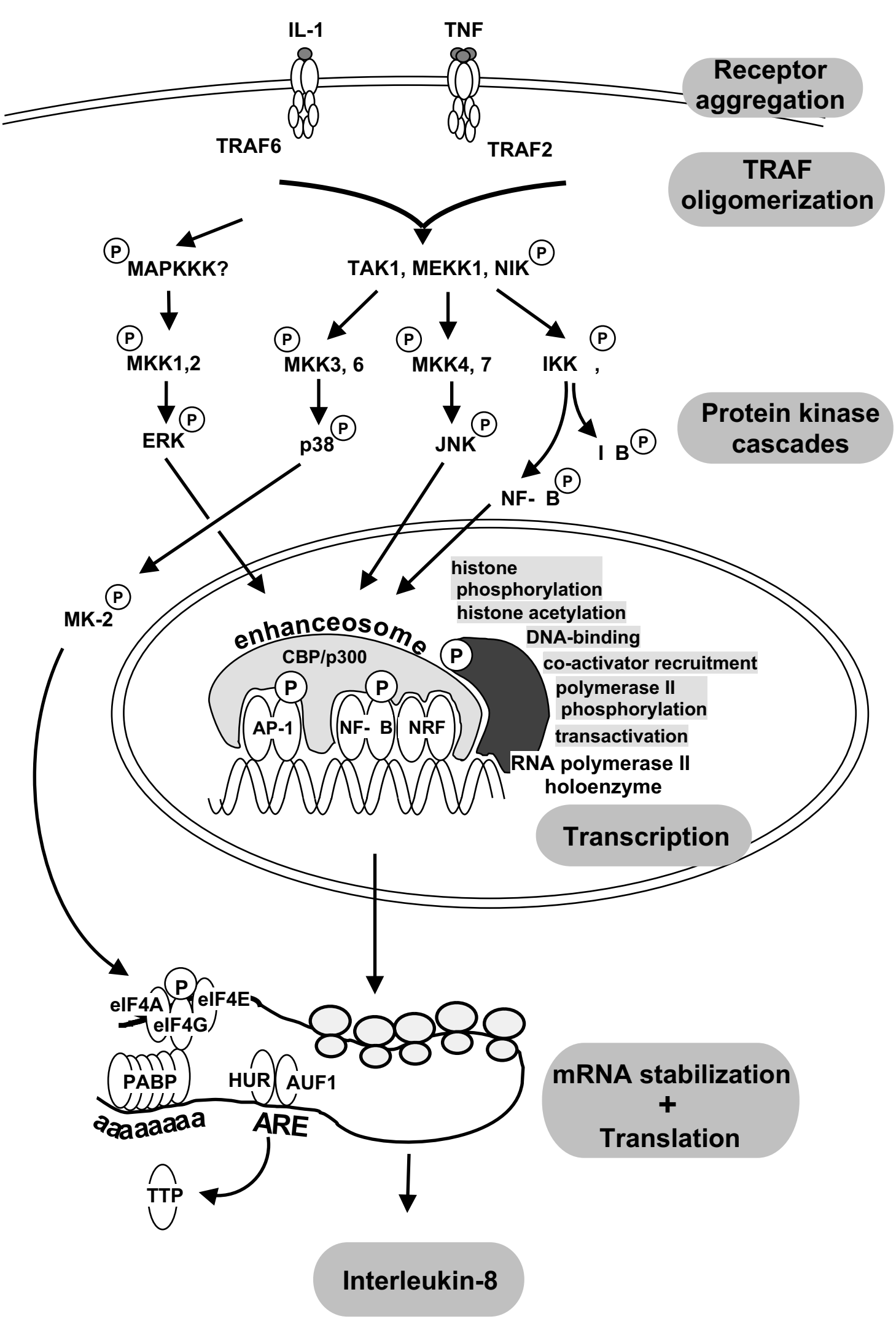
IL-1
TNF
Receptor aggregation
TRAF6
TRAF2
TRAF oligomerization
MAPKKK?
TAK1, MEKK1, NIK
MKK1,2
MKK3, 6
MKK4, 7
IKK ,
Protein kinase cascades
ERK
p38
JNK
I B
NF- B
MK-2
histone phosphorylation
histone acetylation
DNA-binding
co-activator recruitment
polymerase II phosphorylation
transactivation
RNA polymerase II holoenzyme
enhanceosome
CBP/p300
AP-1
NF- B
NRF
Transcription
eIF4A
eIF4E
eIF4G
PABP
HUR
AUF1
aaaaaaaa
ARE
TTP
mRNA stabilization + Translation
Interleukin-8

from Hoffmann et al., J.Leukocyte Biol., 2002

FIG.3. ESSENTIAL SIGNAL TRANSDUCTION STEPS IN CYTOKINE-MEDIATED IL-8 GENE REGULATION.

In unstimulated cells the NF-κB repressing factor NRF prevents IL-8 transcription (60). Interleukin (IL)-1 or tumor necrosis factor (TNF)-α binding to the cell surface results in formation of multimeric receptor complexes that recruit the adaptor proteins TRAF6 or TRAF2, respectively (48, 103, 104). TRAF oligomerization triggers activation of MAPKKK, such as TAK1, NIK or MEKK1 by unknown mechanisms (48, 103, 104). TAK1 or MEKK1 activate both, the MKK7-JNK and the IκB kinase (IKK)-β and -γ pathways (59-61, 71, 72). The direct targets of JNK as well as the proteins binding to the AP-1 site have not been identified, whereas IKK phosphorylates IκB, allowing release of NF-κB (25). The p65 subunit of NF-κB translocates to the nucleus and binds to the NF-κB site of the IL-8 promoter (24, 60). There it interacts with constitutively bound NRF and AP-1 transcription factors (60, 61). Post-translational modifications such as phosphorylation of the transactivation domains of AP-1 (23) and NF-κB (21), coactivator (CBP/p300) recruitment (28) and histone phosphorylation or –acetylation (28, 82, 94) result in chromatin remodelling and strong IL-8 transcription. The *cis*-elements for AP-1, NF-κB or NRF can not be altered without decreasing JNK or NF-κB mediated IL-8 trancription (60, 61), favouring a model where all the proteins involved in transcription interact to form a multi-protein complex. This enhanceosome-like structure favours maximal contact with the RNA polymerase II holoenzyme which itself becomes phosphorylated (83). The newly synthesized transcript is then rapidly stabilized by the p38 MAPK pathway which targets AU-rich elements (ARE) in the IL-8 mRNA through an unknown mechanism that may involve proteins binding to the ARE (e.g. AUF-1 or HUR) (47). Essential steps in signal transmission and gene expression are shaded in gray.

Abbreviations: AP-1, activating protein 1, AUF-1, AU-binding factor 1, CBP, CREB-binding protein, eIF, elongation initiation factor, IκB, inhibitor of NF-κB, JNK, JUN N-terminal protein kinase, HUR, Embryonic lethal abnormal vision (Elav)-like RNA-binding protein HuR, MAPK, mitogen-activated protein (MAP) kinase, MAPKKK, MAPK kinase kinase, MEKK1, Mitogen-activated ERK kinase kinase 1, MKK7, MAPK kinase 7, MK-2, MAPK-activated protein kinase-2; NIK, NF-κB -inducing kinase, NRF, NF-κB repressing factor, P, phosphorylation, PABP, polyA-binding protein, TRAF, TNF-receptor associated factor, TAK1, TGF-β-activated protein kinase.