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Lessons from studying the AU-rich elements in chronic inflammation and autoimmunity

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ABSTRACT

AU-rich elements (AREs) comprise one of the most widely studied families of regulatory RNA structures met in RNAs engaged in complex immunological reactions. A multitude of genetic, molecular, holistic and functional studies have been utilized for the analyses of the AREs and their interactions to proteins that bind to them. Data stemming from these studies brought forth a world of RNA-related check-points against infection, chronic inflammation, tumor associated immunity, and autoimmunity; and the interest to capitalize the interactions of AREs for clinical management and therapy. They also provided lessons on the cellular capabilities of post-transcriptional control. Originally thought as transcript-restricted regulators of turnover and translation, ARE-binding proteins do in fact harbor great versatility and interactivity across nuclear and cytoplasmic compartments; and act as functional coordinators of immune-cellular programs. Harnessing these deterministic functions requires extensive knowledge of their synergies or antagonisms at a cell-specific level; but holds great promise since it can provide the efficacy of combinatorial therapies with single agents.

1. Introduction

The control of immunological stress, inflammation, memory and tolerance requires the prudent use of RNAs needed by all cells engaged in these reactions. Post-transcriptional regulation (PTR) provides checkpoints in the processes aiding RNAs to mature, become functional and be selectively used for protein synthesis. For RNAs engaged in immune and inflammatory reactions these steps do not occur automatically; rather they proceed via the signal-induced engagement of machines for RNA splicing, maturation, editing, localization and -ultimately- destruction and ribosomal translation [1]. These machines are guided towards principle RNA sequences or RNA structures with strong conformations and/or terminal modifications (e.g. 5′ m7G cap, polyA signals and tails, viral IRES, intron-exon boundaries). Yet, their engagement can be differentiated if RNA contains regulatory RNA structures like RNA secondary structures (RSS's) capable of binding signal-induced factors which in turn facilitate or impede the activity of post-transcriptional machines. RSS's reside in proximal or distant locations within the body of RNAs; they acquire less rigid and dynamic conformations which can be altered during the life cycle of RNA. The importance of RSS's in immune homeostasis is indicated by their enrichment in the lengthy UTRs of cytokine and chemokine mRNAs whose control is necessary to avoid pathology [2].

In the immune universe, RSS's are commonly found in a majority of induced mRNAs-both coding and non-coding [2]. They are “seen” by a vast collection of highly conserved proteins broadly termed as RNA-binding proteins (RBPs) [3]. RBPs have modular structures with domains capable for RNA recognition, signal integration and catalytic events. However, they do not act *in solo*; they rather team up to target individual RNAs and form ribonucleoprotein complexes (RNPs). RNPs are continuously remodeled with some RBPs being exchanged by others to destine RNAs towards different fates. The development of holistic approaches [4] for RBP:RNA interactions indicated that RNPs do not target individual RNAs but rather “read” collections of RSSs across “functionally relevant” RNAs to coordinate their use suggesting they may affect whole cellular programs [5]. The prominence of RBPs and RNPs in immunity is validated by mouse mutants with modifications in RBP genes which support their involvement as drivers or modifiers of autoinflammatory or autoimmune syndromes [1].

Several examples of RSS's of relevance to immunology have been described; however, the most celebrated example is that of the called Adenyl-Uridinyl (AU)-rich elements and the factors associated with it.

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2. AU-rich elements: simple yet variable RSSs associated with complex RBP-mediated events in immunity

The primary sequence of the AU-rich elements is simple yet variable; it ranges from loosely defined U and AU stretches to defined AUUUA pentamer or UUAAUUAUU nonamer motifs whose number correlates to their functional potency. Their distribution is wide, covering > 10% of the eukaryotic transcripts. Notably, such transcripts are of biomedical value since they include those encoding cytokines and chemokines, cell cycle regulators, metabolic and death controllers -now catalogued in several databases [6,7]. Moreover, their immunological history co-insides with that of cytokines like TNF [8,9]; growth factors like GM-CSF [10]; and interferons [11].

The functional analysis of the *Tnf* 3′ARE was a milestone in immunological ARE research. Its genetic deletion in mice augmented TNF synthesis in several tissues; and promoted inflammatory polyarthritis, inflammatory bowel disease [9] and comorbidities [12]. Besides its value as a model of TNF-mediated pathologies, this mouse revealed that the *Tnf* 3′ARE is under the control of MAPK/SAPK and anti-inflammatory signals and that it acts as a silencer of ectopic TNF synthesis [13]. Through the analysis of cytokine mRNAs, AREs were brought in the spotlight of immunology and their dysfunction connected to chronic inflammatory diseases, autoimmunity and comorbidities including cancer.

In mature mRNAs, AREs reside in UTRs and in proximity to principle structures like poly-A tails and 5'caps; as such they were considered as autonomous regulators of mRNA stability and translation in the cytoplasm [14]. However, it is now clear that they act in concert with other RSS's including miRNA binding sites [15]. Finally, AREs were identified in the intronic regions of unspliced pre-mRNAs in the nucleus [16] –suggesting that they may also be involved in the control of RNA maturation, splicing, nucleocytoplasmic transport or proofreading activities.

The pleiotropy of cytoplasmic and nuclear events incurred by the presence of AREs is validated by the network RBPs that associated with them. The catalogue of these “AREBPs” contains proteins with *bona fide* domains for RNA recognition like RNA recognition motifs (RRM); CCCH tandem zinc finger domains; and KH domains [3,17–19]. Other putative ARE-recognizing proteins lacking such domains have been identified [20,21]; however, their functions are withstanding. Currently, most of our knowledge on the mechanics of AREs stem from the analysis of the original catalogue.

Based on the analyses of AREs, AREBPs can instruct the recruitment of machines capable for deadenylation, decapping and exonucleolysis; and/or restriction in translation initiation. Due to that, classical AREBPs have been considered mostly as “RNA suppressors” modified by activating signals or competing with “RNA activators”. In that sense AREBPs efficiently determine activation or deactivation of immune cell programs as they can restrict the collection of signaling and inflammatory mediators whose inappropriate release can destroy or transform the tissue microenvironment; or alter immune homeostasis towards autoimmunity. However, a majority of ARE-BPs is also located in the nucleus; and they also seem to travel with their RNA targets to the cytoplasm. As such, the properties of AREBPs have been extended towards regulation of RNA splicing and transport thus connecting all aspects of PTR (Fig. 1). Below, we will point briefly on prototypical AREBPs functioning in cytoplasmic and nuclear checkpoints of immune-cellular reactions (Fig. 2) engaged in physiology and pathology.

3. The TISS11/Zfp36 family: endpoint determinants safegurding inflammation, memory and tolerance

The TISS11/Zfp36 family of proteins includes 3 members with C3H tandem zinc finger domains conserved between mice and humans: Tristetraprolin (TTP, TISS11, Zfp36), Zfp36L1 (TISS11B, butyrate responsive factor 1, BRF1) and Zfp36L2 (TISS11D, butyrate responsive

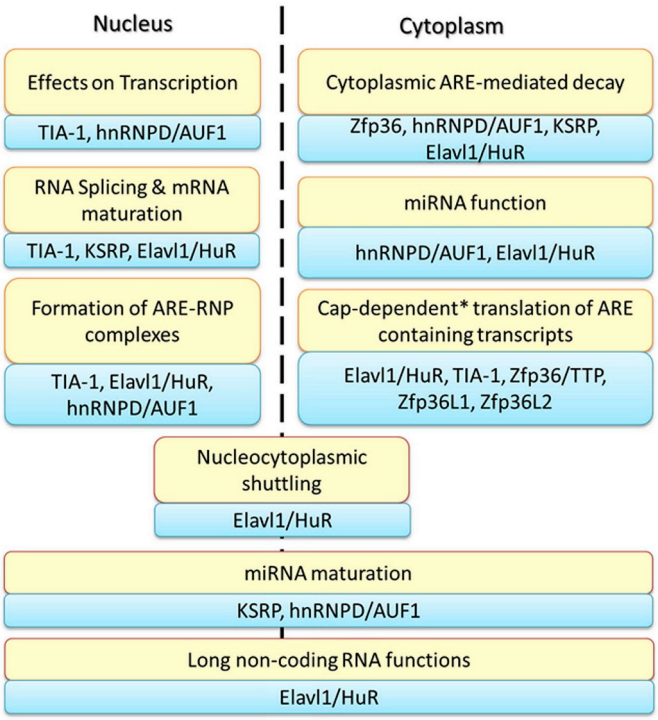

Fig. 1. AREBPs in the control of post-transcriptional processes. Shown are simplified annotations (yellow) of key nuclear, cytoplasmic and spanning post-transcriptional processes and the collections of AREBPs (cyan) involved in each these processes which suggests a extensive degree of connectivity. (*) As indicated in the functions of AREBPs extend also to the regulation of cap-independent translation via IRES's. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

factor 2, BRF2) [22]. The archetype -TTP- binds specifically to defined 3′AREs via its zinc finger domains and promotes mRNA degradation [159,160]. To do so, TTP interacts and recruits the CCR4-NOT complex which in turn deadenylates mRNAs rendering them susceptible to exonucleolytic destruction [23]. TTP also interacts with the Dcp1a/Dcp2 complex involved in decapping and the RNA exosome for exonucleolysis [24].

In resting macrophages and DCs the expression of TTP is limiting-perhaps via an autonomous loop since the TTP protein can bind and promote the degradation of its mRNA. Initial TLR, TNFR, Type I and gamma IFN signals induce the NF-kβ or STAT driven transcription of the *Ttp* gene. However, the destabilizing activity of the TTP protein is blocked via phosphorylation-through the p38/SAPK pathway that is activated by the same signals which may be followed by ubiquitination and proteasomal degradation [25]. This allows macrophages to accumulate pro-inflammatory mRNAs for NF-kB, TNF, GM-CSF, IL-27 and related chemokines that enhance pro-inflammatory and effector T-cell responses [26–29]; and DCs to produce IL-23 supporting Th17 responses [30]. During the continuum of an inflammatory response, TTP is dephosphorylated either due to cessation of pro-inflammatory signals; or as instructed by immunomodulatory signals (e.g. IL-10, IL-4, IL-13 and TGFβ) which also enhance its expression. Under the latter conditions, dephosphorylated TTP binds to its ARE-bearing targets, promotes their destruction, limits the pro-inflammatory response and aids its resolution. For macrophages, this may also aid the transition from a pro-inflammatory macrophage phenotype (i.e. M1) to alternative and regenerative phenotypes (i.e. M2) [31]. TTP is also required to destabilize anti-apoptotic mRNAs in murine neutrophils activated at an infection site [32], thus balancing neutrophil death and efferocytosis versus infection control.

Animal models provide testament to the pathological implications

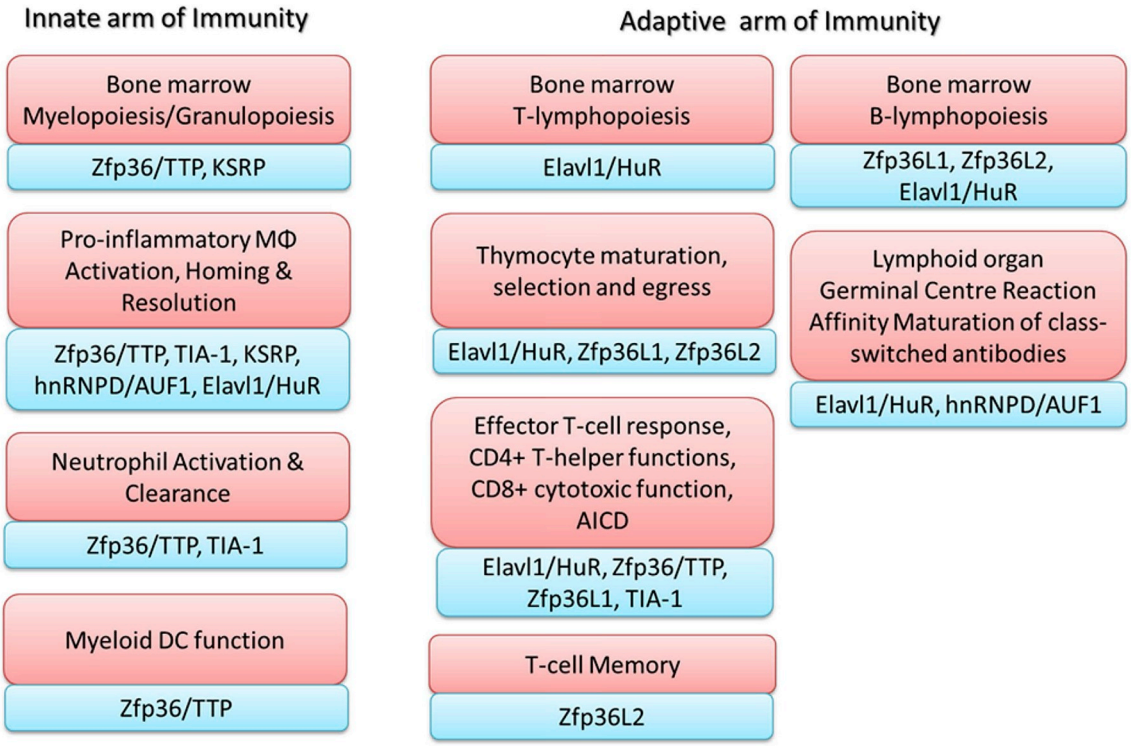

Fig. 2. Examples of AREBP involvement in the control of innate and adaptive immunity. Shown are simplified annotations (red) of key processes involved in the development, maturation and function of immune cells and the collections of AREBPs (cyan) implicated in the control of each these processes. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

stemming from the dysfunction Zfp36. The obligatory deletion of TTP in the mouse supports an autoinflammatory/autoimmune syndrome with symptoms of cachexia, arthritis, dermatitis and myeloid hyperplasia due to the excessive synthesis of TNF, GM-CSF, CCL3, IL-23 and IL-17 [28,30,33]. In contrast, TTP overexpressing animals rendered as such via the deletion of the 3′ARE located in the *Ttp* mRNA, appear resistant to acute inflammatory, autoimmune and infectious models [34].

Myeloid restricted mutants appear sensitive to acute inflammatory insults and are excessively capable of restricting infections but are protected from insulin resistance, fatty-liver disease and thymoma growth [31,35–37]. Yet, they do not develop spontaneous disease, suggesting that TTP affects additional arms of immunity [37]. TTP is also active in effector $CD4^+$ T-cells and interacts with many important mRNAs including that of IFNγ; in these cells, however, TTP did not only promoted degradation but also actively repressed the translation of cytokine mRNAs [38]. The means of TTP's interference towards translation remain unclear; however, evidence has come forth for its interaction to factors capable of stalling the initiation of translation [39,40].

A more distinctive role towards lymphocyte ontogeny and activation is imposed by other proteins of the TISS11/Zfp36 family. The combinatorial loss of ZFP36L1 and L2 in mouse thymic progenitors bypass their requirement for a pre-TCR signals due to augmented Notch synthesis and inefficient DNA-damage checkpoint controls [41,42] leading to T-cell acute lymphoblastic leukemias (T-ALL). Similarly, such mice displayed a profound block in B-cell development due to a defect in cell cycle regulation and sustained quiescence at the checkpoint of antigen receptor rearrangement [43].

A proposition for Zfp36L1 acting similar to TTP in effector T-cells has been put forward [38]. However, in resting memory $CD4^+$ T-cells neither TTP nor Zfp36L1 are prominently expressed. Instead, Zfp63L2 is expressed in these cells and acts to inhibit the translation of effector mRNAs, without degrading them so as to keep them ready for the recall response, like the *Ifn*γ mRNA [44]. This suggests that Zfp36 family members act discriminatively to aid conversions between resting and activated memory T-cell subsets. A similar mode of function has also been demonstrated for $CD8^+$ tumor associated lymphocytes where the *Ifn*γ mRNA is destabilized by Zfp36L2 in the absence of costimulatory signals; and its loss alleviates this block to enhance IFNγ-mediated anti-tumor activities [45].

The analysis of Zfp36 members unveiled the true deterministic potential of ARE-mediated decay and translation over immunological checkpoints; and the pathological outcome of their dysfunction. As exemplified by these RBPs, cellular determination by ARE-BPs proceeds by limiting the functional quantities of selected key transcripts and not by qualitative changes in transcripts with different functions qualitative means. However, other AREBPs appear to have more diverse functions connecting the qualitative to the quantitative aspects of PTR.

3.1. TIA-1 and TIAL-1: qualitative checkpoints of stress and death

TIA-1 (T-cell intracellular antigen 1; cytotoxic granule-associated RNA binding protein 1) was originally identified as a component of cytotoxic T-lymphocyte (CTL) granules with a nucleolytic activity capable of inducing DNA fragmentation in their targets; and as a protein highly expressed in granules of anaplastic T- and NK cell lymphomas [46]. However, the granule-associated protein is the carboxy-terminal fragment of a protein with multiple nuclear and cytoplasmic functions in RNA regulation. A close relative to TIA-1 was also identified in a similar fashion and reasonably coined as TIAR (TIA-1-related protein) or as now formerly known TIA-L1 (TIA-1 like protein-1) [47].

TIA-1 and TIA-L1 belong to the RNA recognition motif family (RRM) of RBPs but can also bind DNA. They primarily reside in the nucleus; there they may act to regulate transcription by binding to T-rich regions of DNA to slow down and allow coupling of RNA polymerase II. However, their most important nuclear function is the enhancement of splicing by binding to U-rich elements found in weak 5′-splice sites, and facilitating the recruitment of the spliceosome [48]. A paradigm of

importance in autoimmunity is the control over the mRNA encoding the Fas receptor which is present as two alternatively spliced variants containing or lacking the 6th exon. In activated T-cell lines, Fas signals can phosphorylate TIA-1 and TIA-L1 which in turn can promote the inclusion of the 6th exon; this leads to the synthesis of the membrane-bound, pro-apoptotic form of the receptor at the expense of the soluble, anti-apoptotic form that skips this exon [48–50]. Both the nucleolytic functions and their effect upon Fas suggest that TIA-1/TIA-L1 directly could be involved in death programs of importance in inflammation and autoimmunity like e.g. of autoreactive lymphocytes or of stressed tissues which in turn induce inflammation.

Around 2000 however, a novel and most prominent cytoplasmic function as suppressors of mRNA translation was revealed for these RBPs. Upon strong environmental or genotoxic stress TIA-1 and TIA-L1 move to the cytoplasm, self-aggregate, attract translation initiation and form foci of inactive, non-canonical pre-initiation complexes known as Stress Granules (SGs) [51]. SGs are rich in ARE-BPs and neighbor sites of mRNA degradation (like P-bodies) and translation (ribosomes); as such they may act as checkpoints for mRNA to be used or destroyed [52]. In that sense, TIA-1 and TIA-L1 act to limit the translation of certain while allowing the translation of other stress associated transcripts. For TIA-1 this indeed includes mRNAs containing a U-stretch in their 3′UTR [53]; however, TIA-L1 binds to C-rich rather than U-rich [54] suggesting that these two RBPs may have different specificities. This was verified in part by the corresponding genetic mutants of these RBPs. The genetic mutation of TIA-L1 led to developmental phenotype, incapable of revealing its immunological functions. TIA-1 deficient mutants were more revealing and validated the functions of this RBP in the translational silencing of immune mRNAs.

TIA-1-deficient mice are developing normally, yet they appear susceptible to endotoxemia [55], dust-mite induced pulmonary inflammation [56] and develop mild signs of arthritis as they age [57]. These phenotypes correlated with the uncontrollable translation of the mRNAs of TNF and COX2 in activated macrophages; of IL-4 and IL-13 in TCR-activated T-cells [56] and of IL-10 signalers in NK cells [58]. Several pieces of evidence suggest that TIA-1 acts in synergy within RNPs towards translational suppression-as would be predicted via its functions as a stress-granule organizer. The susceptibilities and cytokine distortions observed in TIA-1 mutants are altered in different genetic backgrounds which could connect to genetic variation in RBPs. Moreover, the effect upon cytokine mRNAs varies amongst cell indicating differences in cell-specific RNP components [59]. Finally, the combinatorial loss of both of TIA-1 and TTP indicated their additive roles in arthritis and neutrophil activation [57]; but, macrophages from these mice produce less TNF than either of the single mutants indicating that effects by other RNP controllers may come into effect. Alternatively, these variations may also be due to variations in death programs originally ascribed to be mediated by TIA-1. As it stands, the cellular functions of TIA-1 is response to stress and inflammation are inferred from the analyses of its whole body mutations; as such they remain to be validated via its induced, tissue specific mutations.

3.2. KSRP: connecting miRNA biogenesis to ARE functions

K-homology splicing regulatory protein (KSRP) is a multi-domain single-stranded nucleic acid-binding protein originally identified as a nuclear factor involved in transcription and splicing [60,61]. Subsequently, it was reported that two of its KH domains bind AREs [62], and can promote mRNA degradation by recruitment of poly (A)-specific ribonuclease (PARN) and exonucleolytic enzymes to mRNAs [63,64]. However, a more elaborate function was revealed for this RBP since it can also bind to the terminal loop of immature miRNA and interacts with the Drosha and Dicer ribonuclease complexes to promote maturation of selective miRNAs [65,66]. Finally, KSRP may also have an important function in viral control. As exemplified for enteroviruses, KSRP can recognize viral internal ribosomal entry site (IRES) to inhibit viral translation [67].

Information pertaining to its functions in inflammation is limited but important. KSRP is involved in human myelopoiesis via its control over the maturation miRs acting in differentiation checkpoints like e.g. miR-129. There, high level of KSRP expression leads to granulocyte maturation while lower expression favors differentiation into monocyte [68]. KSRP has been linked to the maturation of miR-155, which affects expression of many immune mRNAs including inflammation. As such, its loss in innate immune cells, embryonic fibroblasts or activated glia enhances pro-inflammatory cytokines and signalers, immunoregulatory mediators and type I interferons suggesting its potential involvement in the response to viral infections and the control of autoinflammatory syndromes [69–73].

However, *in vivo* investigation of the role of KSRP in inflammatory response using the model of inflammatory arthritis displayed opposite results. KSRP deficient mice exhibit reduced sensitivity to collagen type II antibody-induced arthritis associated with a reduction in CXCL-1, iNOS and TNF but an increase in IFNγ; and a reduced infiltration of monocytes and neutrophils [74]. The reason for this discrepancy remains to be determined; but suggests that KSRP may have both positive and negative functions in RNA regulation.

3.3. AUF1: pleiotropic check-points against degeneration

The heterogeneous nuclear ribonucleoprotein D (hnRNP D) is also called AUF1 (AU-rich element binding factor-1) since it was the first identified AREBP [75]. In fact, it is a collection of four proteins, generated by the alternative splicing of a common pre-mRNA which share affinities for AU and U stretches but also for GU-rich elements [76].

Original studies on cellular systems suggested that AUF1 can induce -indirectly- ARE-mediated decay in immune cells for such targets as TNF-a, IL-1β, IL-3, IL-6, IL-10, GM-CSF [77], iNOS [78] and the NFkB activating kinase TAK-1 [79]. To do so, AUF1 may initially form a large multi-subunit complex impeding the translation of target which can in turn lead to their degradation [80]. However, it seems more likely AUF1 engages in a complex with miRNAs. First, AUF1 binds within the coding region the 3' UTR region of the *Dicer* mRNA repressing its expression and function towards miRNA maturation [81]. Importantly, AUF1 can promote the loading miRNA to their targets. Recent evidence suggests that assists loading of miRNAs, like let7-b [82] and other miRNA-binding factors [83] to AGO2, a primary factor of the RISC complex, and to their mRNA targets.

However, there are examples where AUF1 does function solely as a suppressor of mRNAs. An immunological example, involves the IL-8 mRNA which is stabilized by AUF1 [84], for the migration of inflammatory cells.

An extensive functional diversity was revealed for AUF1 in a mouse model of AUF1 whole body genetic deletion. Initially, this mouse model mice suffered from growth retardation and increased susceptibility to endotoxemia correlating with stabilized mRNAs encoding pro-inflammatory cytokines in myeloid cells [85]. Aged mice develop spontaneous chronic dermatitis similar to adult onset psoriasis with elevated TNF, IL-1β and IL-2 from T-cells and macrophages and elevated serum IgE levels [86]. Moreover, AUF1 mutants displayed increased apoptosis of splenic folicular B-cells [87].

Subsequent analyses revealed that these phenotypic distortions could be due to a fundamental defect incurred by AUF1's loss: protection from telomere erosion and senescence. However, it is not via an RNA-mediated mechanism. AUF1 seems able to bind and activate the promoter of Tert, a catalytic subunit of the telomerase, leading to telomere maintenance [88]. In order to maintain telomere length, telomerase assembles a complex comprising of TERT and TERC as well as other components [89]. It remains to be determined whether this is a dominant function across tissue settings; if it holds true then AUF1 loss-of-function mutations can provide the impetus for premature senescence and death to support inflammation and autoimmunity.

Of course this does not preclude AUF1 functions as an AREBP or miRNA loader capable of suppressing mRNA usage. This is exemplified in its analyses for muscle development and control over matrix-metalloproteases like MMP9 which could have implications in the context of inflammatory syndromes like arthritis and cancer. However, it necessitates performing a careful dissection of AUF1's immunocellular functions via conditional genetics.

4. HuR: the all mighty controller

Deductive logic dictates mRNA suppressors -like the AREBPs described above- act against mRNA activators whose chronic function can promote uncontrollable programs and degeneration. It is therefore not surprising that a family of presumed “mRNA activators” -the Elavl/Hu family of RBPs- got so much attention over the years. This family includes the ubiquitously expressed Elavl1; the neuronal Elavl2 & 3; and Elavl4 which is mostly neuronal but also expressed in selective peripheral epithelia. Their name stems from mutations in their unique orthologue in flies which causes Embryonic Lethality and Abnormal Vision. Clinical immunologists identified them independently as four dominant antigens met in paraneoplastic syndromes and named them as Human Antigens (Hu) A-D.

HuR (or Elavl1) represents one of the most studied RNA binding proteins; it is ubiquitously expressed and binds to loosely defined U-stretches [90,91], presumably in the nucleus where it resides in most cells. Historical evidence assumed three main functions for HuR [92,93]. The first is the delivery of its mRNA targets from the nucleus to cytoplasmic locations. This is prominent under conditions of proliferation inflammatory and oncogenic stress and is mediated by a selective set of karyopherins and, in some instances, may require HuR's phosphorylation or methylation [93]. The second is the enhancement of cytoplasmic mRNA stability by competition for binding to its target sites, proximal miRNA binding sites and polyA-tails to protect from exonucleolytic attack [92,94]. The third is the promotion of translation initiation via unclear means which may include an indirect effect in the cycle of eiF2 or of eiF4 [95,96]. Conversely, the level of HuR in the cytoplasm can be limited via its retrograde transport back to nucleus; or via caspase mediated cleavage. The latter has an additional effect - to release some of HuR's protein interactors that are capable to induce apoptosis [93,97–99]. However, holistic approaches revealed the outstanding diversity of HuR's interactions which extends to introns [90,91]; long non-coding RNAs [100–102]; precursors and mature miRNAs [94,103]; and circular RNAs [104]. Finally, HuR has been implicated in RNA editing [105], single-stranded RNA virus replication [106–108], and DNA related processes including DNA methylation [109].

Given, the diversity of its targets and assumed functions, HuR appears as non-discriminatory yet essential to life. Indeed, obligatory mutants of HuR in the mouse manifest defects in several programs of embryonic and extraembryonic development [110,111]. Some of these embryonic defects related to immune development like the lack of a mature spleen and problems in hematopoiesis [110,112]. However, HuR's roles in immunological processes are being unvailed via its tissue specific deletion and/or overexpression.

HuR has been strongly connected to lymphocyte ontogeny and function. Several studies indicated that HuR strongly moves to the cytoplasm and binds its targets upon TCR crosslinking, integrin mediated co-activation or co-stimulatory signaling [113,114]. *In vitro* studies suggested that HuR may be required for the expression of Cd3ζ and thus competent TCRs [115]; for Th2, Th17 and selected regulatory T-cells functions by enhancing the expression of IL-4 [116], IL-13 [117], GM-CSF [118] and CD83 [119]; for T-cell dependent B-cell responses by CD40 signaling [120]; and for activation-induced cell death via its control over the expression of FasL and the splicing of Fas alongside to TIA-1 [121]. Several T-cell restricted mutants of HuR have been employed to validate these data.

The deletion of HuR from the early DN thymocyte stage revealed that HuR controls transition from the DN to the DP pool, optimal positive selection, central tolerance via negative selection; and the translocation of mature $CD4^+$ and $CD8^+$ cells from the thymus to the periphery [122]. Its deletion in late stage thymocytes bypassed the defects in thymopoiesis; however, such mice showed impediments in peripheral $CD4^+$ T-cell activation correlating with defects in Il2ra/CD25 signals and a dosage dependent effect on Gata-3 instructed Th2 differentiation [123,124]. The loss of HuR in activated T-cells also affected Th17 function and homing, due to losses in IL-17 and Ccr6 [125,126]. The involvement of T-cell HuR in autoimmunity was most profoundly exemplified in Experimental Autoimmune Encephalomyelitis (EAE) which models Multiple Sclerosis [126]. T-cell mutants appear resistant to the acute phases of EAE validating HuR's involvement in the elicitation of Th17 reactions.

HuR has dominant roles also in B-cells. Its mutation in B-cells, compromises in part their representation in the bone marrow but mostly eliminates Germinal Center reactions and antibody affinity maturation; this related to the defective splicing of a regulator of mitochondrial metabolism and repression in co-stimulatory signals [127,128].

The functions of HuR in developmental and lymphocytic programs, abide to its functions as a physiological RNA-activator. Moreover, they are in line with studies in stressed non-immune compartments where HuR has a proven role in the regulation of apoptosis, cell cycle control and as driver of cellular transformation. One interesting example involves the intestinal epithelia, where a pathological role for HuR is supported by the clinical connection of its elevation and cytoplasmic translocation to intestinal cancers. These correlated: (a) positively to the degree of transformation, malignancy and tumor angiogenesis; and (b) negatively to the overall survival of patients with rectal and colonic tumor [129–136]. The analyses of mutants devoid of HuR in intestinal epithelia supported its role in tumor promotion, particularly for Familial Adenomatous Polyposis [137] and rendered HuR as a pharmacological target of clinical relevance in intestinal disease and colon cancer [138].

However, its functions in myeloid-derived cells -as revealed by the corresponding mutants- do not abide to this rule. Mice lacking HuR in myeloid cells are highly sensitive to endotoxemia, chemically-induced colitis, ischemic injury and -most intriguingly- colitis associated cancer [139,140]; whereas they are highly capable of clearing bacterial infections like in the case of *Citrobacter Rodentium* [139]. This was compatible with macrophage over-activity associated with the increased translation –and in some cases stability- of several ARE-containing cytokine mRNAs, increased bactericidal, chemotactic and pro-tumorigenic functions. Conversely, mice engineered to overexpress HuR –either in macrophages or in their totality- were rendered as resistant to endotoxemia, colitis, chemically induced colitis, colitis-associated cancer and hepatitis; but have problems in the clearance of bacterial infections [139–141]. Despite the fact that many cytokine mRNAs appeared as stabilized when HuR was augmented, their translation was impaired indicating that HuR has rather a regulatory role towards the pro-inflammatory protein synthesis [140,141]. The application of HuR inhibitors against intestinal inflammation and cancer was most profoundly challenged during pre-clinical testings. In models of familial colorectal cancer, the pharmacologic inhibition of HuR suppressed tumor growth and progression; however, it exacerbated inflammation and tumor progression in Colitis-Associated Cancer [142] validating HuR's bipolar functions in myeloid versus epithelioid tissues.

The case of HuR in myeloid cells constitutes an example of its regulatory functions which phenocopy in part the effects of TTP, TIA-1, AUF1 and KSRP mutations. As such they challenge the idea of it being their antagonist. There are several possibilities to be explored. The first entails that HuR is required to promote the expression of mRNA suppressors since their mRNAs contain AREs. However, there is no clear indication that their levels change in the absence of HuR. However,

considering that HuR is an RBP that participates in RNPs, it may facilitate the sequestration and function of mRNA suppressors. Indeed, several examples of such unorthodox synergies arose in the literature between HuR and TIA-1, AUF1 and non-coding RNAs. However, at a cellular level there is a third explanation: that HuR may arm opposing programs that in turn may be discriminated by means of mRNA suppressors. In macrophages, this may entail a role for HuR in their transition from the pro-inflammatory (M1) state to the immunomodulatory (M2) state. If that holds true, then our view on AREBPs needs to include their functions as determinants of cellular plasticity by adaptation.

5. AREBPs as RNP components-integration of PTR circuitries

In 2002 Maniatis & Reed summed up evidence to suggest that there is extensive coupling between nuclear transcription, maturation, proofing and export and proposed “a model in which the machines are tethered to each other to form ‘gene expression factories' that maximize the efficiency and specificity of each step in gene expression” [143]. In 2007, J.D. Keene re-evaluated initial data stemming from the holistic analyses of RNA:protein interactions to propose that “mRNAs that encode functionally related proteins are coordinately regulated as post-transcriptional RNA operons or regulons, through a ribonucleoprotein-driven mechanism” of importance in immune response, oxidative metabolism, stress response, circadian rhythms and disease [5]. The retrospective analyses of the data on AREs and AREBPs are in full support of both suppositions. It is now clear that there is no sovereignty in the functions of individual AREBPs towards individual RNAs. Rather they relate between them across RNPs which are so remodeled as to provide the necessary “go” or “no go” decisions for clusters of RNAs whose coordinative regulation is required for cellular programing or reprogramming. In immunity this becomes evident upon the overlapping or antagonistic effects of AREBPs in selected cellular settings (Fig. 2) and connects to immune programs for adaptation -via differentiation, plasticity or death- to ever-changing stressful environments.

Based on the above, AREBPs act in necessary checkpoints to tether or exclude coupling of gene expression machines. However, they do not act alone. The variation AREs suggested that they are not a single RSS but rather a collective of different RSS's; and culminated the search for additional RSS's located on RNAs of biomedical relevance besides miRNA binding sites; and provided novel examples of post-transcriptional determination. A defined stem-loop structure, designated as the Consitutive Decay Element (CDE), may also be located in the vicinity of AREs in pro-inflammatory transcripts. CDE is targeted by Zinc-finger containing proteins which -like TTP- promote exonucleolysis (e.g. Roquin 1 & 2); or endonucleolysis (e.g. Regnase 1) [144]. Another stem-loop like RSS was found in mRNA targets of IFNγ and as such was named as the IFNγ-activated inhibitor of translation (GAIT); it causes translational stalling due to its interaction with an unorthodox RNP assembly of factors that are otherwise acting to promote translation initiation [145]. The potential coexistence of AREs with other RSSs provide support to their coordinative decoding by RNP assemblies. Besides their importance in terms of basic biomedical research, the RNP view of post-transcriptional control is expected to impact their use for clinical management and therapy. The same applies for ARE-RNPs.

6. AREs in human morbidities and co-morbidities

The functional studies presented above demonstrate AREs' importance in infectious diseases, chronic autoinflammatory syndromes like (Chrohn's disease, Ulcerative colitis and Dermatitis), autoimmune syndromes (e.g. Rheumatoid Arthritis, Type 1 Diabetes, Multiple Sclerosis and SLE), Allergy and Tumor associated inflammation **(**Fig. 3**)**. Logically, one would expect that mutations or polymorphisms should have been detected in the genetic analyses of patient cohorts with such diseases. However, evidence for their permutation is scarce, probably due to technical constraints or means to identify such mutations as important. The functionality of RSSs depends upon their conformation and not necessarily by their primary sequence. This means that mutations or polymorphisms may also reside in the vicinity of AREs that could have a conformational impact which is not easily “identifiable”. One possibility would be to perform RNA sequencing reactions before and after their resolution by biochemical tricks. Such an approach has been used in AML where SNPs where identified inside on in the vicinity of RSS's found in 3′UTRs and affected their conformations [146].

The genetics of AREBPs appear more promising but is also limited. For example, the implication of TTP in Rheumatoid arthritis led to the identification of single nucleotide polymorphisms (SNP) within the human ZFP36 promoter in Japanese cohorts. RA patients with a GG genotype were reported to be prone to early onset and high disease activity compared to those with AG or AA genotypes having a twofold increase in promoter activity [147]. Arthritis associated SNPs have also been identified in the coding region of TTP in African-American cohorts [148]. Mutations for AUF1 were identified in Crohn's disease via whole exome sequencing of biopsies and blood from monozygotic twins. A stop gain mutation and a single missense mutation were identified as risk polymorphisms that contribute to Crohn's disease and Inflammatory Bowel diseases [149].

However, peripheral data suggest that AREBPs may function aberrantly in autoimmune and auto-inflammatory syndromes. For example, autoantibodies against TIA-1, AUF1 and HuR have been found in high prevalence in patient's sera of Rheumatoid Arthritis and other Rheumatic diseases such as SLE, Mixed Connective Tissue Disease and Discoid Lupus Erythematosus [150–152]. This could connect with high expression profiles of AREBPs as in the case of several Cancers. For example, during the initial phases of type I diabetes, AUF1 expression increases and connects to the apoptotic loss of pancreatic beta cells [153].

Several reports explored the effects of disease modifying drugs upon RBPs. For example, the TNF antagonist Infliximab alters the representation of TTP and TIA-1 relative to TNF and HuR in PBMCs from responding patients of arthritis but did not do so in non-responders providing a novel discriminative biomarker [150]. The efficacy of B-cell depleting, anti-CD20 antibody Rituximab -given as a replacement therapy in RA when TNF antagonist fail- correlates with a HuR mediated effect upon type I IFNs [154,155]. Finally, the action of aurothiomalate as a suppressor of COX2 in rheumatic diseases connects to its suppressive effect upon the expression of HuR [156].

The wealth of functional data on AREBPs and their capability to affect a range of response-specific RNAs propelled the search for their pharmacological exploitation by single agents affecting a combination of parameters promoting pathological inflammation and autoimmunity. To date, RNA interference-based oligonucleotides or small molecule inhibitors have been screened based on reduced RBP-RNA interaction and changed level of target RNAs. For example, antisense-oligonucleotides to HuR showed promising efficacy in a preclinical model of relapsing-remitting EAE [157]. Similarly, several lead compounds have been identified to data that can affect HuR binding or localization; and show promise as anti-cancer agents-hopefully to be extended to inflammatory syndromes [138]. AUF1 has also been administered via an immunoliposome approach in endothelial cells to inhibit their senescence during aging [158].

However, the differential effect of HuR inhibitors in Familial versus Inflammatory colorectal carcinogenesis shows the potential caveat but also the opportunity of *anti*-AREBP therapies. The problem lies on the erroneous consideration of AREBPs as autonomous mRNA activators or suppressors. Their view as components of RNPs integrating several post-transcriptional events whose specificity emerges by means of their holistic composition -and not by the presence of one RBP- necessitates the development of strategies of targeting “RNPs” and not RBPs. This in turn requires a cell and signal specific view of RNPs -which we are currently lacking. However, the tools are out there.

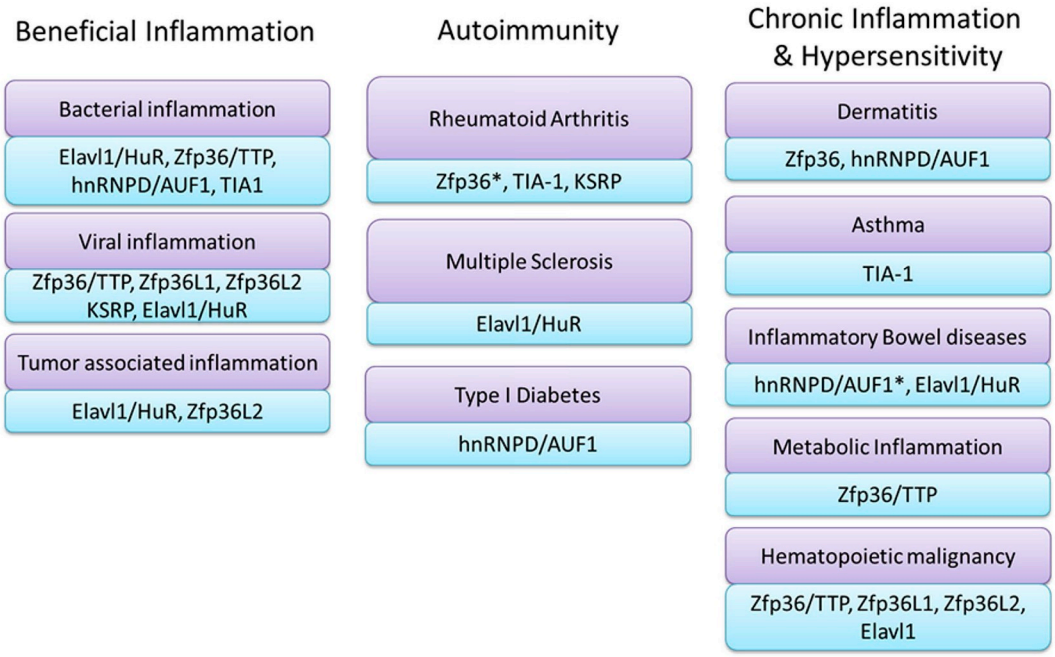

Fig. 3. Involvement of AREBP function and dysfunction in beneficial inflammation, autoimmunity and chronic inflammatory pathologies, based mostly on data from animal models. Shown are simplified annotations (purple) of beneficial inflammatory responses as well as diseases associated with pathological inflammation and the collections of AREBPs (cyan) that connect to those via their function or dysfunction. (*) denote associations derived from human clinical data. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

7. Concluding lessons

From their identification as elements residing in cytokine 3′UTRs to their current view as RRSs connecting a world of cellular events, AREs provided the most definitive example of cellular determination via post-transcriptional check-points. Their extensive heterogeneity and distribution amongst RNAs of immunological relevance and the multi-faceted behavior of their cognitive RBPs are indicative of the evolutionary forces which shaped up the highly complex and sophisticated ARE-interactome. As it is indicative from the functional studies, the disturbance in the factors associated with AREs can support pathological inflammation and autoimmunity via various means. However, researchers need to consider an RNP view of post-transcriptional phenomena where AREs are part of a wider collection of co-existing RSS's; which are decoded by an ever-changing environment of RBP inclusion or exclusion. This requires a shift in our views on immune-modulating therapies based on factors that recognize these RSS and necessitate the exploitation of combinatorial RNPs and not individual RBP. Currently, knowledge on the mechanics of such combinatorial regulation at the biological complexity of the organisms is minimal. Holistic mapping of *cis*-elements and *trans*-binding sites demonstrates huge regulatory potentials of post-transcriptional controllers in inflammation. The more details we learn about cross-talk, molecular assembly, and compartmentalization of RNA-protein complexes in true biological settings, the closer we can get in novel therapeutics.

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