes prolonged. In this issue, Gaestel and colleagues review the intricate role of MAPK pathway signaling in cytokine mRNA decay and in translation. They point out both ARE-dependent and ARE-independent effects, where the latter encompass mechanisms involving the miRNA pathway (Tiedje and others 2014). Vlasova-St. Louis and Bohjanen continue with a further overview of AREs, including their sequence characteristics and ARE-binding proteins, as they relate to cytokines, particularly T-cell lymphokines. Moreover, they elaborate on the emerging role of GU-rich elements (GREs), which interestingly share structural patterns with AREs such as overlap, number, and specific localization of repeats in 3'UTR (Halees and others 2011). The role of CEFL (also called CUGBP1), which binds and regulates GRE-containing

TABLE 1. POTENTIAL POST-TRANSCRIPTIONAL CONTROL DEFECTS IN CYTOKINE EXPRESSION DURING DISEASE

<i>Type of control</i>	<i>Defect</i>	<i>Effector</i>	<i>Targets</i>	<i>Potential disease</i>	<i>References</i>
Transcription	Promoter polymorphism	TTP	COX-2, others	Rheumatoid arthritis	Suzuki and others (2008); Upadhyay and others (2013)
	P53 mutations affecting transcription	TTP/let-7	Lin28	Breast cancer survival	Kim and others (2012)
Signaling	p38 MAPK activation	Cytokines	TTP	Rheumatoid arthritis	Zwerina and others (2006)
	Constitutive ERK activation	TTP	IL-8	Melanoma	Bourcier and others (2011)
Splicing	RAS/TGFβ activation	NA	VEGF	Colon cancer	Kanies and others (2008)
	Differential expression of alternative ARE-deficient transcripts	NA	OSM receptor	Cancer	Khabar and others (2005)
Polyadenylation	Differential expression of alternative ARE-deficient transcripts	NA	FGF2, IGF2BP1	Cancer	Khabar and others (2005); Mayr and Bartel (2009); Touriol and others (1999)
	Differential expression of alternative miRNA-deficient transcripts	miRNAs, others	Many	T-cell proliferative diseases	Sandberg and others (2008)
ARE-mediated mRNA decay	Extended mRNA stabilization	TTP	uPA, uPAR, MMP1/13, IL-16	Invasive breast cancer	Al-Souhibani and others (2010); Milke and others (2013)
miRNA-mediated silencing	miRNA-mediated silencing of RNA destabilizing proteins	miR-29a	TTP/HuR axis	Invasive breast cancer	Al-Ahmadi and others (2013); Gebeshuber and others (2009)
	Cytokine stimulated miRNA overexpression	TNF-α/IL1β/146a	TRAF6/IRAK	Psoriasis, rheumatoid arthritis	Chatzikiyiakidou and others (2010); Xie and others (2013)
	miRNA overexpression	miR-155	C/EBPβ/TNF	Hepatocellular carcinoma	He and others (2009)
	Competition of miRNA-mediated suppression	HNRNPL	VEGF	Cancer cells	Jafarifar and others (2011)
	Deficiency in mRNA destabilizing proteins	TTP	uPA, uPAR, MMP1, VEGF	Invasive breast cancer,	Brennan and others (2009); Young and others (2009)
Regulated expression of RNA stabilizing proteins	Overexpression of RNA stabilizing proteins	HuR	Many	Colon cancer	Srikantan and Gorospe (2012) ^a
	Competition to ARE binding with mRNA decay-promoting protein	TTP	HuR	Colon cancer, breast cancer, brain cancer	Al-Ahmadi and others (2009)
Translational control	Defects in translational repressor activity	TIA/TIAR	TNF	Arthritis	Phillips and others (2004)
Regulated localization of RNA-binding proteins	Aberrant localization of RNA-binding proteins	HuR	Many (IL-8, VEGF, UpA)	Different cancers and inflammatory conditions	Srikantan and Gorospe (2012) ^a
Genetic deletion in mice	Knockdown of AUF1	AUF1	TNF, IL1β	LPS-induced endotoxemia in mice	Lu and others (2006)
	Knockdown of TTP	TTP	TNF; IL-6, others	Arthritis, valvulitis, autoimmunity, inflammatory bowel disease, myeloid hyperplasia, periodontitis	Taylor and others (1996) Ghosh and others (2010) Patil and others (2008)
	Knockdown of TIA	TIA	TNF	Inflammation	Phillips and others (2004)

^aThis review elsewhere contains almost comprehensive coverage of diseases imparted by HuR dysregulation. ARE, AU-rich element; LPS, lipopolysaccharide; MAPK, mitogen-activated protein kinase; miRNA, microRNA; TNF, tumor necrosis factor.

transcripts, is also discussed in the review (Vlasova-St. Louis and Bohjanen 2014).

The abnormalities of the post-transcriptional regulation of cytokine expression in disease are discussed in two reviews in this issue: one focuses on cancer and the other on inflammation. The former addresses the post-transcriptional control of cytokines that promote pro-cancer activities, particularly in angiogenesis (Griseri and Pagès 2014). Thus, angiogenesis is presented, at least partly, as a consequence of the aberrant post-transcriptional control of pro-angiogenic cytokine (such as VEGF) expression. An overall summary of RNA-binding proteins and their role in affecting different types of tumors is also presented in this review. Panganiban and others (2014) include discussions on post-transcriptional control of chemokines in disease, particularly in models of allergic inflammation in human airway epithelium. Chemokines are cytokines that attract various types of immune and nonimmune cells to areas of inflammation or microbial attacks; and thus, transient responses imparted by tight gene regulation are essential for healthy cell trafficking (Hamilton and others 2012). However, in chronic allergic conditions, such as asthma, increased chemokine response is promoted by cytokine-driven activation of RNA-binding protein, such as Hu antigen R (HuR/*ELAVL1*) (Panganiban and others 2014). The latter is a universal RNA stability-promoting protein that has attracted attention in the field because of its numerous mRNA targets (Simone and Keene 2013); thus, it has been covered in several reviews here. Another widely discussed RNA-binding protein, in this special issue, is *TTP/ZFP36* because of its importance in cytokine mRNA regulation and its aberrations across different conditions and diseases (Table 1). A special topic on the structural and evolutionary aspects of the *TTP/ZFP36* family is presented, at the end of the issue (Blackshear and Perera 2014).

Another appreciable portion of the review issue focuses on post-transcriptional regulation of the interferon (IFN) system. IFNs are key proteins that play diverse roles in innate immunity to viruses and in the regulation of the immune system. Regulation of the IFN system, whether during IFN production or during the cellular response to IFN, occurs at many different levels, including post-transcriptional regulation, reviewed earlier (Khabar and Young 2007). Recent work in this area implicated an mRNA decay-promoting RNA-binding protein called KH-type splicing regulatory protein (KSRP) as a negative regulatory factor for IFN production [reviewed here by King and Chen (2014)]. The authors proposed an integrated model for type I IFN post-transcriptional control by KSRP and TTP. Additionally, the role of KSRP in cytokine control and miRNA biogenesis is discussed in the same review (King and Chen 2014).

Ribonuclease L (RNase L) is a part of the IFN system and possesses strong activity against viral mRNAs but has also been proposed as a negative feedback player in IFN response targeting cellular mRNAs (Khabar and others 2003). Hassel's group expands on the role of RNase L as emerging cellular mRNA regulator and discusses the repertoire of known RNase L targets and its consequences in cell cycle and other cellular functions (Brennan-Laun and others 2014). The controlled function of the IFN system allows rapid elimination of microbes and a favorable immunomodulatory action without deleterious consequence for the

host. Another important element in IFN action is the contribution of mTOR/S6K and ERK/MNK pathways in IFN-stimulated mRNA translation, discussed here in the review by the Platanias group (Brennan-Laun and others 2014). These pathways act on translational regulators, one of which is the translation repressor 4E-B, which upregulates mRNA translation upon phosphorylation by mTOR during IFN response (Brennan-Laun and others 2014)—also during other selected cytokine responses (Mazumder and others 2010).

The variety of signaling mediators and effectors participating in the post-transcriptional control of cytokine expression indicates a multitude of potential defects that can arise during disease. This knowledge should add to the appreciation of the potential targeting of the perturbed post-transcriptional events for novel and alternative therapeutic approaches. This special issue highlights the significant players and pathways that govern post-transcriptional regulation of cytokine and IFN expression and thus generating rationale for further investigations, including new drug targets for chronic inflammatory conditions, autoimmune diseases, and cancer.

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