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Chapter 23

Role of CREB Protein Family Members in Human Haematological Malignancies

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1. Introduction

Cyclic AMP Response Element Binding (CREB) protein is a member of the CREB/ATF (Activating Transcription Factor) family of transcription factors playing an important role in the nuclear responses to a variety of external signals that lead to proliferation, differentiation, apoptosis and survival. Other authors' evidences have highlighted a critical role of CREB in the regulation of normal haematopoiesis and leukemogenesis due to the interaction with target genes crucially involved in the cell cycle machinery. Recent findings of our research group have demonstrated that CREB and ATF-1 phosphorylation levels are related to a different sensitivity of T leukaemia cell clones to the cytotoxic action of TNF-related apoptosis inducing ligand (TRAIL) and that low dose radiation treatment of erythroleukaemia cells (K562) can trigger CREB activation and deliver a survival signal. Since one fundamental problem of most malignancies, including those of haematological origin, is the development of multiple mechanisms of resistance, which progressively reduce or suppress the therapeutic efficacy of anticancer treatment, the early identification of biological markers of responsiveness/unresponsiveness and the follow-up of individual response are highly desirable to adjust therapeutic treatments. In light of all these considerations and of the complex molecular interactions involving CREB/ATF family members, the present chapter is aimed at revising literature focusing, in particular, on the involvement of CREB/ATF family members in leukemogenesis and lymphomagenesis, in order to gain more insight into this matter that could result useful to the treatment of leukaemia and lymphoma diseases.

2. CREB family members

The CREB or CREB/ATF multigenic family is composed by several nuclear transcription factors. The prototype of this family is CREB, a 43 kDa – basic-region leucine zipper (bZIP)

transcription factor that elicits responses to a variety of extracellular signals, including stress and growth factors, and that is involved in several cellular processes such as glucose homeostasis, proliferation, ageing and differentiation, survival and apoptosis, memory and learning [1]. The CREB/ATF family of transcription factors includes three homologous genes: cAMP response element binding (*CREB)*, cAMP response element modulator (*CREM*), and activating transcription factor-1 (*ATF-1*), whose structure domains are illustrated in a recent review [2]. These genes generate a group of highly homologous proteins that have been named after their prototypes: CREB, CREM, and ATF-1, respectively [3].

CREB/ATF proteins were initially identified for their binding to the cyclic AMP response element (CRE) in various gene promoters that contain the octanucleotide consensus sequence TGACGTCA [4]. Over the years, cDNA clones encoding identical or homologous proteins have been isolated. Up to now, at least 20 different mammalian proteins with the prefix CREB or ATF have been characterized and grouped into subgroups on the basis of their amino acid similarity [5, 6]. CREB/ATF family members include CREB-1 (also known as CREB), CREB-2 (recently named ATF-4), CREB-3, CREB-5, CREM, ATF-1 (also known as TREB36), ATF-2 (also known as CRE-BP1), ATF-3, ATF-4 (previously named CREB-2), ATF-5 (also known as ATFX), ATF-6, ATF-7 and B-ATF subgroups [7, 8]. Proteins belonging to this class represent a large group of bZIP transcription factors containing highly divergent N-terminal domains, but sharing a C-terminal leucine zipper domain. The basic region in the bZIP domain is rich in basic amino acids and is responsible for specific DNA binding, while the leucine zipper region contains leucine residues and is responsible for dimerization of the proteins by resembling a zipper. Based on the sequence of each bZip domain, these proteins form homodimers or heterodimers both with other members of the family and with other bZIP containing proteins like the activator protein-1 (AP-1), C/EBP, Fos, Jun or Maf family proteins [8]. That implies the expansion of the repertoire and different opportunities of target gene regulation that are further increased by the alternative splice products of *CREB* and *CREM* genes that show repressor or activator properties [5, 7]. Whereas CREB, CREM, and ATF-1 are relatively well characterized and known to regulate gene transcription via binding to CRE sites, ATF-2, ATF-3, and ATF-4 are structurally more distant and their functional properties remain poorly understood. Rather than being activated by the cAMP cascade, ATF-2 is activated by c-Jun N-terminal kinase (JNK) and can dimerize with members of the AP-1 family such as c-Jun to bind to CRE or AP-1 sites [9, 10]. Additionally, ATF-2 homodimers and ATF-2/c-Jun heterodimers can bind to certain CRE-like sites that are insensitive to CREB [11]. ATF-3 and ATF-4 also dimerize with various Jun species and can shift c-Jun DNA binding site preferences from AP-1 to CRE, thereby promoting crosstalk among AP-1 and CREB protein families [9]. In addition, ATF-4 is able to dimerize with Nrf1 (NF-E2 related factor 1) and Nrf2 (NF-E2 related factor 2) and then interact with the antioxidant responsive element (ARE) present in the promoters of many antioxidant genes [12]. ATF-2, ATF-3, and ATF-4 have been considered as cellular stress response proteins [5, 13, 14] but recently they have been also involved in non-stress adaptations. In fact, extensive studies have demonstrated that ATF-3 is an adaptive response gene that is activated by a wide variety of signals including those initiated by cytokines, genotoxic agents or physiological stresses [15]. Interestingly, unlike other ATF family members, emerging evidences have implicated ATF-3 in the host defence against invading pathogens and cancer. These processes are controlled by the efficient coordination of cell responses and genetic regulatory networks which allow this key transcription factor to modulate the

expression of a diverse set of target genes, depending on the cell type and/or the nature of the stimuli [16, 17].

While both CREBs and ATF-1 are ubiquitously expressed, CREMs are mainly present in spermatids [6] and in the neuroendocrine system [18]. Interestingly, a recently published paper on the effects of traumatic brain injury demonstrated the nuclear co-localization of CREM-1 and active caspase-3 in the ispilateral cortex of adult rats, suggesting a possible role for CREM-1 in neuronal apoptosis [19]. In a recent report of our research group on Jurkat leukaemia cells [20], we observed a different cell compartmentalization of CREB protein in dependence of the TRAIL dose employed and induced cytotoxicity. Indeed, both under normal or low serum culture conditions an evident nuclear translocation of phospho-CREB was detected after 1 h treatment only with the lower dose of TRAIL (100 ng/mL) and prevented in the presence of PI3K/Akt and p38 mitogen-activated protein kinase (MAPK) specific inhibitors [20]. In another model under investigation in our laboratories and represented by K562 erythroleukaemia cells induced to differentiation [21], the nuclear localization of the active form of CREB was clearly evident after only 1 h treatment with haemin. Interestingly, CREB positive nuclei resembled the features of apoptotic nuclei, suggesting that CREB phosphorylation is possibly required to determine the nuclear structural changes occurring during erythroblast maturation [21, 22]. Concerning other family members, it has been recently shown that ATF-2 is a nucleocytoplasmic shuttling protein and that its subcellular localization is regulated by AP-1 dimerization [23]. ATF-3 is ubiquitously expressed and localized in the nucleus but maintained at low levels in the absence of cellular stresses. Instead, it is rapidly transcriptionally induced under different conditions, among which hypoxia, DNA damage (induced by UV radiation, ionizing radiation, etoposide), heat or cold shock, serum starvation or stimulation [13, 15]. ATF-4 is of particular interest since it has been demonstrated to translocate from the cytoplasmic membrane to the nucleus in neuronal cells upon γ aminobutyric acid (GABA) receptor activation, to be likely involved in neuronal plasticity by coupling receptor activity to gene expression [24]. Finally, a number of immunofluorescent and cell fractionation experiments indicate that ATF-6 is linked to the endoplasmic reticulum (ER) chaperone Bip/Crp78 and localizes in the precursor form on the ER membrane [25]. Upon ER stress induced by prolonged nutrient deprivation, it translocates to the Golgi where it is cleaved by resident proteases to liberate its active N-terminal domain. In this active form it translocates to the nucleus where it up-regulates a number of target genes involved in energy homeostasis [25].

3. CREB binding proteins

The human CREB-binding protein (CBP) and its paralogue, p300, are highly related proteins that are well conserved amongst mammals. Due to their high degree of sequence similarity, these two proteins are most often functionally interchangeable although they also possess unique functions [26, 27]. CBP was initially recognized as an interaction partner for CREB nuclear transcription factor [28], whereas p300 cDNA was cloned encoding the 300 kDa protein known to be associated with the adenoviral protein E1A [29]. Though encoded by different genes, CBP/p300 share several conserved regions that constitute most of their known functional domains [for details see 27]. Both CBP and p300 have originally been described as transcriptional co-activators that bridge DNA-binding transcription factors to components of

the basal transcriptional machinery, including the TATA-box-binding protein (TBP) [30], TFIIB [31] and, via RNA helicase A, also RNA polymerase II [32]. Due to the huge size of over 2400 amino acids, CBP/p300 can also behave as a scaffold, bridging together a variety of cofactor proteins at the same time and leading to the assembly of multi-competent co-activator complexes [26, 27]. In addition, CBP/p300 interact with protein kinases such as the MAPKs and the cyclin E-Cdk2 complex, thus mediating the phosphorylation of CBP/p300-interacting transcription factors such as ER81 and E2F family members. Both CBP and p300 have been found originally to possess histone acetyltransferase (HAT) activity [33]. This acetyltransferase function has profound consequences for nucleosomal structure and the activity of transcription factors, and thereby affects gene activity in multiple ways. In fact, it is well known that acetylation of multiple sites in the histone tails has been directly associated with transcriptional up-regulation, whereas de-acetylation correlates with transcriptional repression. Mechanistically, histone acetylation promotes the accessibility of DNA to transcription protein complexes, by facilitating the "unwiring" of the chromatin structure. During the last years, both CBP and p300 have been regarded as protein acetyltransferases rather than only HAT since they have shown the capacity to acetylate a number of non-histone nuclear proteins, including the tumour suppressor protein p53, dTCF, EKLF (erythroid Kruppel-like factor), GATA-1, NF-Y and other basal transcription factors [34, 35]. Thus, in light of the number of proteins interacting with CBP/p300, it is not surprising to find that many physiological processes, including cell growth, cell division, cell differentiation, cell transformation, embryogenesis and apoptosis, are dependent on CBP/p300 function [27, 28, 34]. Moreover, the importance of CBP/p300 is underscored by the fact that genetic alterations as well as their functional dysregulation are strongly linked to human diseases [36, 37].

Previous studies have shown that CBP and p300 play distinct roles in haematopoiesis and act non-redundantly in microenvironment-mediated haematopoietic regulation in spite of their high homology [38-40]. It has been widely documented that both proteins interact with crucial transcriptional regulators in virtually all haematopoietic lineages. Intriguingly, CBP/p300 can promote, on one hand, normal differentiation and cell cycle arrest (by cooperating with GATA-1) and, on the other hand, cell cycle progression and transformation by cooperating with c-Myb and PU.1, an Ets family transcription factor. It is conceivable that an overexpressed oncoprotein might compete with differentiation-inducing factors for CBP/p300 function. Furthermore, during normal development, CBP/p300 could differentially partition among transcriptional regulators with opposing functions, thus controlling the balance between proliferation and differentiation. As an example, the down-modulation of the proto-oncoproteins PU.1 and c-Myb during the erythroleukaemia MEL cell line maturation might increase availability of CBP/p300 for differentiation-associated factors such as GATA-1, NF-E2 and EKLF. Moreover, besides the involvement in erythroid cell lineage differentiation, CBP and, very likely, p300 target a broad range of myeloid and lymphoid expressed transcription factors [38-40].

Because of its central role in transcription, it is not surprising that aberrations in *CREBBP* can affect many tissues [17]. In humans, chromosomal translocations involving the *CREBBP* gene have been observed in leukaemia and myelodysplastic syndrome [38]. Mutations of *CREBBP* in the germline have been associated to the Rubinstein-Taybi syndrome (RTS), an autosomal dominant disease characterized by mental retardation, skeletal abnormalities and a high

propensity to develop cancer, including leukaemia [36]. Similarly, *CREBBP*(+/-) mice show abnormalities in bone, haematopoietic tissues and neural tissues and an increased tendency to develop haematological malignancies with age [41]. In earlier studies, in *CREBBP*(+/-) HSCs (haematopoietic stem cells) a number of cell-intrinsic defects have been described, including diminished HSC self-renewal and excessive myeloid differentiation [42]. The combination of skeletal and haematopoietic defects in *CREBBP*(+/-) mice suggests the involvement of the bone marrow (BM) microenvironment in the haematopoietic phenotype of these mice. One of the genes whose transcription is directly regulated by CBP is matrix metalloproteinase 9 (MMP9) that was reported to be a microenvironmental regulator of haematopoiesis [43]. Interestingly, *CREBBP* heterozygosity in the BM microenvironment results in reduced levels of MMP9 and soluble kit ligand (KITL) and increased expression of endothelial cell adhesion molecule 1 (ESAM1) and cadherin 5 (CDH5) on a subset of endothelial cells. In addition, it has been reported that the loss of a single *CREBBP* allele is deleterious for the BM microenvironment, leading to defective haematopoiesis. In fact, the *CREBBP*(+/-) microenvironment poorly supports HSCs, promotes excessive myelopoiesis and reduces lymphopoiesis. Furthermore, it has been reported that *CREBBP*(+/-) mice have reduced bone volume due to increased osteoclastogenesis. A concomitant reduction in CFU-fibroblasts (CFU-Fs) and osteoblasts per tissue area was also identified and likely contributes to fewer HSC niches [41]. Thus, all these findings reveal the importance of CBP in the development and function of the BM microenvironment and underscore the multiple levels at which this protein acts to regulate haematopoiesis. Indeed, half of the normal complement of *CREBBP*, but not of *EP300*, in the BM microenvironment has a deleterious effect on haematopoiesis via multiple mechanisms, leading to the development of excessive myelopoiesis, disrupting the proper architecture of the BM and resulting in poor maintenance of HSC number and quality.

4. CREB physiological roles and signalling pathways

CREB is a multi-functional transcriptional activator that is involved in many signalling pathways under normal and pathologic conditions. CREB mediates its transcriptional responses following phosphorylation at Ser133 [7] and the consequent association with the 256 kDa co-activator CBP [28] or related family members like p300 [29]. Both Ser133 phosphorylation and CBP association play an essential role for gene transactivation mediated by an octanucleotide CRE consensus sequence placed in the promoters of many cellular genes [29]. In more detail, CREB transactivation domain, that is the site able to interact with other nuclear factors, contains a constitutive glutamine rich domain termed Q2 and an inducible domain, termed the kinase-inducible domain (KID), regulated by cellular kinases [2]. The Q2 domain interacts with a TATA binding protein-associated factor and is constitutively active; instead, the KID region promotes isomerization by recruiting the co-activator factors CBP and p300 to the gene promoters and is active only when it is phosphorylated at Ser133 by a variety of cellular kinases. Recent studies using a genome-wide analysis showed that the number of putative target genes for CREB is about 5000, among which immediate-early genes, including *c-FOS*, *AP-1*/*JunB* and early growth response protein 1 (*EGR-1*) [44], as well as genes crucially

involved in the cell cycle machinery, namely *Cyclin A1* and *D1* [7]. In this respect, it has been found that Cyclin A is up-regulated in cell lines, transgenic mice and patient bone marrow that show increased CREB levels [44]. It is still to unravel whether this occurs through a direct or indirect mechanism. To address this issue or, in other words, to determine whether CREB overexpression results in target gene activation through increased occupancy of binding sites or by altering levels of Ser133 phosphorylation, several authors proposed to use chromatin immunoprecipitation assays. Moreover, microarray analysis of potential CREB target genes will help in understanding the downstream pathways through which CREB contributes to normal and aberrant haematopoiesis. By interacting with its huge number of target genes CREB plays a critical role in the regulation of various biological processes including haematopoiesis, liver gluconeogenesis, pituitary gland physiology, circadian rhythm, spermatogenesis, learning and memory [1, 45, 46]. Concerning haematopoiesis, CREB is a downstream target of haematopoietic growth factor signalling activated by granulocyte-macrophage–colony stimulating factor (GM-CSF) and interleukin-3 (IL-3), thus resulting a crucial factor for normal myelopoiesis [44]. In addition, it appears to play a role in primary erythroblast differentiation [47] as well as in megacaryocyte differentiation where it is activated in a MAPK-dependent manner [48]. More recently, it has also been involved in HSC and uncommitted progenitor proliferation and survival through its effects on cell cycle control [45, 46]. A growing body of evidences is unravelling the role of CREB in the regulation of the immune system [49]. Indeed, several immune-related genes contain a cAMP responsive element, as in the case of IL-2, IL-6, IL-10 and TNF-α. In monocytes and macrophages CREB exerts anti-apoptotic survival effects. Moreover, CREB promotes normal B and T cell survival and proliferation when it is phosphorylated in response to signalling by the B-cell receptor or different kinases [49]. Particularly well characterized is the regulatory role that CREB plays in the nervous system. Actually, numerous papers have demonstrated CREB involvement in promoting neuronal survival, precursor proliferation, neurite outgrowth and neuronal differentiation in certain neuronal populations [50], highlighting the importance of CREB signalling in learning and memory processes in several organisms [2, 51].

In the late 1980s, it was discovered that cAMP mediates the hormonal stimulation of several cellular processes by regulating the phosphorylation of critical proteins among which CREB transcription factor [52]. Although it was initially identified as a target of the cAMP signalling pathway, studies on activation of immediate-early genes revealed that CREB is a substrate for kinases other than cAMP-dependent protein kinase A (PKA) and that various signalling routes converge on CREB and CREM, controlling their function by modulating their phosphorylation states [52, 53]. As above mentioned, almost all the signalling pathways that activate CREB lead to the phosphorylation of Ser133, which is required for CREB-induced gene transcription, but additional sites on CREB or on linked proteins can be phosphorylated exerting a modulation of CREB activity [35]. For example, Ser133 phosphorylation primes CREB for phosphorylation by Glycogen synthase kinase 3 (GSK-3) at Ser129. However, unlike Ser133 phosphorylation, the physiologic consequences of Ser129 phosphorylation are not well defined, although evidence suggests that it is also linked to CREB activation [54]. In different systems a number of different kinases have been shown to stimulate CREB phosphorylation and several CREB kinase candidates have been identified so far. PKA, which is activated by cAMP, is the major

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kinase that targets Ser133 in many processes [1, 3]. Other signalling molecules responsible for CREB Ser133 phosphorylation include mitogen- and stress-activated kinase 1 (MSK-1), extracellular signal-regulated kinase (ERK), calcium/calmodulin-dependent kinases (CaMKs), p90 ribosomal S6 kinase (RSK), MAPKs and Akt/protein kinase B (PKB) [1, 3, 7, 55, 56]. Both MAPK and Akt have been shown to enhance the survival of cultured cells by stimulating CREB-dependent target gene expression [56]. CREB activity is also regulated by a family of cytoplasmic co-activators known as transducers of regulated CREB activity (TORCs) and including TORC1, TORC2 and TORC3. TORCs are activated by extracellular stimuli represented by nutrients (glucose) and hormones. Once activated, they translocate into the nucleus where they bind to the bZIP domain of CREB exerting its activation through a phospho-Ser133-independent mechanism. All TORCs are regarded as strong activators of CREB-dependent transcription [57].

In Fig. 1 the main factors and signalling molecules leading to CREB activation in haematopoietic cells are schematically represented.

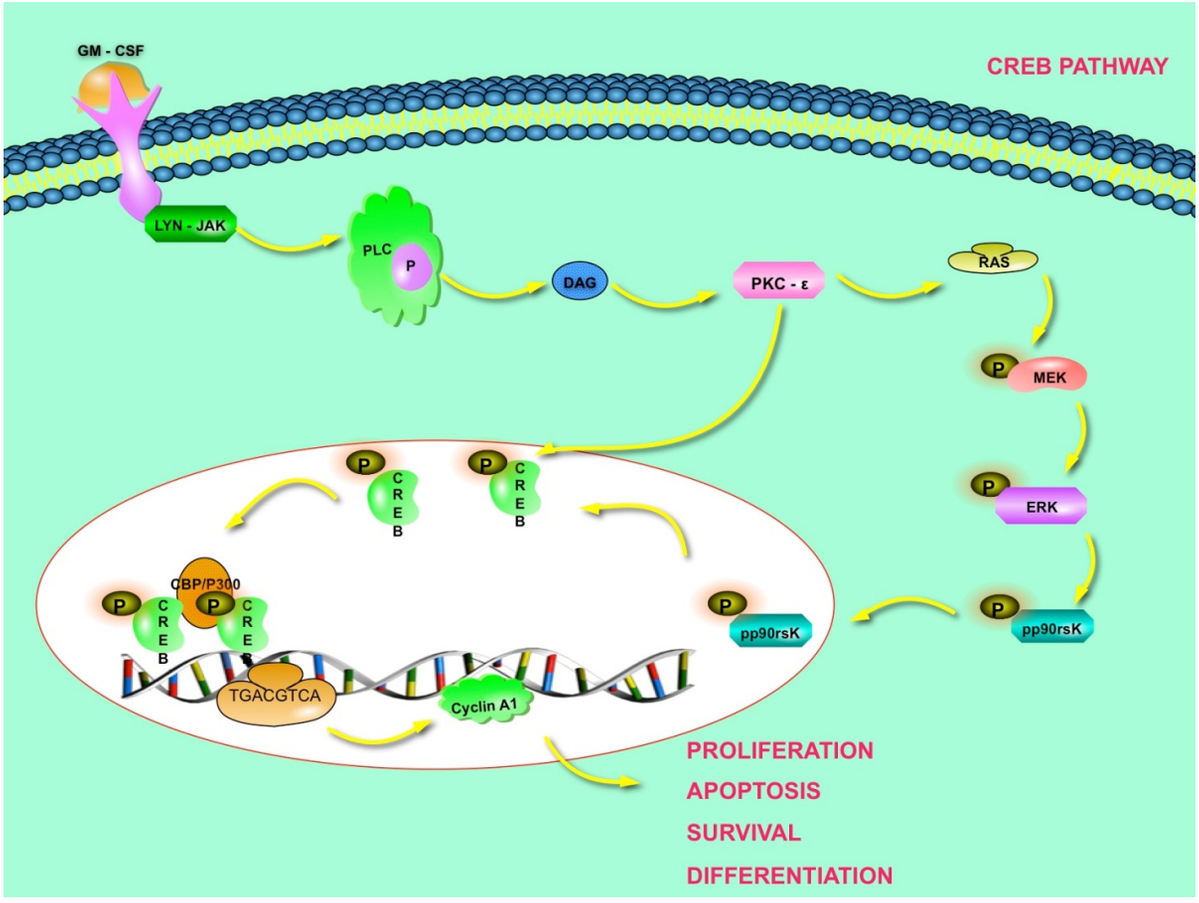

Figure 1. Schematic representation of the main factors and signalling molecules leading to CREB activation in haematopoietic cells. A various array of extracellular stimuli promote CREB activation through phosphorylation or through interaction with CREB co-activators to enhance the expression of CREB responsive genes. CREB target genes, including Cyclin A1, are able to mediate effects on cellular proliferation, apoptosis, survival and differentiation. PLC: phospholipase-C; DAG: 1,2-diacylglycerol; PKC-ε: protein kinase C-ε.

5. CREB family members and leukemogenesis

Recent data suggest that CREB acts as a proto-oncogene in haematopoietic cells and contributes to the leukaemia phenotype [37, 38, 45, 46]. It has been shown anyway that CREB is able to promote tumour formation only when other oncogenes are also activated. In fact, its overexpression is not sufficient to induce acute leukaemia *in vivo*. This is consistent with similar observations obtained with translocations, such as AML1-ETO (Acute Myeloid Leukaemia Eight-Twenty-One), a chimeric protein that requires additional mutations to develop leukaemia in mouse models [58]. In previous works different strategies have been delineated to identify the oncogenes cooperating with CREB to drive leukemogenesis: one way is represented by crossing different transgenic mice of known oncogenes such as *K-RAS*, *MEIS 1*, *PML/RARα* etc. to *CREB* transgenic mice; another approach consists in infecting *CREB* transgenics with a retrovirus such as the Molony murine leukaemia virus to insertionally activate cooperating oncogenes. The latter approach has also the potential to identify novel collaborators of CREB besides the already known CBP and p300. Identifying novel oncogenic alterations that cause leukaemia and discovering the signalling pathways involved will be of great value to gain a better knowledge of the disease and to lead to novel and more efficient therapeutic measures.

Several CREB family members have been implicated in different malignant conditions. The first malignancy to be discovered was the clear cell sarcoma of the soft tissue (CSST). In this solid tumour, the cells are induced to proliferation by an Ewing's Sarcoma (EWS)-ATF-1 fusion oncoprotein derived by a chromosomal translocation that fuses the DNA-binding and bZip domain of ATF-1 to the EWS gene. In haematological malignancies, CREB has been implicated in the pathogenesis of human T lymphotropic virus I (HTLV-I) related T-cell leukaemia [59] and also associated with the genesis of follicular lymphoma, where CREB binds to the CRE site in the promoter of translocated Bcl-2 [46]. Other leukaemia-associated chromosomal translocations involving the CBP and p300 genes were also linked to haematological malignancies. These translocations generally result in fusion products that preserve most of the CBP and p300 molecules, suggesting that the disease mechanism does not simply involve loss of function of CBP, as is the case in Rubinstein-Taybi syndrome, but often implies an altered cofactor function (dominant positive or dominant negative) through fusion to another molecule. The most frequent chromosomal translocations targeting *CREBBP* and *EP300* have been described in specific subtypes of myeloid leukaemia and are represented by Mixed-Lineage Leukaemia 1 (*MLL)-EP300*, *MLL-CREBBP*, *MOZ-CREBBP* and *MOZ-EP300* [37, 60]. Interestingly, most translocations involving CREB-related genes result in leukaemia of the myeloid/monocytic lineage, highlighting the importance of CREB and CREB-interacting proteins in the regulation of haematopoietic cell differentiation and proliferation [45, 46]. Actually, previous work demonstrated that bone marrow cells from patients with acute myeloid or lymphoid leukaemia expressed higher levels of CREB compared to patients not affected by leukaemia or with normal bone marrow [60]. Moreover, it appears that an elevated CREB expression is associated with an increased risk of relapse or persistent disease and decreased event-free survival [45]. This is consistent with the observation that leukaemia cell lines

expressing CREB at elevated levels show an increased growth/proliferation rate in normal conditions and an increased survival when exposed to stress like serum starvation [61]. On the contrary, down-regulation of endogenous CREB in leukaemia cell lines by siRNA resulted in reduced cell viability [20, 45], indicating that CREB is a critical regulator of growth and survival in both myeloid and lymphoid leukaemia cells. Unfortunately, chromosomal translocations have also been involved in drug-induced leukaemia. For instance, the involvement of 11q23-balanced translocations in acute leukaemia after treatment with drugs that inhibit the function of DNA topoisomerase II (topo II) is being recognized with increasing frequency. It has been shown that the gene at 11q23, involved in all of these treatment-related leukaemias, is *MLL* (also called ALL1, Htrx, and HRX). In general, the translocations occurring in these leukaemias are the same as those occurring in *de novo* leukaemia [eg. t(9;11), t(11;19), and t(4;11)]. Interestingly, the t(11;16)(q23;p13.3) has been cloned and has been shown to involve both *MLL* and *CREBBP* [62]. Besides chromosomal translocations, another way for CREB to contribute to tumorigenesis is through the suppression of cellular genes either by competing with or binding to sites occupied by other transcription factors or by confiscating the transcriptional machinery [63].

5.1. Acute myeloid leukaemia

Acute leukaemia derives from the clonal expansion of haematopoietic stem/progenitor cells that have lost their ability to undergo terminal differentiation. Since transcription factors control HSC production and differentiation, it is conceivable that disorders of the haematopoietic system often involve alterations of the regulatory network of transcription factors. In haematological malignancies transcription factors can be overexpressed, involved in chromosomal translocations or become targets of somatic mutations that disrupt their normal function [37, 60-63]. Previous studies have demonstrated that *CREB* is a proto-oncogene whose overexpression promotes cellular proliferation in haematopoietic cells [1, 3]. The abnormal proliferation and survival of myeloid cells *in vitro* and *in vivo* appears to be due to the up-regulation of CREB target genes such as *Cyclin A1* [60, 63]. Transgenic mice that overexpress CREB in myeloid cells develop a myeloproliferative disease with splenomegaly and aberrant myelopoiesis. However, CREB overexpressing mice do not spontaneously develop acute myeloid leukaemia (AML) [61]. To identify genes that accelerate leukaemia in CREB transgenic mice retroviral insertional mutagenesis has been used. The mutagenesis screen identified several integration sites, including oncogenes *Gfi1*, *Myb*, and *Ras*. Among transcription factors, *Sox4* was identified with the screen as a gene that cooperates with *CREB* in myeloid leukemogenesis by contributing to increased proliferation of haematopoietic progenitor cells [64]. Moreover, chromatin immunoprecipitation assays have demonstrated that *CREB* is a direct target of *Sox4*. In fact, it has been shown that the transduction of *CREB* transgenic mouse bone marrow cells with a Sox4 retrovirus increases survival and self-renewal of cells *in vitro* and results in increased expression of CREB target genes. Consistently, leukaemia blasts from the majority of AML patients have higher levels of CREB, phospho-CREB, and Sox4 protein expression in the bone marrow [64]. The increase in both CREB protein and mRNA levels in primary AML cells is possibly due to *CREB* gene amplification in the blast cells. Furthermore, a higher level of CREB has been found to correlate with a less favourable prognosis and an

increased risk of relapse and decreased event-free survival in a small cohort of AML patients [45, 61]. Generally, AML in adults has a 20% five-year disease free survival despite treatment with aggressive cytotoxic chemotherapy and two thirds of AML patients do not experience significant periods of remission. Therefore, in light of its important role in the pathogenesis of leukaemia, CREB has been indicated as a potential prognostic marker of disease progression in AML and a molecular target for future treatment of leukaemia.

Clinical and experimental findings underline that AML is induced by numerous functionally cooperating genetic alterations, including chromosomal translocations that lead to the expression of fusion proteins often behaving as aberrant transcription factors. Several AML-associated lesions target chromatin regulators like histone methyltransferases or histone acetyltransferases, including MLL1 or CBP/p300 [65]. As already mentioned, CBP is an adapter protein that is involved in regulating transcription and histone acetylation, through which it is thought to contribute to an increased level of gene expression. The *CBP* gene was recently identified as a partner gene in the t(8;16) that occurs in *de novo* acute myelomonocytic leukaemia (AML-M4) and rarely in treatment-related AML [66]. The fusion gene could alter the CBP protein so that it becomes constitutively active or, alternatively, it could modify the chromatin-association functions of *MLL* gene [38, 40]. *MLL* and *HOXB4*, a member of the homeobox domain transcription factors, have been identified as regulators of HSC maturation during early haematopoiesis [67]. *HOXB4* belongs to the *HOX* genes, a family of oncogenes implicated in the pathogenesis of various human cancers and highly expressed in the majority of AML. In a recent report Wang et al. [54] demonstrated the association of CREB and its co-activators TORC and CBP with homeodomain protein MEIS1, a HOX DNA-binding cofactor and critical downstream mediator of the *MLL* oncogenic program. This MEIS-CREB nexus is regulated by GSK-3, a multi-functional serine/threonine kinase that impairs the proliferation and induces the differentiation of a variety of cancers, including leukaemias, induced by *MLL* oncogenes. This kinase mediates CREB activation through phosphorylation at Ser129. In fact, CREB Ser129 mutation antagonizes *HOX*/*MEIS* activity and decreases colony-forming abilities of *HOX*/*MEIS* or *MLL* transformed cells. These and other similar observations provide a molecular rationale for targeting *HOX*-associated transcription through GSK-3 inhibition in a subset of leukaemias.

Myelodysplastic syndromes (MDS) include a heterogeneous group of clonal haematopoietic stem cell malignancies with significant morbidity and high mortality. The incidence of MDS increases markedly with age and the disease is most prevalent in individuals who are white and male. Because of an ageing population and an improving awareness of the disease, the documented disease burden is expected to worsen in the near future. Due to the poor survival of individuals with MDS, it is important to identify prognostic factors to better risk-stratify patients for more effective treatments [68]. Genomic instability is associated with progression of the disease so that a part of patients develops AML. It has been reported that an increased incidence of haematological malignancies occurs in *CREBBP* heterozygous mice and other authors have shown that *CREBBP* is one of the genes altered by chromosomal translocations in patients suffering from therapy-related myelodysplastic syndrome [69]. Moreover, it has been demonstrated that *CREBBP*(+/-) mice invariably develop myelodysplastic/myeloproli-

ferative neoplasm within 9-12 months of age. They are also hypersensitive to ionizing radiation and show a marked decrease in poly(ADP-ribose) polymerase-1 activity after irradiation. In addition, protein levels of XRCC1 (X-ray repair complementing defective repair in Chinese hamster cells 1) and APEX1 (APEX nuclease), key components of base excision repair machinery, are reduced in un-irradiated *CREBBP*(+/-) cells or upon targeted knockdown of *CREBBP* levels. These results provide validation of a new myelodysplastic/myeloproliferative neoplasm mouse model and, more importantly, point at a defective repair of DNA damage as a contributing factor to the pathogenesis of this currently incurable disease [46].

5.2. Acute lymphoblastic leukaemia

Acute lymphoblastic leukaemia (ALL) is a heterogeneous disease characterized by the predominance of immature haematopoietic cells, in which malignant cells express phenotypes of either T-cell or B-cell lineages [61]. ALLs account for the 25-30% of all cancer diagnoses in children. CREB involvement in the molecular events related to *in vitro* and *in vivo* lymphoblastic proliferation is still little known, whereas a lot of evidences disclose a role of *CREB* as a proto-oncogene in haematopoiesis and in AML. *CREB* can be overexpressed in the 84% of ALL patients (73/86) at diagnosis but neither in remission nor in non-leukaemia samples [70]. By contrast, the parallel expression of the cAMP early inducible repressor (*ICER*), which represses CREB activity by competing for the CRE consensus site, appears down-regulated at diagnosis but neither in remission nor in control samples [70]. Thus, it is presumable that *CREB* overexpression leads to target gene up-regulation and increase in cell proliferation and survival that are not counteracted by the insufficient level of *ICER* expression. Besides this hypothesis, Pigazzi et al. [71] have also demonstrated the co-expression of miR34b in *CREB* overexpressing myeloid leukaemia cells providing new information about myeloid transformation and therapeutic strategies. Despite the apparently good prognosis, the 15% of high hyper-diploid (HD) childhood ALL cases relapse [72, 73]. Relapsed ALL is a leading cause of death due to disease in young people, but the molecular mechanisms of treatment failure are still to be elucidated. Genome-wide profiling of structural DNA alterations in ALL identified multiple sub-microscopic somatic mutations targeting key cellular pathways and demonstrated evolution in genetic alterations from diagnosis to relapse [74]. Many of the mutations that have been identified concern the transcriptional co-activators *CREBBP* and *NCOR1*, the transcription factors *ERG*, *SPI1*, *TCF4* and *TCF7L2*, components of the Ras signalling pathway, histone genes, genes involved in histone modification (*CREBBP* and *CTCF*) and genes target of DNA copy number alterations [74]. The parallel analysis of an extended cohort of diagnosis-relapsed cases and acute leukaemia cases that did not relapse showed that the 18.3% of relapsed cases had sequence or deletion mutations of *CREBBP* [72, 74]. *CREBBP* is expressed in leukaemia cells and normal B-cell progenitors, and the mutant *CREBBP* alleles are expressed in ALL cell lines harbouring mutations. Mutations at diagnosis or acquired at relapse consist in truncated alleles or deleterious substitutions in conserved residues of the histone acetyltransferase domain, impairing histone acetylation and transcriptional regulation of *CREBBP* targets, including glucocorticoid responsive genes. In mice the homozygous deletion of *CREBBP* or *EP300* is lethal due to developmental abnormalities whereas *CREBBP*(+/−) mice show defects in B lymphoid development and an increased incidence of haematopoietic

tumours [75]. Both *CREBBP* and *EP300* sequence mutations have been reported in solid tumours and, more recently, also in haematological malignancies, whereas rare *EP300* mutations have been detected in an ALL cell lines and myelodysplasia [74, 76]. A lot of detected mutations at relapse, the same identified at diagnosis in other clones, prove that mutations confer resistance to therapy. Many identified mutations are target in transcriptional and epigenetic regulation as a mechanism of resistance in ALL. It is worth outlining that the high incidence of *CREBBP* mutations found in relapse-prone HD ALL cases discloses the possibility of a targeted customized treatment in this genetic subgroup [73].

In our laboratory we have investigated the role of PI3K/Akt pathway and CREB family members in a number of lymphoid and erythroleukaemia cell lines treated with chemical and physical agents inducing cell death by apoptosis or necrosis [20, 21, 47, 77-80]. We first detected with Western Blotting a high constitutive level of CREB phosphorylation at Ser133 in Jurkat T cells under normal serum culture conditions [20]. Under low serum culture conditions, an early (within 1 h) and transient increase in CREB phosphorylation was observed in response to TRAIL treatment and reduced upon pre-treatment with LY294002 or SB253580, demonstrating the PI3K/Akt- and p38 MAPK-dependency of this effect. Interestingly, both phospho-CREB and phospho-ATF-1 were down-regulated in response to TRAIL treatment of normal primary cells derived from haematopoietic precursors (HUVEC, HEMA), whereas both of them were up-regulated in the neoplastic counterparts (K562 cell line) [20, 21]. The PI3K/Akt pathway dependency of CREB/ATF-1 phosphorylation induced by TRAIL treatment was demonstrated both in primary cells and in leukaemia cell lines of different origin and TRAIL sensitivity, showing that the observed phenomenon is a general feature of TRAIL action in leukaemia [77, 80]. In addition, the observation of CREB cleavage products upon TRAIL/LY294002 combined treatment of sensitive leukaemia cells was consistent with previous reports on other neoplastic cell lines [81] and compatible with the TRAIL-mediated activation of the caspase cascade and cleavage of anti-apoptotic molecules. The parallel analysis with immune fluorescence demonstrated the nuclear translocation of the phosphorylated form of CREB upon treatment with 100 ng/mL TRAIL, whereas the immune labelling was mainly detectable in the cytoplasm compartment upon the higher more cytotoxic dose (1000 ng/mL) as shown in Fig. 2. A further enhancement of apoptotic cell death was obtained with the use of CREB1 siRNA technology leading us to hypothesize that CREB activation can have an important role in the complex crosstalk among pro- and anti-apoptotic pathways in Jurkat T cells [20, 80].

5.3. Chronic myelogenous leukaemia

Chronic myelogenous leukaemia (CML) is characterized in the 85-90% of the cases by the presence of the Philadelphia (Ph) chromosome and the *BCR-ABL* fusion gene. A further 5-10% of the cases display other translocations, most commonly complex variants, that involve one or more chromosomal regions in addition to bands 9q34 and 22q11, but also simple variants that typically involve 22q11 and a chromosome other than 9q34. However, genes that cooperate with *BCR-ABL* leading to acute leukaemia are not well understood neither the role played by CREB in CML has been clarified. Preliminary observations of the group of Kathleen Sakamoto indicate that CREB is highly expressed in blood and bone marrow cells from patients with CML in chronic phase, but not in normal bone marrow cells

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[82]. The same authors previously showed that inhibition of CREB by using RNA interference (RNAi) technology resulted in decreased proliferation and survival of bcr-abl-expressing K562 cells [45, 83], whereas other authors reported that CREB antisense oligonucleotides were able to induce death of human leukaemia cells and bone marrow cells from patients affected with both AML and CML [84]. A critical factor for the genesis of acute leukaemia or acute transformation of CML appears to be the formation of fusion genes between *NUP98* and members of the *HOX* gene family [85]. Interestingly, all the NUP98-HOX-involved fusion products exhibit dual binding ability to both CREB binding protein, a co-activator, and histone deacetylase 1, a co-repressor, acting as both trans-activators and trans-repressors and contributing to the genesis of acute leukaemia or acute transformation of CML [86].

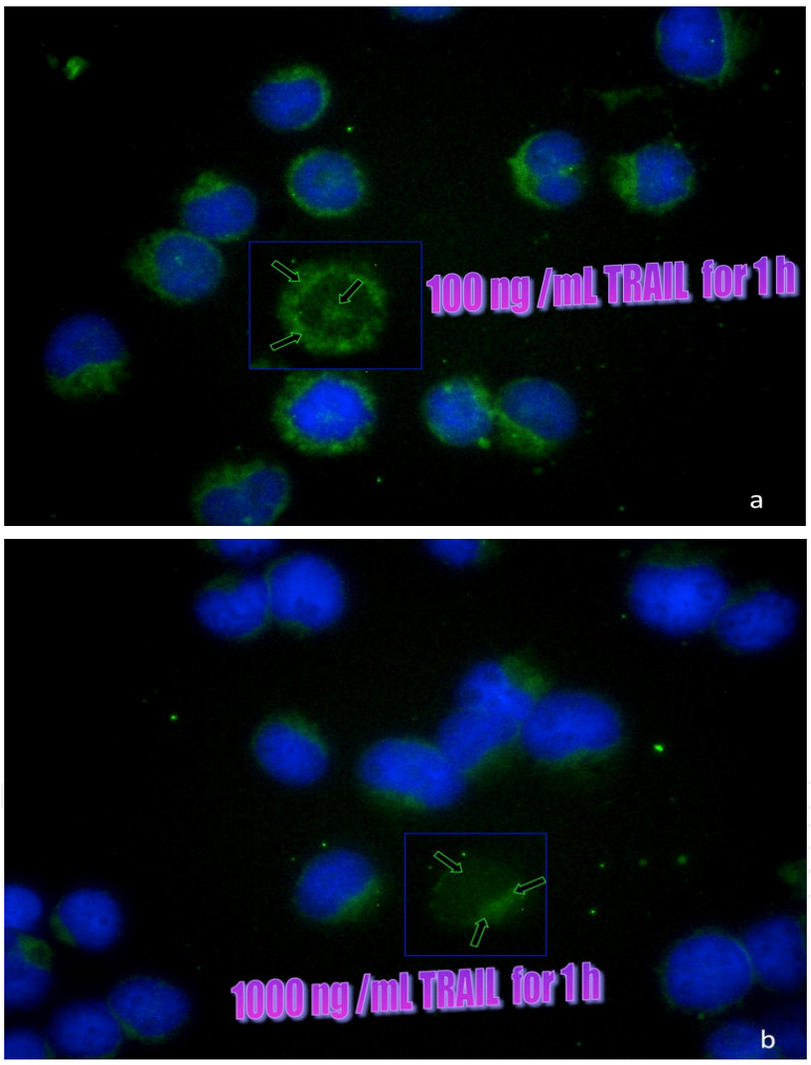

Figure 2. a, b: Phospho-CREB localization in Jurkat T cells upon TRAIL treatment. An evident nuclear translocation of phospho-CREB (green fluorescence) was detected upon 1 h treatment only with the lower dose of TRAIL (panel a), whereas the labelling was located at cytoplasm level upon the higher more cytotoxic dose (panel b). Nuclei were counterstained with 6-diamino-2-phenylindole (DAPI) (blue fluorescence). Green and blue fluorescence single emissions are overlapped in the merge panels. The insets show green fluorescence single emission. Original magnification: 40X. The figure has been adapted from [20].

5.4. Chronic lymphocytic leukaemia

Chronic lymphocytic leukaemia (CLL) originates from the abnormal accumulation of antigen-stimulated B cells that escape normal cell death mechanisms and/or undergo increased proliferation [87]. CLL is the most prevalent adult leukaemia in the Western world, yet no curative treatment exists. Many studies have explored the use of family-specific cyclic nucleotide phosphodiesterase (PDE) inhibitors in light of the potent effects of cAMP signalling on immune system function [88, 89]. Among the 11 currently known families of cyclic nucleotide PDEs, all but three are capable of catabolizing cAMP and at least 5 PDE families (PDE1-4, PDE7 and PDE8) are expressed in lymphoid cells and regulated by either mitogens or agents that induce cAMP-mediated signalling. Previous work has established that inhibition of PDE4 is sufficient to selectively induce apoptosis in CLL cells by increasing the concentration of cAMP [88]. In a recent paper Meyers et al. [89] examined how CLL cells differ from normal haematopoietic cells with regard to their sensitivity to PDE4 inhibitor-mediated cAMP accumulation, CREB phosphorylation and gene expression. Interestingly, it was discovered that upon exposure to rolipram, a prototypical PDE4 inhibitor, cAMP intracellular levels rapidly rose in both CLL and normal B cells, whereas no such increase was detected in T cells. Likewise, ATF-1/CREB Ser63/133 phosphorylation was induced by rolipram in nearly all CLL and B cells, whereas normal T cells displayed a lower response. Based on these findings and on previous observations of a reduced basal cAMP signalling in CLL cells, the authors suggested the involvement of specific PDE or splice isoforms in the reduced basal apoptotic index of CLL cells [89]. Looking for etiological agents, other authors have identified a stromal cell–derived factor-1 (SDF-1)-dependent mechanism as a microenvironmental regulatory mechanism of CLL cell survival [90]. It is known that SDF-1 is a chemokine that plays an important role in B-cell development. In fact, high levels of SDF-1 are produced by stromal cells within the marrow to retain B-cell precursors in close contact with them, within the supportive haematopoietic microenvironment [91], and to prevent their premature release into the circulation. Upon *in vitro* treatment of CLL cells with synthetic SDF-1α, a rapid and transient activation of p44/42 MAPK (ERK1/2) signalling pathway was observed and related to CLL cell survival. Downward MAPK activation transcription-dependent and -independent mechanisms were involved. In fact, MAPK was able to promote cell survival directly by inactivating the pro-apoptotic BAD protein and indirectly by activating CREB, which, in turn, is important for the transcriptional up-regulation of the anti-apoptotic *BCL-2* gene [92]. Thus, SDF-1 engages B lineage CLL cells through the stromal cell receptor CXCR4 and affects components of the cell death machinery, leading to the noted resistance of CLL cells to apoptosis.

5.5. Human T Lymphotropic Virus 1 (HTLV-1) related T cell leukaemia

Human T-cell leukaemia virus type-I (HTLV-1) is the first discovered human retrovirus [93]. It has been recognized as the etiological agent of an aggressive malignancy known as adult T-cell leukaemia (ATL) as well as of the neurological syndrome TSP/HAM and of other clinical disorders. *In vitro* HTLV-1 is able to infect a number of different cell types, whereas in natural human infections it generally targets mature CD4+ helper T cells or, less frequently, CD8+ T

cells. Although the mechanism of HTLV-1 pathogenicity is not fully understood yet, it is widely believed that a virally encoded trans-activator protein, called Tax, is centrally involved in this mechanism. In a recent review Azran et al. [94] provide valuable insights into the molecular mechanisms of HTLV-1 leukemogenesis. In particular, the authors detail the signalling pathways recruited by Tax to set infected T cells into continuous uncontrolled replication and to destabilize their genome, enabling, thereby, accumulation of mutations that can contribute to the leukemogenic process. Tax is able to modulate the expression of many viral genes via the viral long terminal repeat (LTR) and cellular genes through the CREB/ATF-, AP-1-, serum responsive factor (SRF)- and NF-κB-associated pathways, employing the CBP/p300 and p/CAF (p300/CBP-associated factor) co-activators for achieving the full transcriptional activation competence of each of these pathways. It is worth noting that Tax responsive elements (TxRE) contain a centered sequence TGACG(T/A)(C/G)(T/A) that is imperfectly homologous to the consensus cAMP responsive element (CRE; TGACGTCA). Thus, the presence of Tax is necessary for CREB to form a stable complex with the viral CRE. In fact, by interacting with the bZIP region of CREB, Tax enhances CREB dimerization and increases, thereby, its affinity to CRE. In particular, it has been recently shown that CREB is the most prominent factor that cooperates with Tax in activating HTLV-1 LTR region expression [95]. Moreover, it has been demonstrated that while, in the absence of Tax, CREB can activate HTLV-1 LTR expression only if phosphorylated by PKA, another member of the family, namely CREB2, can markedly activate the viral LTR without phosphorylation and can mediate a much stronger activation of the viral LTR by Tax than CREB does [94, 96]. Interestingly, mutant models disrupting Tax activation of the CREB protein resulted in the preferential immortalization of CD8+ lymphocytes, rather than CD4+ lymphocytes, whereas the disruption of Tax interaction with CBP did not affect lymphocyte immortalization [97].

5.6. Lymphoma

Lymphomas are haematological malignancies of the lymphoid system. Deregulated gene expression is a hallmark of cancer and is well documented in B-cell lymphomas [98]. B cells are particularly susceptible to malignant transformation since the mechanisms involved in antibody diversification can cause chromosomal translocations and oncogenic mutations. B-cell lymphomas include Hodgkin lymphoma (HL) and non-Hodgkin lymphoma (B-NHL). B-NHL consists of a heterogeneous group of diseases whose pathogenesis is associated with multiple genetic lesions affecting oncogenes and tumour-suppressor genes and whose treatment is related to the different grade of malignancy. The most common type of B-NHL is represented by the diffuse large B-cell lymphoma (DLBCL), which generally arises as a clinical evolution of the follicular lymphoma (FL). A number of papers have demonstrated the involvement of CREB family members in the pathogenesis of lymphoma. It has been previously found that CREB acts as a positive regulator of the translocated *BCL-2* allele in FLs with the t(14;18) translocation [60] and that the high constitutive expression of *ATF-3* is linked to the viability of Hodgkin/Reed-Sternberg cells and, thus, considered as a molecular hallmark of classical HL [99]. More recently, a number of studies have disclosed the implication of the HAT proteins CBP and p300 as tumour suppressors in B-cell neoplasms [100-102]. Nevertheless, the various mechanisms through which each of these cofactors specifically contributes to

lymphomagenesis are still to be elucidated. As before mentioned, CBP and p300 function as co-activators of transcription factors and acetylate proteins relevant to lymphomagenesis such as p53, NF-κB, Bcl-6 and Hsp90 [100, 103, 104]. In particular, p300 acts as a co-activator of NF-κB, activates p53 but attenuates Hsp90 chaperone functions and, moreover, transcriptional repressor *BCL-6* is frequently translocated and hyper-mutated in DLBCL where it results inversely correlated with p300 [100]. Importantly, de-acetylated Hsp90 represses p53 but maintains *BCL-6* expression, which suppresses p300 and its essential cofactor BAT3, which is necessary for p53 acetylation and activation. Somatic heterozygous mutations or deletions of the *CREBBP* locus occur in more than the 50% of DLBCL and the 32% of FL cases, whereas *EP300* mutations occur in the 10% of DLBCLs. All cases seem to have in common the disruption of the HAT catalytic domain, and the resulting truncated or mutant proteins may have dominant negative or gain of function properties, or may simply result in a reduced dosage of histone acetyltransferases. Structural alterations inactivating *CREBBP* and, less often, *EP300* have been recently documented and linked to the pathogenesis of both most common types of B-NHL [102]. According to Pasqualucci et al. [102] point mutations at the HAT coding domain of *CREBBP* and *EP300* result in specific defects in acetylation-mediated inactivation of the Bcl-6 oncoprotein and activation of the p53 tumour-suppressor, representing major pathogenetic mechanisms shared by the most common forms of B-NHL. Suppression of p300 either through Bcl-6 or inactivating mutations plays a key role in DLBCL. In fact, treatment of DLBCL cells with Bcl-6 inhibitors leads to p300 protein expression and acetyltransferase activity with subsequent acetylation of p53 (which induces p53 transcriptional functions) and Hsp90 (which suppresses Hsp90 chaperone activity) [100]. Moreover, the combination of Bcl-6 and histone deacetylase inhibitors (HDACI) leads to even higher p300 activity and synergistic killing of lymphoma cells *in vitro* and *in vivo* [100]. Interestingly, the direct effect of HDACI on non-histone proteins as DNA binding transcriptional factors (NF-κB, p53, CREB, GATA, c-myc, Bcl-6, E2F, IRF) can also affect cell growth and differentiation [101]. Furthermore, in light of HDACI effects on cell cycle regulatory molecules (Cyclin D1, p21 and p27) there is enough evidence that indicates these novel pleiotropic drugs as promising compounds for the treatment of B- and even T-cell malignancies in addition to conventional chemotherapy [105].

5.7. Multiple myeloma

Multiple myeloma (MM), also known as plasma cell myeloma or Kahler's disease, is a B-cell malignancy characterized by the accumulation in the bone marrow of plasma cells with a low proliferation index and an extended life span. Most cases of myeloma also feature the production of a paraprotein, an abnormal antibody that can cause kidney problems. MM cell lines as well as *de novo* MM cells express multiple anti-apoptotic proteins, often do not encode functional p53 and frequently contain a dysregulated Akt pathway [104-107]. A number of factors related to MM cell growth and survival and linked to CREB family members have been identified [108]. Among these factors, the myeloid cell leukaemia-1 (Mcl-1) protein, an anti-apoptotic member of the Bcl-2 family, has been considered as a critical regulator of MM cell survival and proposed as an attractive therapeutic target [108]. *Mcl-1* is an immediate early gene activated in response to GM-CSF and IL-3. It has been previously reported that *Mcl-1* activation can occur in dependence of the PI3K/Akt pathway through a transcription factor

complex containing CREB [109]. Recent reports have demonstrated that Mcl-1 specific down-regulation or repression is able to initiate apoptosis in MM [110]. To this end, proteasome inhibitors like bortezomib have been used though with contrasting results. In fact, it has been shown that accumulated and cleaved Mcl-1 products by proteasome inhibition have either a pro- or an anti-apoptotic function. In particular, Hu et al. [111] have investigated the role of endoplasmic reticulum unfolded protein response (UPR) in order to unravel the mechanisms underlying Mcl-1 accumulation following treatment with proteasome inhibitors, discovering the enhanced translation of ATF-4, an important effector of UPR, upon proteasome inhibition, and indicating ATF-4 as responsible for bortezomib resistance of MM [111]. Besides Mcl-1, novel factors are being identified as important players in the pathogenesis of MM. Recent studies have suggested that X-box–binding protein 1 (XBP1), a bZIP transcription factor of the CREB/ATF family, has an important role in the survival of MM cells [112]. XBP1 is required for B lymphocyte terminal differentiation to plasma cells and is essential for immunoglobulin secretion. Abundant or deregulated expression of *XBP1* has been detected in MM cells [113, 114] and in hepatocellular carcinomas [115]. Due to the production of abundant immunoglobulins and cytokines, MM cells must be able to survive under conditions of chronic ER stress involving UPR and including constitutive activation of the ER-located transmembrane kinase/endoribonuclease (RNase) protein IRE1α-XBP1 pathway. This pathway, implicated in the proliferation and survival of MM cells, has been considered as a prognostic factor [116] and, moreover, as a possible target of chemo/immunotherapy [114, 117]. A growing body of evidence attributes a pathogenetic role to several microRNAs (miRNA) resulting up-regulated in MM and targeting p/CAF, a positive regulator of p53 [118]. Other authors have indicated a possible role of CREB family members in IL-6-mediated effects on myeloma cell growth and survival [119].

6. Concluding remarks

CREB/ATF family is a growing family of transcription factors involved in a number of physiological and pathological processes. Day by day, new family members are being identified for their primary role in normal or aberrant haematopoiesis and proposed as therapeutic targets of anticancer drugs [112]. In fact, by regulating gene expression, transcription factors are often the final mediators of such central processes as proliferation, survival, self-renewal and invasion. Based on these effects, it is conceivable that inhibition of transcription factors can revert the malignant behaviour of many tumour types and can potentially achieve a very high therapeutic index [86]. Actually, in light of its important role in the pathogenesis of leukaemia, CREB has been indicated as a potential prognostic marker of disease progression in AML and a molecular target for future treatment of leukaemia. In addition, CREB has also been implicated in many solid tumours including hepatocellular carcinoma, osteosarcoma, lung adenocarcinoma, melanoma and lymphoma [46]. Indeed, since *CREB* overexpression results in a poor prognosis for the patient, the regulation of CREB activity might represent a useful strategy to treat solid tumours like prostate, breast and lung cancer, as well as haematological malignancies like AML and lymphoma. However, a key question

concerns whether the activation of CREB (or other transcription factors) seen in cancer cells is directly driving the cell malignant phenotype, or whether it is merely a by-product of activation of one of the upstream pathways or only a partner in a more complex scenario. This is a crucial point, since CREB would represent a good molecular target only if it were a main player in the specific tumour biology. Unfortunately, clinical and experimental evidences suggest that several functionally cooperating genetic alterations, including chromosomal translocations, lead to the expression of fusion proteins that play a key role in the pathogenesis of the leukaemia phenotype. CREB itself can promote cellular transformation as a fusion protein or by cooperating with other oncogenes or transcription factors. Furthermore, due to the recruitment of chromatin modulating mechanisms in the transforming activity of leukemogenic factors, transcriptional therapies aimed at inhibiting DNA methyltransferases, histone deacetylases or acetyltransferases, like CBP and p300, are emerging as new frontiers for cancer treatment. Unlike HDACI, which have been used in several phase I/II clinical trials, HAT inhibitors have been less extensively investigated for their potential use in cancer therapy. Indeed, interesting results obtained with clinical treatment of solid tumours [120] suggest that p300 inhibition may be a promising anticancer approach. To overcome the numerous side effects and the mostly transient clinical responses exerted by epigenetic compounds used as a single treatment [121], combinatorial therapy involving epigenetic agents together with conventional or targeted agents is increasingly seen as a more attractive opportunity. Therefore, further preclinical investigations aimed at better dissecting epigenetic mechanisms driving induction, maintenance and potential reversibility of the leukaemia state are welcome and functional to select the most potent drugs and combinations and to develop more efficient and long-lasting targeted therapeutic strategies. We hope to have contributed with this chapter to make the state of the art on the role of CREB in leukaemia and lymphoma neoplasms in order to allow further steps moving ahead from bench to bedside.

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