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Review

The AP-1 transcriptional complex: Local switch or remote command?

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ABSTRACT

The ubiquitous family of AP-1 dimeric transcription complexes is involved in virtually all cellular and physiological functions. It is paramount for cells to reprogram gene expression in response to cues of many sorts and is involved in many tumorigenic processes. How AP-1 controls gene transcription has largely remained elusive till recently. The advent of the "omics" technologies permitting genome-wide studies of transcription factors has however changed and improved our view of AP-1 mechanistical actions. If these studies confirm that AP-1 can sometimes act as a local transcriptional switch operating in the vicinity of transcription start sites (TSS), they strikingly indicate that AP-1 principally operates as a remote command binding to distal enhancers, placing chromatin architecture dynamics at the heart of its transcriptional actions. They also unveil novel constraints operating on AP-1, as well as novel mechanisms used to regulate gene expression via transcription-pioneering-, chromatin-remodeling- and chromatin accessibility maintenance effects.

1. Introduction

Activator Protein 1 (AP-1) is a ubiquitous family of dimeric transcription complexes involved in a plethora of cellular and physiological functions (Fig. 1). It is acknowledged as a master integrator of a myriad of extracellular signals allowing cells to adapt to changes in their environment [1–4]. AP-1 has also been implicated in various severe diseases. These include transplant rejection, fibrosis, organ injury and a variety of inflammatory pathologies such as rheumatoid arthritis, asthma and psoriasis [5–10]. In addition, cancer is undoubtedly the most documented pathology involving AP-1 where its activity is often dysregulated and contributes to cell transformation, tumor progression, aggressiveness and resistance to treatments [2,4,8,11–14]. Although AP-1 components can sometimes act as oncogenes or tumor suppressors on their own, they most often act as crucial effectors of upstream oncogenic events. The best documented, but not the only ones, are those affecting the MAPK pathway activity. In this case, dysregulated signaling can trigger exacerbated expression of different AP-1 constituent genes, as well as stabilization and functional activation of AP-1 proteins [15–25]. Ultimately, this leads to alterations of tumor cell transcriptional programs (see Section 3.2). Due to its crucial role in various pathologies, the AP-1 complex itself, as well as its regulators and effectors, constitute attractive therapeutic targets and are the subject of intense investigations worldwide [3,26]. For example, several small AP-1 activity inhibitory molecules have already been developed and tested with positive effects in preclinical models of lung cancer metastasis [27], intervertebral disc degeneration [28] and cartilage destruction [29]. One of them is under phase II clinal trial for rheumatoid arthritis in Japan [26].

AP-1 dimers are contributed by various multigene families of proteins harboring a highly conserved basic leucine zipper domain (bZip) where the leucine zipper (LZ) serves for dimerization and the basic region (BR) for binding to specific DNA motifs (Fig. 1). AP-1 is most often defined as the collection of dimers made up of the members of the Jun (c-Jun, JunB, JunD) and Fos (c-Fos, FosB, Fra-1, Fra-2) multigene families (the terms "Fos-" and "Jun proteins" will be used below, not only when referring to the whole Fos and Jun family members, but also when the Fos or Jun components at play are unknown, which is the case in a number of genome-wide studies). An extended definition for AP-1, however, also includes the members of the ATF- (ATF-2, ATF-3/LRF1, ATF-4, ATF-5, ATF-6B, ATF-7, BATF, BATF-2, BATF-3, JDP2) and MAF (c-MAF, MAFA, -B, -F, -G, -K and Nrl) multigene families [30]. The expression/inducibility of the latter proteins is however more tissue/cell-restricted than that of Fos and Jun proteins [11].

Depending on their compositions, AP-1 dimers bind to different types of palindromic sequences. Thus, Fos:Jun and Jun:Jun dimers preferentially bind to DNA motifs referred to as 12-O-tetradecanoylphorbol-13-acetate (TPA)-responsive element (TRE; also called

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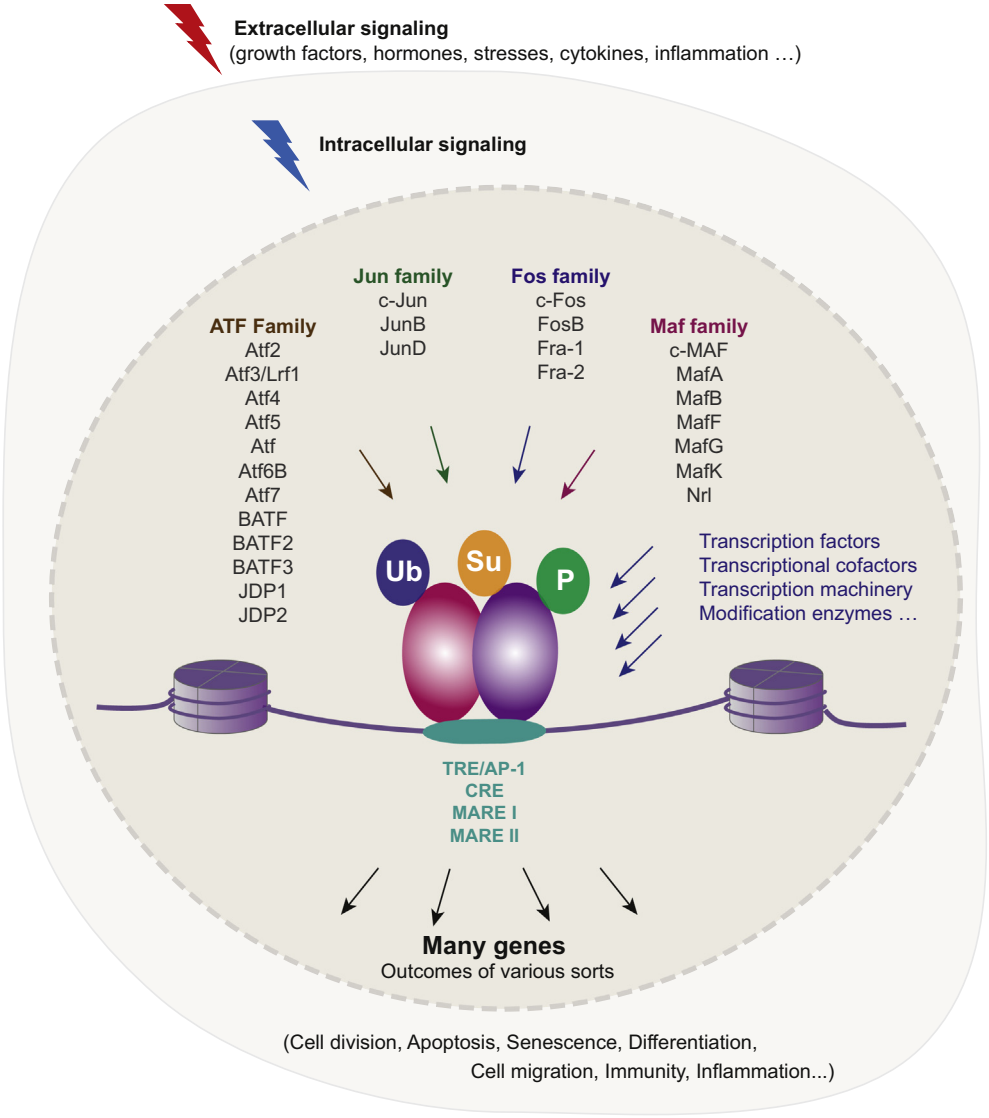

Fig. 1. The complexity of the nuclear integrator AP-1 allows cellular responses to diverse extracellular cues. AP-1 is a generic name for different sets of homo- or heterodimers made up of members of the Fos, Jun, Maf and ATF multigene families. Although AP-1 is ubiquitously found in cells and tissues, not all of possible AP-1 components are expressed or activated at the same time in the same cell. Moreover, the AP-1 components cannot associate indifferently between them, privileged possibilities of interactions exist (see [3,30]). The best studied AP-1 dimers are, by far, those formed by the members of the Fos and Jun multigene families. AP-1 dimers recognize specific DNA motifs that are found at many places in the genome, explaining the wide number of genes whose transcription is controlled (or partly controlled) by AP-1. AP-1 component levels are finely tuned in cells. They depend on intracellular signaling, which can alter the abundance of AP-1-constituting proteins via transcriptional regulation of their genes and/or protein stabilization/destabilization. Several post-translational modifications that include phosphorylation (P), ubiquitylation (Ub) and SUMOylation (Su) regulate their degradation rate and activity, as well as their intracellular/intranuclear localization/availability. Moreover, AP-1 dimers collaborate with a number of other actors to exert their transcriptional part and to affect cell transcriptome regulation. AP-1 is involved in many, if not all, cellular and physiological functions. It acts as a master integrator of a myriad of extracellular signals. The outcomes of such stimulations are numerous and depend on the cell populations concerned and the physiological context. Due to its central role in cell- and whole organism physiology, dysregulation or pathologic exploitation of AP-1 has been reported in various severe diseases such as cancer [13]. Concerning the latter, AP-1 constituents have rarely been described for exerting an oncogenic role by themselves. Rather, they act as essential effectors of other oncogenes (and/or after loss of certain tumor suppressors) to contribute to cell transformation, inflammation promotion, tumor progression, resistance to treatments, etc.

AP-1 motif) and, with however slightly lower affinity, cAMP-responsive element (CRE). The consensus sequences for TRE/AP-1 and CRE are 5′-TGA(C/G)TCA and 5′- TCACGTCA motifs, respectively. However, Fos:Jun and Jun:Jun dimers can also bind to variant sequences in the cell genome, as deduced not only from in vitro binding experiments (SELEX and bandshift assays, for example) but also from various ChIP-seq analyses conducted using biological material (cell lines and tissues). On their side, ATF-containing dimers preferentially bind to cAMP-responsive element (CRE) whereas MAF-containing dimers bind either to MARE I or MARE II motifs that are extensions of TRE and CRE motifs, respectively [11]. Fos and Jun proteins are, by far, the best and most studied AP-1 proteins and will be principally considered below.

Whereas the Jun proteins can homodimerize or heterodimerize with members of their own family, the Fos ones cannot do so. They must heterodimerize with non-Fos family AP-1 components such as the Jun proteins [11]. Of note, Fos:Jun dimers have stronger affinity for DNA than the Jun:Jun ones and, usually, also show stronger transcription-stimulating activity, at least in cell transfection reporter assays [31]. It has long been known that the composition of AP-1 dimers rapidly adapts to variations of concentrations in Fos and Jun proteins within the cell in response to external cues, indicating that dimerization/dedimerization events can be minute-range dynamic processes in vivo [32,33]. There is also accumulating evidence that, depending on the signal, the cell context and the combination of Fos and Jun family components, AP-1 switches on/off different transcriptional programs or genes, making the study of AP-1 functions particularly challenging. As a consequence of both the molecular complexity and the dynamics of AP-1 composition, clear-cut conclusions on the precise role(s) of each one of its constituents in a given situation are most often difficult to draw.

There is an important two-fold paradox with AP-1, which has been known to be a transcription factor (TF) since the late 80's [34]. First, despite > 30,000 references found in a Medline search using keywords such as Fos, Jun or AP-1, the unambiguous identification of most of its actual target genes is far from being complete. Second, the mechanisms by which AP-1 controls transcription are also still ill-understood. In fact, our view of AP-1 transcriptional actions has been biased considerably by technical limitations for many years. In particular, regulation studies mostly focused on gene promoter regions via resorting to cell transfection of reporter genes or chromatin immunoprecipitation experiments restricted to specific gene loci. However, the advent of the "omics" technologies permitting transcriptome/genome-wide studies of transcription led to reconsider this view in recent years. In brief, they

showed that, even though AP-1 can act as a local transcriptional switch operating in the vicinity of transcription start sites (TSS), this transcription complex principally operates as a remote command binding to distal enhancers brought into the proximity of target gene promoters owing to long-range chromatin interactions. These studies also allowed to identify novel molecular actions of AP-1, in particular via cooperation with other transcription factors/complexes. Due to space limitations, all of them could not be covered in this review and priority was given to the most recent literature.

2. Gene promoters and enhancers

In the context of this review, it is important to have some general considerations on gene promoters and enhancers, as well as on their molecular characteristics, as a number of points are still debated, affecting our current view of AP-1 actions.

A first important question concerns the discrimination between enhancers and promoters of coding genes. On the one hand, gene promoters have long been defined as the DNA regions immediately surrounding TSSs that allow for initiation of transcription. On the other hand, enhancers were defined as regulatory elements involved in the spatial and temporal regulation of gene expression patterns that can be located far away from their cognate gene promoters. However, the wealth of genome-wide studies published in the recent years has shown that defining precisely promoters and enhancers is often not an easy task. A simple illustration of this difficulty is that there exists no clear definition of promoter limits. These are arbitrarily defined by the various authors and largely differ among studies. They can range from ± 100 bp around TSSs up to some kbs and certain authors consider only the sequences upstream of TSSs. Moreover, if certain enhancers are located far away from their target genes, others are located in close vicinity to their cognate TSS, making it difficult to disentangle the limits between the enhancer and the promoter moieties. Additionally, not facilitating the discrimination between enhancers and promoters, both regulatory elements share a number of structural and functional features. This include, for example, localization in open regions of chromatin and binding of TFs, as well as the ability to promote RNA polymerase II (Pol II)-mediated transcription [35]. Recent research has also shown that certain promoters (Epromoters) can exert enhancer activity on other remote promoters they interact with, owing to chromatin looping [35–37]. Nevertheless, there is a general agreement on the fact that, in addition to the presence of TFs, general transcription factors (GTFs) and Pol II, promoters are also marked by (i) enrichment of lysine 4 trimethylation of histone H3 (H3K4me3) in the proximity of TSSs and (ii) acetylation of histone H3 lysine 27 (H3K37ac) when they are active [38].

Enhancers were originally proposed to act independently of their location and orientation with respect to their target genes, based on reporter gene transfection experiments. However, genome-wide chromosome conformation capture techniques (3C and its derivatives) have recently shown that enhancer-promoter interactions are constrained within topologically-associating domains (TADs) that emerge as fundamental chromatin structural units [39]. Despite that the various investigations on enhancers rarely used the exact same criteria to identify them, which complicates the comparison of data and conclusions between studies, a consensus has emerged in the recent years on their nature [40–44]. However, caution is still required before ascertaining that a DNA segment actually exerts enhancer activity [45]. Enhancers are short domains (100–500 bp in length) found in open regions of chromatin that are located from the kb- up to the Mb range away from target genes. They harbor transcription factor binding sites (TFBS) and act as molecular platforms targeting the transcription machinery to their cognate target genes owing to chromatin interactions that are not necessarily stable. 10^6 such regulatory elements are likely to be present in the mammalian genome but no > 1–2% of them are active at a given time in a given cell. Enhancers are H3K4me1-marked with a high H3K4me1/H3K4me3 signal ratio. As for promoters, high H3K27ac signals are indicative of activity. Moreover, enhancers are also characterized by (i) enrichment in H2A.Z and H3.3 histone isoforms permitting higher nucleosome turnover, (ii) the presence of the CBP/p300 lysine acetyl transferases, (iii) the presence of RNA Pol II and (iv) active transcription giving rise to short unstable eRNAs, the role of which is subjected to intense research [46–49]. Whatever their role, their discovery led to a breakthrough in active enhancer definition and putative assignment of enhancers to the promoters they control by the FANTOM5 consortium [44].

It should be noted that enhancer sequences generally have higher affinity for histone octamers and are, therefore, spontaneously prone to form nucleosomes [50]. A key issue is therefore their selection and activation. The so-called pioneer transcription factors, capable of engaging nucleosomal DNA and recruiting chromatin remodeling factors, play a crucial role in this process [51]. Other still largely open questions are how transcription factors cooperate at enhancer elements to stimulate transcription and how chromatin looping bringing into proximity enhancers and promoters is regulated. Cooperation between enhancers to stimulate common target gene(s), via the formation of regulatory hubs constitutes another burning issue (see Sections 3.3 and 5) [42,52].

Noteworthy, certain regions of the genome, termed superenhancers, show an unusually high cumulative binding of transcription factors over length of > 10 kb and an enrichment of transcriptional regulators such as Cdk7, Brd4 or Mediator, as well as a higher enrichment in H3K27ac and a stronger production of eRNAs [53]. However, whether they represent novel transcriptional entities functionally different from classical enhancers and whether their effects are significantly higher than the sum of the effects of their individual constituents is still a matter of debate [42,53–55].

As illustrated below, all questions applying to enhancers also apply to AP-1. It is however important to underline that both the experimental systems and the methodological approaches used to study AP-1-binding regulatory elements differ between studies and that none of them takes all the above-described features of enhancers into account, making comparisons between literature reports uneasy.

3. AP-1 principally binds to distal transcriptional enhancers

Recent genome-wide studies have shown that AP-1 is likely to exert its transcription-regulatory actions through distal enhancer- rather than gene promoter regions. This notion has principally emerged from 3 major types of studies that are successively reviewed below: (i) global genomics approaches in diverse and unrelated biological systems, (ii) cancer biology and (iii) developmental and cellular biology. It is however important to stress that some of these investigations are only correlative and still lack substantial functional validation. Moreover, in a number of studies, the targets of studied enhancers have been assigned to the nearest gene (which can be located dozens of kbs away). Although this is undoubtedly justified in certain cases, many reports using chromosome conformation capture (3C)-derived techniques [56] (see Box 1 for more information) or other methodological approaches [44] indicate that this is very often misleading.

3.1. Global genomics approaches in unrelated biological systems

Through measurements of multiple histone modifications across the genome in several cell types, the ENCODE project consortium segmented the genome into different predicted regulatory activity elements (strong or weak enhancers and repressive elements). Moreover, it functionally tested a number of them in the K562 human erythroleukemia cell line using a massively parallel reporter assay (MPRA) measuring RNA production. The AP-1 TFBS was found to be the most significantly enriched motif in most active *cis*-regulatory elements where it was usually associated with DNAse I-hyper sensitive sites

Box 1
Synopsis of the main techniques mentioned in this review.

3C-based techniques

All of the following techniques are based on 3C library constructions that contain short rearranged DNA fragments reflecting the spatial proximity of loci in native chromatin. They are obtained by digestion of crosslinked chromatin by restriction enzymes, followed by ligation.

- 3C: one-to-one approach: conceived to monitor interactions between two specific loci at a time. Interactions are analyzed by quantitative or semi-quantitative PCR.
- 4C: one-to-all approach: similarly to 3C, 4C interrogates the interactions of one locus but with all the genome. The chimeric rearranged DNA fragments are analyzed by deep sequencing.
- MC-4C: 4C coupled to the nanopore sequencing technology. This technology allows to sequence large individual chimeric fragments and gives information on DNA interactions at the single molecule level
- Tri-C: 4C in specific conditions where fragments of about 450 pb and containing multiple ligation junctions are generated. After capture of the locus of interest-containing fragments, rearranged chimeric DNA molecules are analyzed by deep sequencing.

Chromatin accessibility detection

- DNAse I hypersensitive site (DHS) mapping. DHSs are regions of chromatin sensitive to cleavage by the endonuclease DNAse I. In these regions of the genome, chromatin has lost its condensed structure, exposing the DNA and making it accessible. Several methods exist to characterize them. Among these, DNAse-seq allows genome-wide sequencing of regions sensitive to cleavage by DNAse I.
- FAIRE-seq (Formaldehyde-Assisted Isolation of Regulatory Elements) is a successor of DNase-seq for genome-wide identification of open chromatin regions. It has the advantage over DHS mapping not to require cell permeabilization or purification of nuclei. It exploits the biochemical properties of protein-bound DNA to separate them from nucleosome-depleted regions in the genome before high throughput sequencing to map condensed- versus open regions of chromatin.
- ATAC-seq: Assay for Transposase Accessible Chromatin and sequencing. The hyperactive mutant of transposase Tn5 inserts sequencing adaptors in open regions of the genome. After purification, the tagged DNA fragments are sequenced. This technique allows to assess chromatin accessibility on a genome-wide level with a higher resolution than DNAse-seq and FAIRE-seq.

(DHSs, which are open chromatin regions usually associated with active or poised regulatory DNA elements), suggesting that AP-1 contributes to the activity of many distal enhancers in K562 cells [57]. Along the same line, systematic analysis of > 400 ChIP-seq data sets for diverse TFs available from the ENCODE project also showed that the AP-1/TRE motif (and to a lesser extent the CRE motif) is either the most enriched in the vicinity of other TFBSs or overlaps with them [58]. Other studies have also pointed to a foreseeable role of AP-1 mainly at the enhancer level: (i) comparison of promoter and enhancer activities using MPRAs in neuronal cells has shown that, in contrast to promoters, active enhancers are enriched in AP-1 TFBSs [59], (ii) Epromoters that exert enhancer activity on other distally located promoters are enriched in AP-1 TFBSs [36] and (iii) identification of genetic sources of regulatory differences between species has shown that gained and lost DHSs between the same cell type in different primate species (human, chimpanzee and macaque) correlate with higher or lower AP-1 motif scores, respectively, and with differences in the expression of putative target genes, suggesting that AP-1 may be involved in chromatin structure changes by having a role of pioneer factor [60].

3.2. Cancer studies

Interestingly, a number of studies, which were not initially designed to investigate the function of AP-1, suggested a role for distal AP-1 TFBS-containing enhancers in carcinogenesis.

While investigating the role of YAP/TAZ (which are nuclear effectors of the Hippo pathway regulating organ growth and tumorigenesis) in breast cancer, Zanconato et al. [61] recently discovered that the YAP/TAZ transcriptional response is pervasively mediated by both TEAD family factors (which recruit YAP/TAZ at the DNA level) and AP-1 proteins. These TFs bind to composite *cis*-regulatory elements harboring TEAD- and AP-1-binding motifs located distally from genes and act synergistically to activate target genes involved in S-phase and mitosis control owing to chromatin loops bringing about enhancers and promoters. Of note, the authors provide functional evidence that gain or loss of AP-1 promotes or represses YAP/TAZ-induced oncogenic growth, respectively. In the same vein, another study of transcriptional and chromatin landscape reprogramming in melanoma identified TEAD and AP-1, not only as master regulators of the invasive gene network, via binding to common enhancer regions, but also as crucial regulators of resistance to treatment by MAPK pathway inhibitors [62]. However, the molecular mechanisms of TEAD/AP-1 cooperation were not investigated. This point was addressed in other cancer cell contexts (neuroblastoma, colorectal, lung and endometrial carcinomas), where both TFs cooperate to promote cell migration and invasion. The TEAD/AP-1 interaction was shown to engage the SRC1–3 co-activators, which bridges the interaction between the two TFs, to control cell migration and invasion through a core of target genes. In this process, TEAD and AP-1 mainly co-occupy active enhancers and to a lesser extent (12%) promoters [63].

A cooperation between AP-1 and oncogenic Ets has been suggested in other cancers. They include the majority of prostate cancers, many gastrointestinal stroma tumors and a fraction of melanoma, where the tumor phenotype is contributed by overexpression of at least one of the protooncogenic Ets genes (Erg, Etv1, Etv4 and Etv5). Indeed, genome-wide analyses revealed that oncogenic Ets proteins bind sequences that significantly differ from those bound by non-oncogenic Ets and that juxtapose ETS- and AP-1 TFBSs. Importantly, JunD was found bound to 31% of the Etv4 bound-regions but the functional cooperation was not investigated [64]. Cooperation between TFs involving AP-1 has also been reported during TGF-β-induced EMT in lung adenocarcinoma A549 cells [65]. Together with JunB, Ets2 and Hnf4A utilize a “clique” motif, physically interact and cumulatively bind to EMT-associated gene (super)enhancers.

Besides this, a superenhancer landscape-based analysis of the core regulatory circuitries (CRCs) controlling gene expression programs in neuroblastoma has unveiled two main cell identity groups, strengthening the idea of heterogeneity in this tumor type, and has suggested a role for AP-1 in neuroblastoma aggressiveness [66]. On the one hand, sympathetic noradrenergic cell identity was shown associated to superenhancers bound by the Phox2b, Hand2 and Gata3 TFs that participate in the control of normal sympathetic neuron specification and differentiation and, on the other hand, multipotent neural crest cell (NCC) identity was associated to superenhancers enriched in AP-1 motifs and was characterized by an enhanced resistance to therapeutic drugs. However, no formal functional evidence on the actual role of AP-

1 transcription complex was provided [66].

To improve the identification of enhancers that are actually functional in a given cell type, Franco et al. [67] recently developed a computing pipeline termed TFSEE (Total Functional Score of Enhancer Elements), which integrates the magnitude of enhancer transcription (eRNA levels), TF mRNA expression levels (RNA-seq), histone modification (ChIP-seq) and TFBS motif search. When applying this method to breast cancer, the authors revealed key breast cancer subtype-specific TFs that operate at transcribed enhancers to control gene expression programs responsible for the diverse cancer cellular phenotypes. In particular, they showed that Fra-1 is enriched at most of the transcribed enhancers tested in Triple Negative Breast Cancer (TNBC) cell lines, where it regulates cell proliferation and viability and whose overexpression is predictive of patient poor outcomes. This is especially interesting, as Fra-1 and Jun are known to be overexpressed and to play important roles in oncogenesis and tumor aggressiveness in TNBCs [68].

Likewise, investigations conducted in diverse cancer situations allowed to compare enhancer activities between control and pathological conditions, providing stronger functional support to the idea of an actual contribution of AP-1 to the activity of distal enhancers. For example, in esophageal adenocarcinoma, genes encoding chromatin-remodeling enzymes are frequently mutated. Chromatin changes were interrogated in this context using ATAC-seq (see Box 1) in both cancer and normal esophageal cell lines [69]. Most chromatin changes (1600 out of > 50,000 accessible loci) were found within intergenic and intronic regions and only a minority in promoters. Motif search analysis revealed that AP-1 and Ets TFBSs were found in the differentially open chromatin sites in cancer cells and the binding of Jun and ETV1 was validated in ChIP-seq experiments. However, no obvious distance constraints that would indicate a specific binding mode driving cooperative DNA-binding could be seen. Functional studies using a dominant negative version of Fos (DN-FOS) also point to an important role for AP-1 in ETV1 (PEA3 member)-regulated gene expression in esophageal adenocarcinoma cells. It is interesting to note that PEA3 and AP-1 proteins (with the exception of Fra-2) are often overexpressed in patient-derived samples with a possible driver role for Fra-1 and c-Fos [69].

To characterize variant enhancer loci (VEL) located in non-coding regions of the genome that may be drivers in colorectal carcinogenesis, epigenetic enhancer profiling was carried out in normal crypt epithelium and compared to that of a cohort of colorectal specimen [70]. The authors found enhancers highly recurrently activated in colorectal cancers that are associated with dysregulation of predicted target genes critical for tumorigenesis. Interestingly, these enhancers are (i) most often constituent of superenhancers, (ii) associated with risk loci by genome-wide association studies (GWAS) and (iii) occupied by AP-1 and cohesin complex members. Moreover, this correlates with high expression of certain Jun and ATF proteins in colorectal tumors. Following a similar approach, Morrow et al. [71] identified VELs that are responsible for the metastatic phenotype of human osteosarcoma (Met-VELs) through epigenetic profiling of primary and metastatic tumors, as well as between near isogenic pairs of highly metastatic and non-metastatic osteosarcoma cell lines. Gained and lost Met-VELs were functionally associated with changes in metastasis-dependent target gene expression. Interestingly, the most enriched TFBS in both gained and lost Met-VELs is that for AP-1. Moreover, the bindings of Fos and Fra1 were verified by ChIP-seq, further supporting the idea that AP-1 may have both transcription-stimulating and -inhibiting actions in metastatic osteosarcoma.

Finally, while investigating how aberrant chromatin reprogramming and changes in gene expression rewire specific regulatory networks among the different acute myeloid leukemia (AML) subtypes, Assi et al. [72] have shown that the latter adopt unique chromatin landscapes characterized by AML-specific distal *cis*-regulatory elements. Interestingly, these elements display two main features. On the one hand, they show preferential transcription factor motif occupancy that most likely underlies differences in leukemia types. On the other hand, they present recurrently occupied AP-1 TFBSs that are likely to be relevant for leukemogenesis of all AML subtypes, as inhibition of AP-1 activity via ectopic expression of a dominant negative mutant of Fos (DN-FOS) inhibited development of AMLs from 2 different subtypes in xenografted immunocompromised mice.

3.3. Developmental and cellular biology studies

Several studies aiming at elucidating enhancer landscape changes during differentiation or stimulation of specific transduction pathways have revealed major roles for AP-1 in enhancer function and/or chromatin accessibility. Two of these are, however, described below (Section 4.2) when addressing AP-1 mechanistical actions [73,74].

It has long been known that AP-1 is necessary for skin homeostasis and differentiation. In this context, the epidermal differentiation complex (EDC) locus comprises a syntenic and linear cluster of genes whose concomitant expression is a hallmark feature of differentiation in the developing skin epidermis, as they code for cross-linked proteins (including among others: SPPR, LCE, FLG, FLG-like, S100) forming the cornified envelope. While studying how the expression of these genes is coordinated, Oh et al. [75] identified a human distal regulatory enhancer ("923", meaning 923 kb from the TSS of S100A10, which is the most 5′ gene of the locus), the activity of which is modulated by c-Jun/AP-1 binding and responds to developmental and spatiotemporal cues at the onset of differentiation in mouse embryos.

The role of AP-1 was also studied in blood development using in vitro differentiation of mouse embryonic stem cells. Through coupling genome-wide TF binding- and gene expression analyses to functional assays, it has been shown that AP-1 collaborates with TEAD4 to shift the balance between vascular smooth muscle and blood cell development at the hemangioblast stage [76]. Interestingly, TEAD4 binding to specific *cis*-regulatory elements regulating vasculogenesis genes appeared to be dependent on AP-1, suggesting a TEAD4-recruiting role for AP-1 most probably via direct interactions. Importantly, AP-1/TEAD4 cooperation was shown to occur prior to the endothelial-to-hematopoeitic transition. Later, when hematopoietic fate is acquired, vasculogenesis-controlling genes get repressed with AP-1 and TEAD4 footprints becoming no longer detectable at their *cis*-regulatory elements.

Furthermore, genome-wide regulatory landscapes of primary human aortic endothelial cells (HAEC) were assessed under basal and activated conditions to elucidate transcriptional networks specifying vascular homeostasis and inflammation [77]. This provided evidence that a large fraction of detected enhancers is endothelial cell (EC)-specific and that AP-1 and Ets transcription factors co-bind a large fraction of them to regulate EC-specific genes. However, exposure of HAECs to oxidized phospholipids or pro-inflammatory cytokines results in the formation of several hundreds of de novo enhancers. The analysis of TFBS enrichment coupled to that of TF expression changes suggested that CEBPD, IRF1, and NF-κB are the coordinators of the response to cytokines, whereas NRF2 is involved in the response to oxidized phospholipids, indicating that different TFs regulate the networks controlling the endothelium in physiological and diseased states.

In a seminal work in macrophages, Ghisletti et al. [78] characterized the enhancers that are switched on to control inflammatory gene expression in macrophages stimulated by bacterial lipopolysaccharide (LPS). The authors showed that they contain TFBSs for lineage-restricted TFs such as PU.1 but also ubiquitous stress-inducible TFs including NF-κB, IRF and AP-1. More recently, another study was conducted to address chromatin dynamics during macrophage differentiation using the human myeloid cell line THP-1 induced to differentiate by PMA (phorbol 12-myristate 13-acetate) [52]. Enhancer hubs were identified that are enriched in AP-1-binding sites, suggesting a major role for distal AP-1-dependent enhancers in regulation of gene expression during macrophage development (also see Section 5 below).

Along the same line, the reciprocal effects of IFNγ and IL-4 on transcriptional programs underlying macrophage polarization were studied [79]. The authors found that these two cytokines inhibited the epigenomic and transcriptional changes induced by each of them alone. In this process, computational and functional analyses revealed that, while TFBSs for the transcription factors STAT1 and IRF1 at distal *cis*-regulatory elements were associated with robust and IL-4-resistant responses to IFN-γ, co-binding of the AP-1 protein JunB generated vulnerability to IL-4-mediated inhibition.

Finally, DNA elements that may control sensory experience-dependent gene expression rewiring in neuronal cells were addressed genome-wide using mouse cortical neurons submitted to in vitro depolarization [80]. The authors found that the subset of enhancers enriched for H3K4me1 and binding of the transcriptional coactivator CBP also shows increased levels of the active transcription-associated histone mark H3K27ac after membrane depolarization to regulate activity-dependent transcription. Interestingly, a subset of these distal enhancers appeared to require binding of Fos to become active. Along the same line and using ATAC-seq, it was recently asked whether chromatin accessibility landscapes of adult mouse dentate granule neurons in vivo could undergo changes upon synchronous neuronal activation [81]. The authors showed that 1 h activation was amply sufficient to detect genome-wide changes, enrichment of gained-open sites at active enhancer regions and at binding sites for AP-1 components, including c-Fos, with some of these changes being stable for at least 24 h.

4. Enhancer selection by AP-1 or selection of AP-1 by enhancers?

There is a series of paramount and intermingled questions relating to recognition of enhancers by AP-1. Among them, one can mention: (i) what are the TFBSs recognized by AP-1, (ii) are they always the same depending on the cell context, (iii) can they be functionally redundant in enhancers harboring multiple AP-1 TFBSs, (iv) what AP-1 dimer recognizes which TFBSs, (v) are these dimers the same or can they change according to cell signaling alteration, (vi) does AP-1 binding to specific TRE/CRE TFBSs depend on other transcription factors and/or co-factors, etc…? The available literature indicates that many of these questions remain open and, for those that have received a beginning of an answer, this answer remains far from being unique or final.

A first point to consider when addressing these issues is that > 400,000 consensus TRE/AP-1 sequences reside in the human genome, not taking into account all variant sequences that could bind AP-1 dimers [82]. As the number of peaks identified in the various ChIP-seq experiments addressing the location of AP-1 constituents in chromatin is usually in the 10^4 range, this indicates that only a minor fraction of TRE/AP-1 sites are actually bound by AP-1 transcription complexes in vivo. Though this is partly explained by various factors such as the rate-limiting abundances of AP-1-constituting proteins in the cell, the dynamic control of AP-1 proteins distribution within the cell and the nucleus [83,84] or the epigenetic status of the target sites (i.e. being within accessible or condensed/repressed chromatin regions), the available data (see Sections 4.1 and 4.2) also point to the existence of drastic mechanisms for AP-1 TFBS selection. Besides this, a wealth of observations indicates that the Fos and Jun family proteins can exert unique biological roles that cannot be compensated for by other family members in many, but not all, situations. Thus, gene knock-out- and knock-in experiments have shown that certain Fos and Jun proteins can show overlapping biological functions in particular cases [2,85–88]. This can only be explained by partly overlapping mechanistic actions, which are, however, still unclear. Moreover, it has also long been known that certain Fos or Jun family proteins can exert opposite functions, depending on the cell or signaling contexts [14]. For example, JunB has been proposed to exert tumor suppressor activity in the myeloid lineage [89,90] and to be a gatekeeper for B-lymphoid leukemia [91,92]. In contrast, it contributes, with c-Jun, to Hodgkin lymphoma [93]. Along the same line, Fos is oncogenic in the osteogenic lineage [94] whereas it has tumor suppressor activity in the absence of p53 in muscle precursor cells [95]. On their own, these observations already indicate that it must always be kept in mind that the transcriptional mechanisms controlled by the Fos and Jun proteins are multiple and dependent on the target genes, the cell context, the environmental cues at play and, possibly, the nature of the enhancers selected.

4.1. AP-1 binding to DNA: intrinsic properties of AP-1 binding sites and influence of their genomic environment

Crucial to the understanding of in vivo enhancer selection by AP-1 are the biophysical bases of TRE/AP-1 motif recognition by AP-1 dimers and how this binding is conditioned by the genomic environment of these motifs. Moreover, elucidating the mechanisms at play may provide molecular bases to identify pharmacological inhibitors of this transcription complex. Such a possibility was recently illustrated in a virtual screen of 2000 natural products that revealed veratramine as a specific small molecule inhibitor selectively recognizing and binding AP-1 DNA targets [96]. Possible off-target effects of veratramine must, however, still be assessed more extensively.

Over the years, there has been accumulating evidence that, not only the AP-1 TFBS sequence, but also its environment may alter the binding of AP-1 dimers (Fig. 2). In vitro binding assays and structural analyses (see [30] for details) have first provided precious information on how AP-1 complexes recognize their target TFBSs, even though most reports principally focused on c-Fos:c-Jun heterodimers. Key in this recognition is the bZip (basic-zipper) domain, which is centrally positioned within Fos family proteins but C-terminally located within Jun family members. It is comprised of the BR-LZ contiguous domains, where BR is a basic region of approximately 20 amino acids followed by a leucine zipper (LZ) formed of five heptads of amino acid residues, each containing a leucine at every seventh position. The LZ adopts a continuous α-helix secondary structure. In the context of both Jun:Jun and Fos:Jun dimers, α-helices wrap around each other in a coiled coil structural motif [31,97]. This intermolecular arrangement juxtaposes the basic regions at the N-termini of the bZips into close proximity, which permits them to get inserted into the major groove of DNA at AP-1 TFBSs in a manner reminiscent of forceps (scissor-grip model). Whereas the α-helices are maintained together owing to salt bridges and inter-helical hydrophobic contacts, hydrogen bonding between the basic residues' sidechains of the basic regions and the DNA bases is responsible for binding of bZip domains to DNA with high affinity. Several reports suggest that AP-1 components bind to DNA primarily as monomers and that dimerization occurs in association with DNA, leading to high affinity binding and reduced exchange between Fos and Jun proteins [32,98–101]. Biophysical studies combined to site-directed mutagenesis point to an intricate network of energetically-coupled residues within c-Fos and c-Jun BRs that underlies the ability of one monomer to increase the binding of the second one in an allosteric manner upon recognition of the consensus TRE/AP-1 motif [101]. Remarkably, basic residues within the two proteins are, not only engaged in close intermolecular ion pairing and hydrogen bonding contacts with the TRE/AP-1 motifs, but also make contacts with nucleotides flanking these motifs.

Moreover, in contrast to the fact that the sequence of bZips are highly conserved between Fos and Jun family members, the basic residues are poorly conserved among the other bZip proteins, underlying how they most probably contribute to the DNA-binding specificity of Fos:Jun and Jun:Jun dimers [101]. Additionally, it has long been known that the binding of AP-1 complexes to DNA is controlled by redox regulation [102,103]. However, the responsible mechanisms have remained enigmatic. More recently, the comparison of a series of crystal structures of the human FosB:JunD heterodimer, particularly abundant in the brain, in the presence and in the absence of DNA provided a first clue to this issue [104]. While both FosB and JunD contain ordered DNA-binding modules even in the absence of DNA,

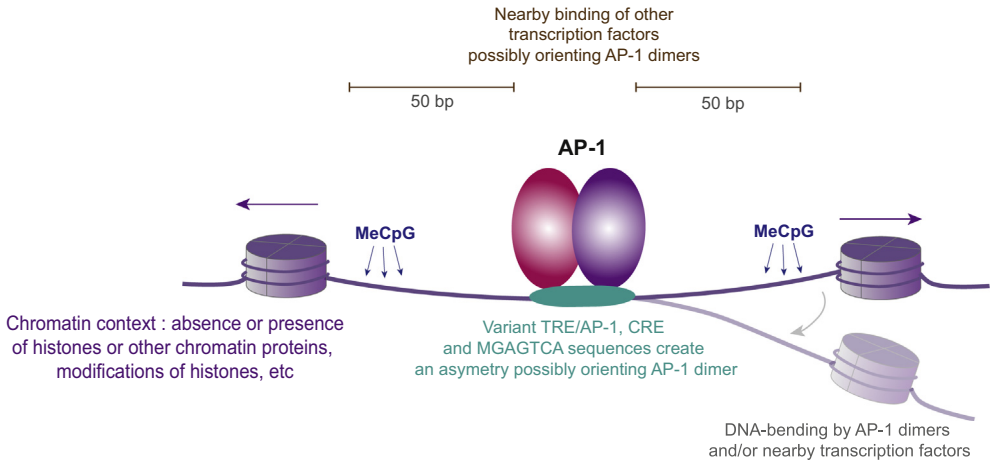

Fig. 2. Influence of the genomic environment on AP-1 binding to its cognate binding sites. The genomic environment can influence the binding of AP-1 dimers at various levels. The overall accessibility of chromatin around AP-1 TFBSs constitutes a first favorable (open chromatin) or unfavorable (heterochromatin) level (not represented). The chromatin context of AP-1 TFBS-bearing regulatory elements constitutes a second level of control. Classical features to be taken into consideration non-exclusively include the presence or the absence of histones or non-histone chromatin proteins, as well as the local post-translational modifications of histones. The region ± 50 bp, and especially ± 10 bp, around AP-1 TFBSs seems crucial for binding and activity of TRE/AP-1 dimers, in particular by allowing binding of other transcription factors [105]. Of note, binding of other TFs in the vicinity of AP-1 sites can orient the latter dimers due to protein-protein interactions dictated by the contact surfaces of the proteins at play. AP-1 influences DNA bending [106]. But, reciprocally, bending of DNA by other non-AP-1 transcription factors can also facilitate or decrease recognition of TRE/AP-1 TFBS by AP-1 dimers. It is of note that variations in the TRE/AP-1 and CRE TFBSs introduce asymmetry in the DNA motifs recognized by AP-1. Such an asymmetry may also result in orientation of bound dimers [107]. The same may occur upon recognition of MCAGCTCA motifs instead of classical TRE/AP-1 motifs as they are intrinsically asymmetric [108]. Finally, methylation of CpG motifs in the vicinity of AP-1 BS can also alter the binding of AP-1 [109].

only JunD is in a conformation capable of binding DNA. The FosB bZip domain must undergo a large conformational rearrangement in order to bind DNA, which is controlled by a redox molecular switch centered on an inter-molecular disulfide bond between FosB and JunD [104].

The ChIP-seq data now available for diverse Fos and Jun family members indicate that the sequences of AP-1 TFBSs can deviate from the optimal TRE/AP1 and CRE sequences. Therefore, an important question relates to the biological and biochemical effects of genetic variation in these motifs. It is worth noting that such sequence variations do not just concern AP-1 TFBSs located at different places in the genome but can also be linked to genetic polymorphisms at the same loci. In the latter case, they were associated with local histone modifications at regulatory elements bearing them and changes in target gene expression [110]. Beyond alteration in affinity, it must be considered that sequence variations can introduce asymmetry in the symmetric CRE and semi-symmetric TRE/AP-1 sites. This might translate into preferential binding orientation of AP-1 dimers onto DNA [111], with, as a consequence, better or lesser cooperation/interaction with other transcription factors and/or cofactors binding in the vicinity of the variant AP-1 TFBSs. This feature is important as Fos:Jun heterodimers and Jun family member heterodimers are inherently asymmetric due to structural differences between the dimerization partners, which offer different interaction surfaces. Biophysical investigations also suggested that genetic variations in the CRE motif introduce differential energetics in the binding of c-Fos:c-Jun heterodimers, which show preference for variants with higher AT contents, at least in vitro [112]. It was also proposed that sequence variations in the CRE motifs may allow it to sample different conformational space possibly affecting recognition by c-Fos:c-Jun heterodimers at distinct regulatory elements [112]. This is an interesting notion as, even though DNA bending was not observed in crystal structure of the c-Fos:c-Jun heterodimers bound to a consensus TRE/AP-1 motif-bearing oligonucleotide [97], several solution studies support the role of intrinsic bendability of DNA as being a key factor in its ability to recruit Fos:Jun heterodimers with high affinity [106,107,113].

Cytosine methylation has recently appeared as a feature altering the binding of AP-1 complexes to their cognate TFBSs. It is well documented that the majority of CpG dinucleotides in the mammalian genome are methylated at cytosine bases, although the methylation pattern is not uniform. In particular, active gene regulatory elements and their flanking sequences are generally hypomethylated and the binding of a number of TFs is diminished upon methylation of their target sequences. While investigating the genome-wide impact of cytosine methylation on DNA binding of a wide array of TFs, Yin et al. [109] showed that a large fraction of bZip proteins displays decreased binding while a minority of them shows unchanged or slightly increased binding. The latter observation is in line with previous reports showing that AP-1 dimers can recognize the 5'-MGAGTCA (meAP-1/TRE) motif where M is methylcytosine (5mC) [108,114], which shares with the thymidine in position 1 of the consensus TRE/AP-1 site a methyl group at the 5-carbon of the pyrimidine. Crystal structure analysis of c-Jun:c-Jun dimers shows that these methyl groups are in van der Waals contact with a conserved dialanine in the AP-1 dimer (Ala265 and Ala266 in human c-Jun) and that methylcytosine entails asymmetry in the TRE/AP-1 TFBS [115]. Such an observation has also been made for the Zta protein encoded by the Epstein-Barr virus. This TF is a close bZip homolog of c-Fos and a key regulator of the viral lytic cycle that can recognize both methylated motifs, 5'-TGAGMCA and 5′-TGAGMGA, within the viral genome [108,115]. Noteworthy, < 2% of the 45,000 potential meAP-1 sites predicted in the human genome are indeed methylated [108]. Their role in gene regulation, however, still remains to be assessed functionally.

As mentioned in the introduction, recognition of DNA by Jun and Fos proteins is not limited to the TRE/AP-1 and CRE motifs and their variants. In addition to the 18 dimers they can form together, Fos and Jun family members, as described earlier, can heterodimerize with other bZip proteins exhibiting distinct binding specificities. Therefore, this extends the repertoire of their binding sites to include sequences composed of different half-sites recognized by their dimerization partners (see [30] for details).

There is also evidence that the genomic environment of AP-1 TFBSs influences the binding of AP-1 dimers. For instance, it has long been known that several members of the NFAT, Ets, Smad and bHLH families of TFs can activate or repress transcription together with Fos and Jun family proteins via binding to regulatory elements adjacent to AP-1 sites (see [30] for details) cooperative binding between AP-1 and another TF has long been described in the case of NFAT. Specifically, X-ray-based structural analysis has shown tight association of c-Fos, c-Jun and NFAT to create a continuous groove for recognition of a 15 bp DNA motif [116]. One of the mechanisms underlying synergy involves protein-protein interactions between AP-1 dimers and these other TFs at composite regulatory elements that possess activities over and above those of their individual constituent binding sites. Multiprotein complexes formed at composite regulatory elements usually show higher

stability as compared to complexes formed by individual transcription factors at their respective recognition sites and, interestingly, can integrate concurrent responses to different signal transduction pathways targeting their components separately. Along the same line, recent interrogation of the role of sequences flanking TRE/AP-1 TFBSs at DNAse I hypersensitive sites and annotated enhancers in the mammalian genome revealed sequence features directly adjacent to the core motif that distinguish high from low activity TRE/AP-1 sites [105]. Overall, the local sequence features underlying high activity sites appeared localized within 50 bp, with most of them within 10 bp of the TRE/AP-1 core motif. Some of these nearby features are motifs for other TFs that genetically interact with the AP-1 site whereas others are extensions of the TRE/AP-1 core motif. In the latter case, this causes the extended sites to match motifs for multiple AP-1 complex-binding proteins. Corroborating former in vitro binding assays, nucleotides directly flanking the AP-1 core motif also help specify high activity sites. Interestingly, differential CpG methylation within 40 bp of AP-1 binding sites was also shown associated with changes in gene expression in Schwann cells after nerve injury, raising the possibility that DNA methylation in the vicinity of TRE/AP-1 TFBSs may have a biologically important and possibly causal relationship with TF binding and activity of AP-1-responsive enhancers [117].

4.2. Selection of AP-1-binding sites in vivo and control of chromatin accessibility by AP-1

As mentioned earlier, only a small minority (less than a few per cent) of potential AP-1 TFBSs are actually bound in vivo, raising the question of how they are selected and utilized. It is commonly accepted that most transcription factors bind chiefly to nucleosome-depleted regions [38,40]. However, certain TFs are also capable of recognizing and engaging nucleosomal DNA, as well as of opening chromatin via the recruitment of other TFs and chromatin remodelers to trigger transcription. For this reason, they are called “pioneer transcription factors” [51]. In this general context, there is accumulating evidence that AP-1 can exert transcription-pioneering-, chromatin-remodeling- and chromatin accessibility maintenance actions.

The ability of AP-1 to bind DNA wrapped around a histone octamer was first demonstrated by Ng et al. at the Fra-2 (*fosl2)* promoter region using in vitro assays [118]. They showed that, following binding to its cognate TFBS, the c-Fos:c-Jun heterodimer can alter the structure of the nucleosome by modifying histone-DNA interactions, thus allowing the binding of another transcription factor (SRY in this case), provided that histones are acetylated. Notably, ability to alter nucleosome structure with, however, the absence of histone displacement from the DNA template was independent of any chromatin-remodeling enzymatic activity, i.e. was an ATP-independent intrinsic property of the c-Fos:c-Jun heterodimer under the experimental condition used.

It is only recently that studies have provided in vivo evidence for a role of AP-1 in chromatin accessibility control. The binding of AP-1 was shown to facilitate the recruitment of the glucocorticoid receptor (GR) at approximately 50% of GR TFBSs in the genome upon hormone stimulation of a mouse mammary epithelial cell line [73]. This was achieved by maintaining the local chromatin environment in an open and accessible configuration independently of any hormone treatment and was largely due to active repositioning of nucleosomes, as ectopic expression of a dominant negative form of c-Fos (A-fos) forming stable heterodimers unable to bind to DNA significantly reduced GR binding as well as chromatin accessibility at many (but not all) sites. Along the same line, genome-wide analysis of DHSs and gene expression in 112 human samples representative of 72 cell types showed the TRE/AP-1 motif to be the most enriched TFBS in both cell-type-specific and ubiquitous DHSs in a manner suggesting a role in regulating open chromatin for AP-1 [119]. Similarly, the fact that mutations producing better matches to AP-1 motif on either the human or chimpanzee genome correlate with the presence of species-specific DHS sites also supports a role for AP-1 in facilitating or maintaining chromatin accessibility [60]. Such a role for AP-1 has also been described under pathological conditions of AP-1 expression. For example, together with NF-κB, hyperactivated AP-1, due to overexpression of its c-Jun and Fra-1 components in certain aggressive mammary cancers, was shown to promote chromatin accessibility at the IL-6 locus, the high expression of which is involved in promoting angiogenesis and metastasis [120]. Strengthening this idea, ectopic expression of Fra-1 in the MCF-7 cell line, which is weakly metastatic and weakly expressing AP-1, significantly increased chromatin accessibility at this locus and was accompanied by a higher expression of the IL-6 gene [120].

Interestingly, AP-1 was also described as a guardian of the somatic cell fate, as its suppression is necessary to permit induced pluripotent stem cells (iPSCs) formation from mouse embryonic fibroblasts (MEFs) [121]. Subsequently, while assessing the opening of chromatin using a variety of techniques including ATAC-seq and histone modification ChIP-seqs, the closing of AP-1-bound enhancers was found critical for the reprogramming of MEFs into iPSCs either with the Yamanaka factors Oct4, Sox2 Klf4/ OSK and c-Myc [121,122] or using chemical-induction of pluripotency [123]. Supporting this view, ectopic overexpression of c-Jun hampered the closure of approximately 60% of fibroblast-specific enhancers, which caused an important defect in chromatin dynamics and efficiently weakened the reprogramming. In parallel, the knockdown of AP-1 components significantly increased the number of reprogrammed cells [121,124,125]. The mechanisms leading to the closing of open chromatin during iPSC induction are still obscure. However, a shift in the P300/HDAC1 equilibrium was noted at MEF enhancers that were lost upon induction of pluripotency, leading to a decrease in the local acetylation on histone H3K27 [122]. Repression of Fra-1 was also shown to be necessary.

Interestingly, Vierbuchen et al. [74] used mouse embryo fibroblasts stimulated by EGF to study enhancer selection during the biological response to a growth factor, a situation that mimics cell expansion facilitating wound healing. Their data suggest a model whereby the activated Ras/MAPK signaling pathway participates actively in enhancer selection by inducing transcription of AP-1 TF genes (that are long-known immediate early response genes). Induced Fos and Jun proteins would then collaboratively bind with cell lineage-specific TFs to nucleosome-embedded enhancers of late response genes and recruit the BAF (SWI/SNF) chromatin-remodeling complex to open chromatin. Consistently with this information, the BAF60 component of the BAF complex was formerly reported to interact with and to stimulate the transactivation potential of c-Fos:c-Jun heterodimers, but not that of the Fra2:JunD complex that has no affinity for it [126]. Altogether, these data support the idea that AP-1 can have transcription-pioneering functions. However, in silico experiments suggest that direct interaction of AP-1 with DNA bound to a histone octamer could be restrained due to steric hindrance within the nucleosomal structure [127], indicating that further studies are needed to fully understand the effect of AP-1 on chromatin dynamics.

5. Active AP-1-bound enhancers and chromatin architecture

The genome-wide data presented earlier in this review underline a crucial role for chromatin looping in the expression of AP-1-regulated genes via bringing about distal enhancers and gene promoters. Further questions are whether AP-1-bound enhancers cooperate with other enhancers (possibly not binding AP-1), how chromatin structure regulation contributes to gene expression and whether AP-1 controls chromatin dynamics.

The existence of chromatin loops involving AP-1-bound enhancers was first formally demonstrated using classical chromosome conformation capture (3C) analyses of specific genes (see Box 1). For example, in human chondrosarcoma cells, induction of the Matrix metalloproteinase 13 (collagenase-3) gene by IL-1β generates a long-range interaction (20 kb) between an AP-1-bound enhancer and the gene

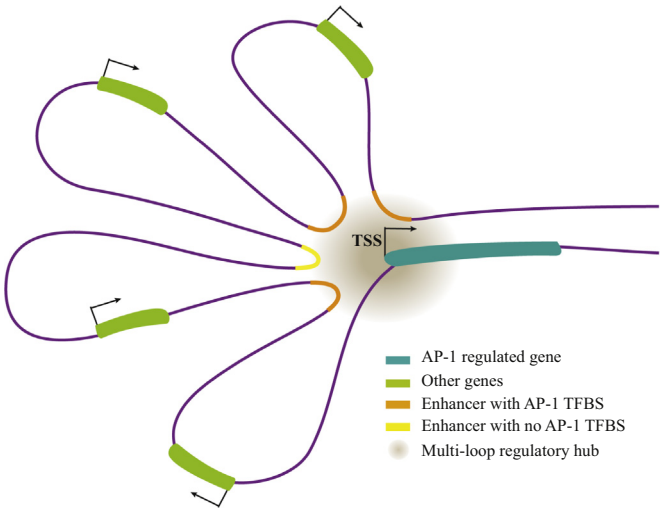

Fig. 3. Model of AP-1-binding at enhancer hubs. Owing to multiple chromatin looping events, enhancer hubs can form to regulate the activity of gene promoters. Some of them can bear TRE/AP-1 TFBSs and others not. Genes not regulated by AP-1 can be found in chromatin loops, underlining that assignment of enhancers to the nearest genes is not always pertinent.

promoter [128]. Upon epidermal differentiation, longer interaction ranges involving the 923 AP-1-bound enhancer were also reported for the expression of the epidermal differentiation complex (EDC) clustered genes, as described earlier [75]. Besides this, 3C has also been used to visualize inducible short-range interactions (kb range or less) involving AP-1-bound promoters [129], between close AP-1-bound enhancers [130] as well as between AP-1- and NF-κB-bound enhancers [131,132]. Interestingly, when the EMT-controlling TF ZEB2 transcription is activated by TNFα in TNBC cells, two ZEB2 transcripts derived from two distinct promoters are produced. The binding of AP-1 to the distal promoter allows the regulation of the expression at both promoters by driving long range chromatin interactions between ZEB2 distal and proximal promoters [129]. Upon induction of the metalloproteinase-9 gene by TNFα in U937 human myeloid leukemia cells [132] and activation of the osteopontin gene by bacterial LPS in mouse macrophages [131], close AP-1- and NF-κB-bound regulatory elements begin to interact physically and functionally to recruit the acetyl transferase p300, which entails local histone acetylation. In this case, DNA looping seems dependent on prior binding of AP-1 and NF-κB to their cognate TFBSs.

Of note, short-range chromatin looping is also crucial for basal 3D organization of at least one of the AP-1 component genes (*junb*) [133]. The main enhancer region, which harbors TFBSs for multiple TFs, is located just downstream of *junb* polyadenylation site and is brought into contact of the paused gene promoter located only 2 kb upstream, explaining the high transcriptional reactivity of *junb* to stimuli of many sorts.

Genome-wide approaches were also used to address the chromatin 3D organization in relation with AP-1-regulated transcription. Using THP-1 human myeloid cells stimulated by PMA as a differentiation model, the formation of multi-loop activation hubs was demonstrated at key macrophage genes [52]. Indeed, the authors observed that transcriptional regulation is accompanied by both gained and preformed chromatin loops that acquire enhancer activity during differentiation. Interestingly, gained loops are enriched for gene promoters and connect several regulatory elements with an average of 3–4 enhancers per promoter. Moreover, ATAC-seq (see Box 1) combined to sequence and motif analyses and to TF footprinting at enhancers sites of activated loops identify enrichment for occupied AP-1 sites. The hubs connecting a gene promoter to multiple distal enhancers are associated with strong upregulation of gene transcription. However, the presence of these hubs was speculated but not functionally validated. Indeed, most 3C-

Box 2

Pending questions. A number of important issues concerning the mechanisms used and controlled by AP-1 are still pending. The list is not exhaustive.

AP-1 binding sites

- What is the fraction of binding sites that can actually be recognized by AP-1 in the genome?
- Are they always the same or can they be significantly different depending on the cell and/or signaling context?
- Is the role of AP-1 binding sites always the same depending on the cell and/or signaling context?
- Is there redundancy between AP-1-binding sites when multiple such sites are found in the same enhancers?

AP-1 dimers

- To which extent can the same AP-1-binding sites be recognized by different AP-1 dimers and for which purpose?
- How is the recognition of specific AP-1-binding sites by specific AP-1 dimers regulated and what is the contribution of cell signaling in this recognition?
- What are the respective molecular roles of AP-1 components within AP-1 dimers? Are they always the same or can they vary according to the target gene, the cell context or signaling events?
- To which extent can redundancy between different AP-1 dimers or between different AP-1 family members affect the activity of regulatory elements hubs or superenhancers?

AP-1 binding and gene regulation

- Can AP-1-binding regulatory elements be shared by different genes? How and when?
- How does AP-1 exert its transcription pioneering, chromatin-remodeling and chromatin accessibility maintenance actions at its different target genes and in different cell and signaling contexts?
- How do AP-1-binding enhancers collaborate with non-AP-1-binding enhancers in enhancer hubs to regulate transcription? Are the roles of the different enhancers equivalent or not?

AP-1 transcriptional co-factors

- How is the binding of AP-1 to AP-1-binding sites coordinated with nearby binding of other transcription factors and what are the fine molecular consequences of coordinated binding to DNA, as illustrated, for example, by TEADs or ETS TFs?
- Does AP-1 binding precede or follow binding of transcriptional co-factors and/or the transcription machinery itself at regulatory elements?

techniques study chromatin interactions across cell populations. Therefore, it is impossible to conclude from these datasets whether all interactions are occurring at the same time in the same cell or whether they represent an average of independent interactions in different cells. Recently, evidence that formation of enhancer hubs and DNA loop collisions may be central for gene regulation has been published in other settings. High-resolution analysis methods developed in these studies, such as multi-contact 4C (MC-4C) [134] or Tri-C [135] should help address how AP-1 TFBS-bearing regulatory sequences and promoters coordinate spatially their actions (see Box 1). In particular, combined with other functional analyses, they should allow to assess whether or not and to which extent AP-1 controls loop/hubs formation (Fig. 3). Another possibility might be that AP-1 exerts its transcriptional action after formation of hubs in different physiopathological situations, or help reinforcing or stabilizing 3D chromatin contacts.

6. Conclusion

In summary, the data accumulated recently in a variety of experimental systems strengthen the fact that AP-1 plays a key role in the transcriptional regulatory networks via binding to promoter regions or proximal to promoter regions. However, they strongly indicate that AP-1 principally exerts its transcriptional effects through binding to distal, or very distal, regulatory elements. This places control of chromatin architecture and dynamics at the heart of AP-1 biology, even though functionally demonstrated assignment of enhancers to their actual target genes has little been addressed formally so far. This also poses novel mechanistic questions with regard to AP-1 transcriptional actions (see Box 2). Among these, one can include its collaboration with other transcription factors, transcriptional cofactors and the transcription machinery itself as well as the transcription-pioneering-, chromatin-remodeling- and chromatin accessibility maintenance functions that have recently been unveiled for AP-1.

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Declaration of interest

None.

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