RAS-MAPK YOLAĞI

DR. HAMİT ÖZYÜREK

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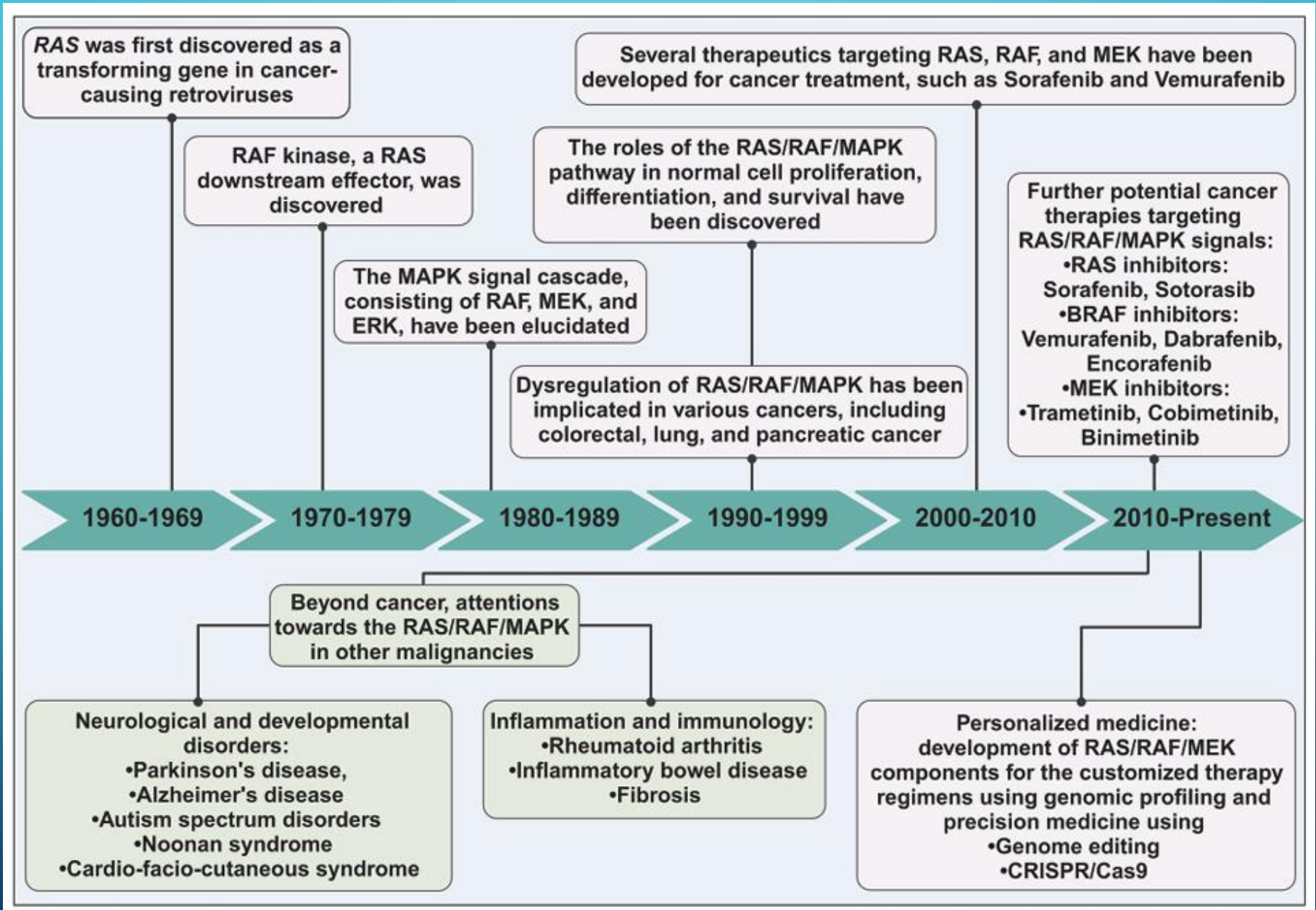
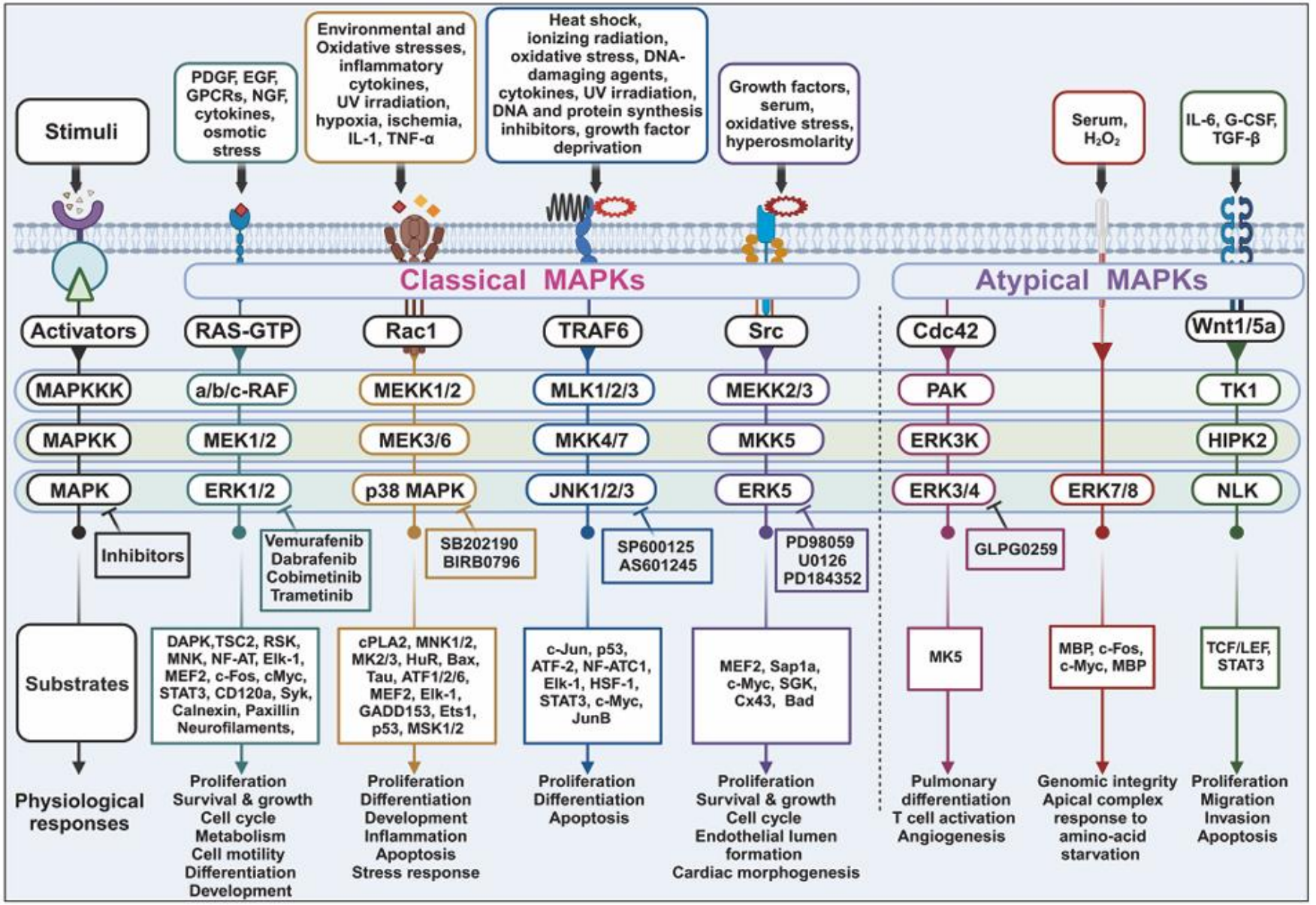
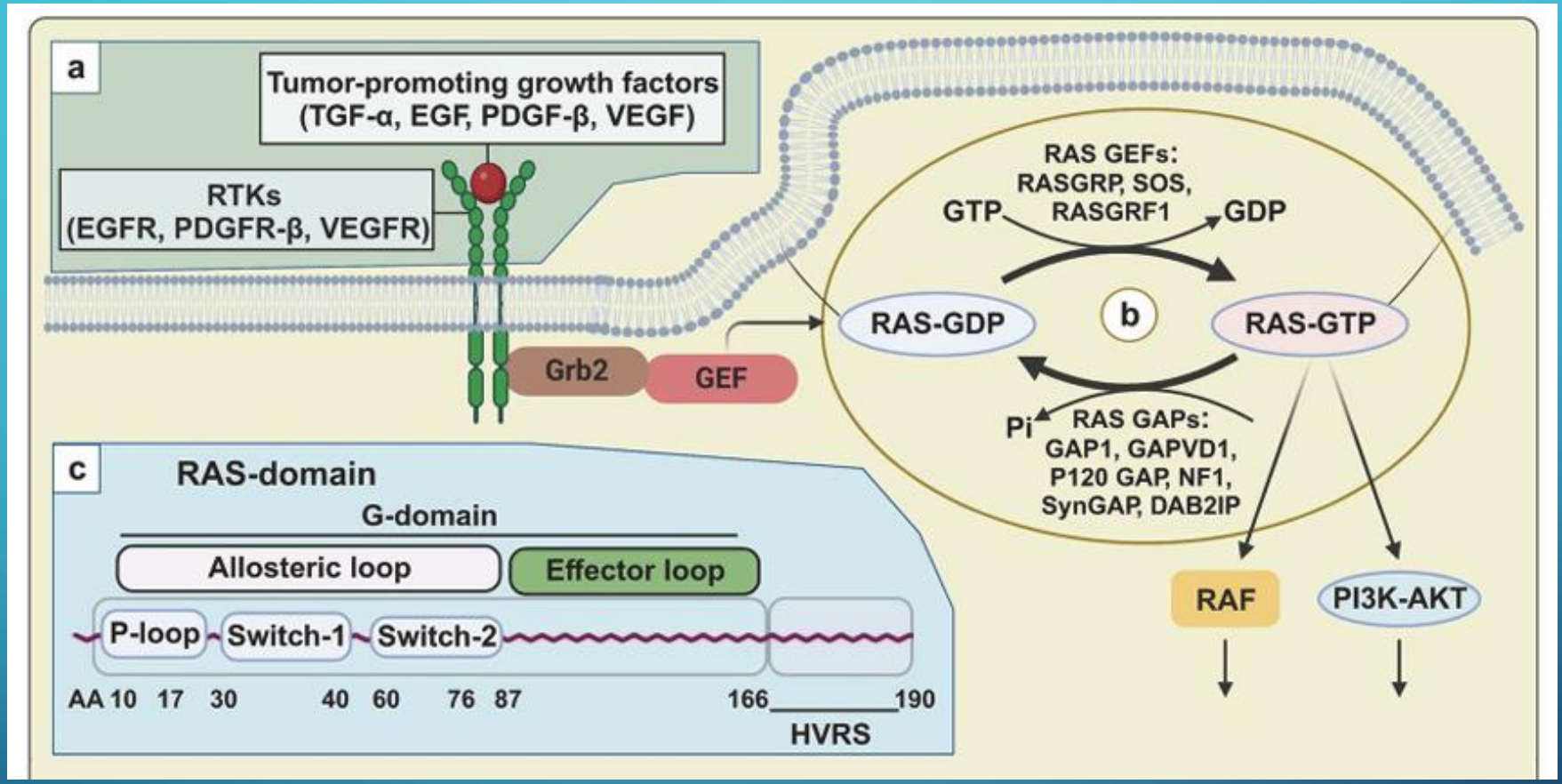
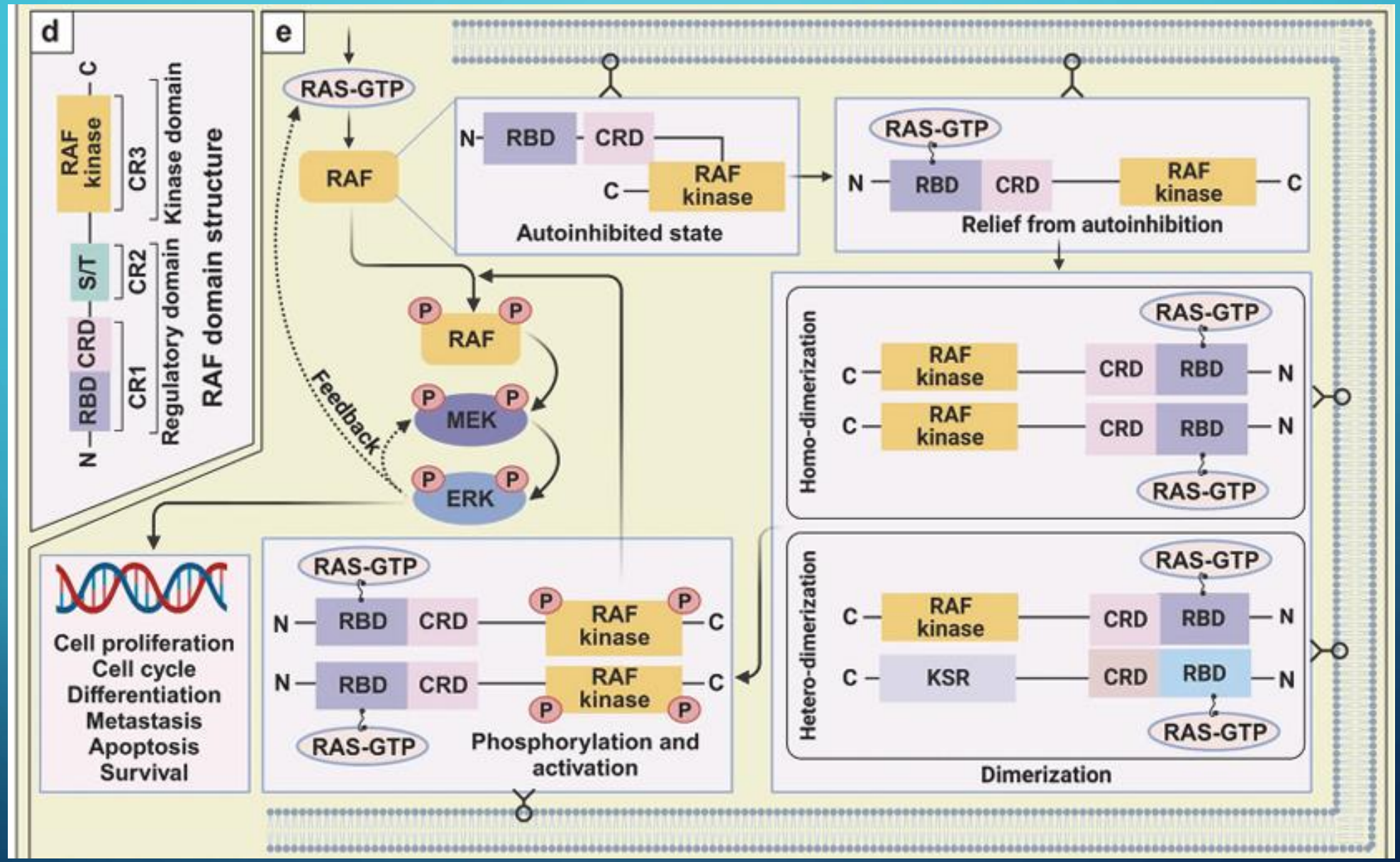
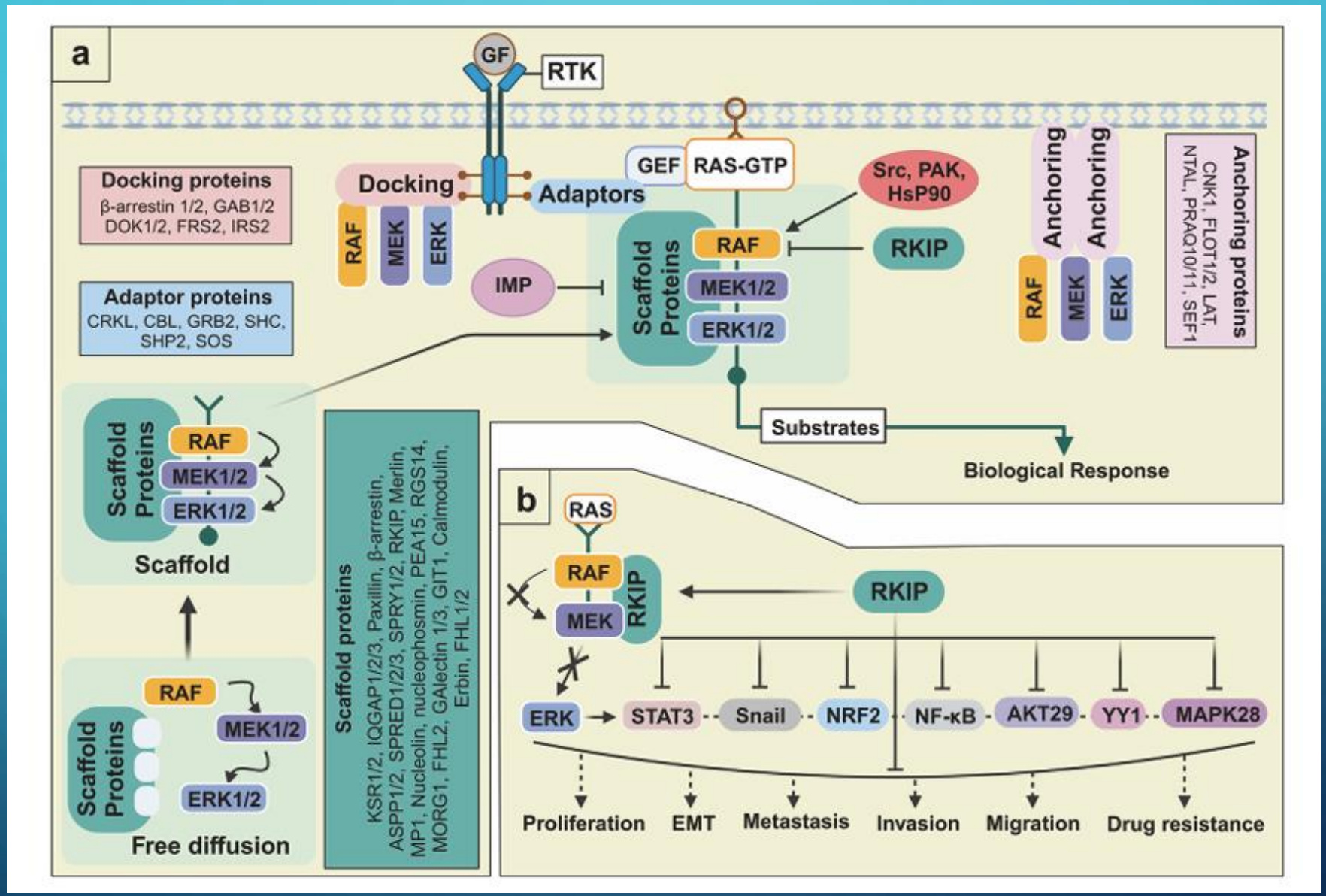
ŞEHİR HASTANESİ ÇOCUK NÖROLOJİ

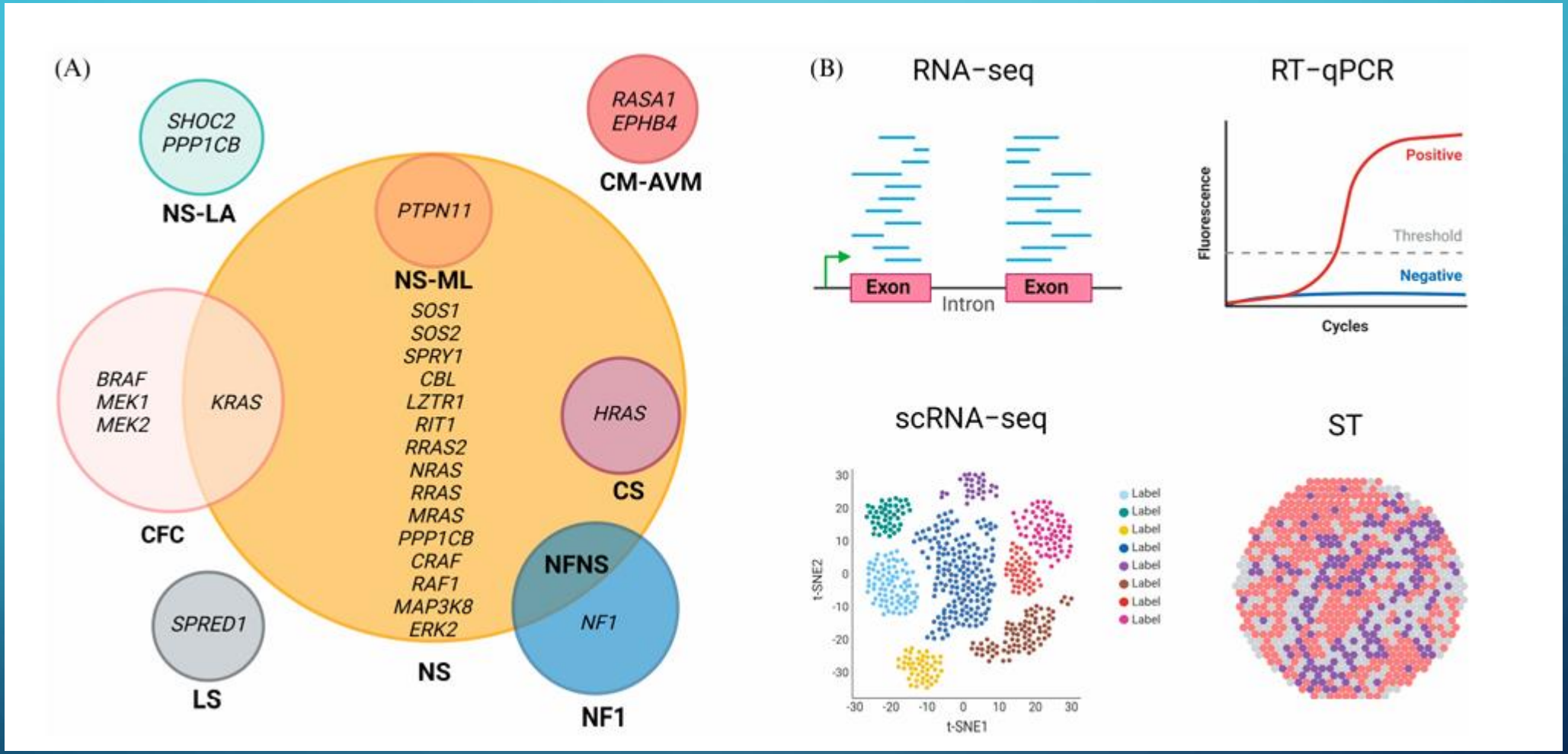

RAS was first discovered as a transforming gene in cancer-causing retroviruses
RAF kinase, a RAS downstream effector, was discovered
The MAPK signal cascade, consisting of RAF, MEK, and ERK, have been elucidated
The roles of the RAS/RAF/MAPK pathway in normal cell proliferation, differentiation, and survival have been discovered
Dysregulation of RAS/RAF/MAPK has been implicated in various cancers, including colorectal, lung, and pancreatic cancer
Several therapeutics targeting RAS, RAF, and MEK have been developed for cancer treatment, such as Sorafenib and Vemurafenib
Further potential cancer therapies targeting RAS/RAF/MAPK signals:
•RAS inhibitors:
Sorafenib, Sotorasib
•BRAF inhibitors:
Vemurafenib, Dabrafenib, Encorafenib
•MEK inhibitors:
•Trametinib, Cobimetinib, Binimetinib
1960-1969
1970-1979
1980-1989
1990-1999
2000-2010
2010-Present
Beyond cancer, attentions towards the RAS/RAF/MAPK in other malignancies
Neurological and developmental disorders:
•Parkinson's disease,
•Alzheimer's disease
•Autism spectrum disorders
•Noonan syndrome
•Cardio-facio-cutaneous syndrome
Inflammation and immunology:
•Rheumatoid arthritis
•Inflammatory bowel disease
•Fibrosis
Personalized medicine:
development of RAS/RAF/MEK components for the customized therapy regimens using genomic profiling and precision medicine using
•Genome editing
•CRISPR/Cas9

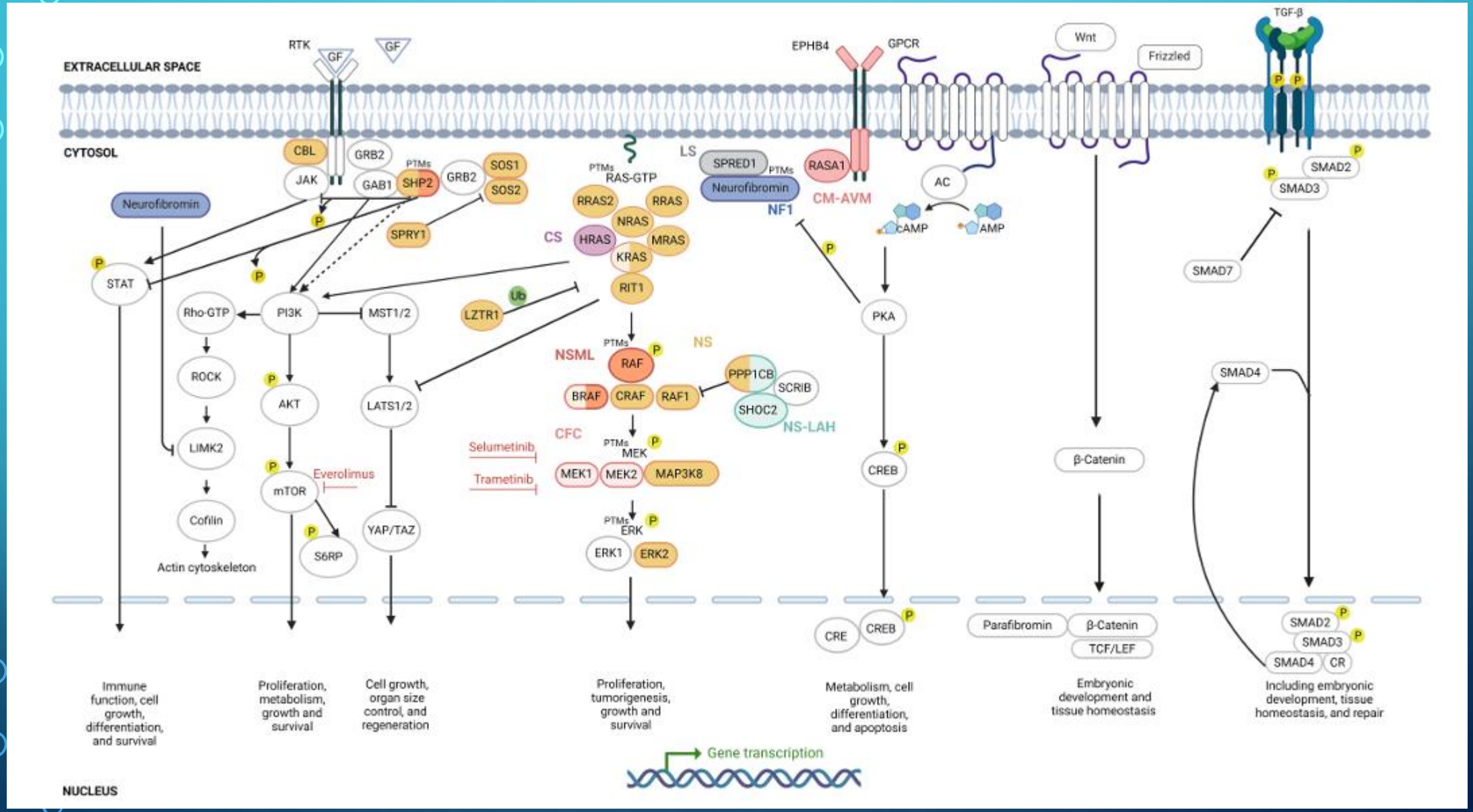

Stimuli
PDGF, EGF, GPCRs, NGF, cytokines, osmotic stress
Environmental and Oxidative stresses, inflammatory cytokines, UV irradiation, hypoxia, ischemia, IL-1, TNF-α
Heat shock, ionizing radiation, oxidative stress, DNA-damaging agents, cytokines, UV irradiation, DNA and protein synthesis inhibitors, growth factor deprivation
Growth factors, serum, oxidative stress, hyperosmolarity
Serum, H_2O_2
IL-6, G-CSF, TGF-β
Classical MAPKs
Atypical MAPKs
Activators
RAS-GTP
Rac1
TRAF6
Src
Cdc42
Wnt1/5a
MAPKKK
a/b/c-RAF
MEKK1/2
MLK1/2/3
MEKK2/3
PAK
TK1
MAPKK
MEK1/2
MEK3/6
MKK4/7
MKK5
ERK3K
HIPK2
MAPK
ERK1/2
p38 MAPK
JNK1/2/3
ERK5
ERK3/4
ERK7/8
NLK
Inhibitors
Vemurafenib
Dabrafenib
Cobimetinib
Trametinib
SB202190
BIRB0796
SP600125
AS601245
PD98059
U0126
PD184352
GLPG0259
Substrates
DAPK,TSC2, RSK, MNK, NF-AT, Elk-1, MEF2, c-Fos, cMyc, STAT3, CD120a, Syk, Calnexin, Paxillin Neurofilaments,
cPLA2, MNK1/2, MK2/3, HuR, Bax, Tau, ATF1/2/6, MEF2, Elk-1, GADD153, Ets1, p53, MSK1/2
c-Jun, p53, ATF-2, NF-ATC1, Elk-1, HSF-1, STAT3, c-Myc, JunB
MEF2, Sap1a, c-Myc, SGK, Cx43, Bad
MK5
MBP, c-Fos, c-Myc, MBP
TCF/LEF, STAT3
Physiological responses
Proliferation
Survival & growth
Cell cycle
Metabolism
Cell motility
Differentiation
Development
Proliferation
Differentiation
Development
Inflammation
Apoptosis
Stress response
Proliferation
Differentiation
Apoptosis
Proliferation
Survival & growth
Cell cycle
Endothelial lumen formation
Cardiac morphogenesis
Pulmonary differentiation
T cell activation
Angiogenesis
Genomic integrity
Apical complex response to amino-acid starvation
Proliferation
Migration
Invasion
Apoptosis


a
Tumor-promoting growth factors
(TGF-α, EGF, PDGF-β, VEGF)
RTKs
(EGFR, PDGFR-β, VEGFR)
Grb2
GEF
RAS GEFs:
RASGRP, SOS,
RASGRF1
GTP
GDP
RAS-GDP
b
RAS-GTP
Pi
RAS GAPs:
GAP1, GAPVD1,
P120 GAP, NF1,
SynGAP, DAB2IP
RAF
PI3K-AKT
c
RAS-domain
G-domain
Allosteric loop
Effector loop
P-loop
Switch-1
Switch-2
AA 10 17 30 40 60 76 87 166 190
HVRS


d
RAF domain structure
Kinase domain
Regulatory domain
RAF kinase
CR3
S/T
CR2
RBD
CRD
CR1
C
N
e
RAS-GTP
RAF
N
RBD
CRD
C
RAF kinase
Autoinhibited state
Relief from autoinhibition
P
MEK
ERK
Feedback
Homo-dimerization
Hetero-dimerization
KSR
Dimerization
Phosphorylation and activation
Cell proliferation
Cell cycle
Differentiation
Metastasis
Apoptosis
Survival


a
GF
RTK
Docking proteins
β-arrestin 1/2, GAB1/2
DOK1/2, FRS2, IRS2
Docking
Adaptors
GEF
RAS-GTP
Src, PAK, HsP90
RAF
MEK
ERK
IMP
Scaffold Proteins
RAF
MEK1/2
ERK1/2
RKIP
Anchoring
Anchoring
RAF
MEK
ERK
Anchoring proteins
CNK1, FLOT1/2, LAT, NTAL, PRAQ10/11, SEF1
Adaptor proteins
CRKL, CBL, GRB2, SHC, SHP2, SOS
Substrates
Biological Response
Scaffold
Free diffusion
Scaffold proteins
KSR1/2, IQGAP1/2/3, Paxillin, β-arrestin, ASPP1/2, SPRED1/2/3, SPRY1/2, RKIP, Merlin, MP1, Nucleolin, nucleophosmin, PEA15, RGS14, MORG1, FHL2, GAlectin 1/3, GIT1, Calmodulin, Erbin, FHL1/2
b
RAS
RAF
MEK
RKIP
ERK
STAT3
Snail
NRF2
NF-κB
AKT29
YY1
MAPK28
Proliferation
EMT
Metastasis
Invasion
Migration
Drug resistance


(A)
SHOC2
PPP1CB
NS-LA
RASA1
EPHB4
CM-AVM
PTPN11
NS-ML
SOS1
SOS2
SPRY1
CBL
LZTR1
RIT1
RRAS2
NRAS
RRAS
MRAS
PPP1CB
CRAF
RAF1
MAP3K8
ERK2
NS
BRAF
MEK1
MEK2
KRAS
CFC
HRAS
CS
NFNS
NF1
NF1
SPRED1
LS
(B)
RNA-seq
Exon
Intron
Exon
RT-qPCR
Positive
Threshold
Negative
Fluorescence
Cycles
scRNA-seq
t-SNE2
t-SNE1
Label
ST


EXTRACELLULAR SPACE
CYTOSOL
NUCLEUS
RTK
GF
GF
CBL
GRB2
JAK
GAB1
PTMs
SHP2
GRB2
SOS1
SOS2
SPRY1
Neurofibromin
STAT
Rho-GTP
PI3K
MST1/2
ROCK
AKT
LATS1/2
LIMK2
Cofilin
Actin cytoskeleton
mTOR
Everolimus
S6RP
YAP/TAZ
Ub
LZTR1
PTMs
RAS-GTP
RRAS2
RRAS
NRAS
CS
HRAS
MRAS
KRAS
RIT1
NSML
PTMs
RAF
NS
BRAF
CRAF
RAF1
PPP1CB
SCRIB
SHOC2
NS-LAH
CFC
PTMs
MEK
MEK1
MEK2
MAP3K8
Selumetinib
Trametinib
PTMs
ERK
ERK1
ERK2
LS
SPRED1
PTMs
Neurofibromin
NF1
EPHB4
GPCR
RASA1
CM-AVM
AC
cAMP
AMP
PKA
CREB
CRE
CREB
Wnt
Frizzled
β-Catenin
Parafibromin
β-Catenin
TCF/LEF
TGF-β
SMAD2
SMAD3
SMAD7
SMAD4
SMAD2
SMAD3
SMAD4
CR
Immune function, cell growth, differentiation, and survival
Proliferation, metabolism, growth and survival
Cell growth, organ size control, and regeneration
Proliferation, tumorigenesis, growth and survival
Metabolism, cell growth, differentiation, and apoptosis
Embryonic development and tissue homeostasis
Including embryonic development, tissue homeostasis, and repair
Gene transcription

REVIEW ARTICLE OPEN

Targeting the RAS/RAF/MAPK pathway for cancer therapy: from mechanism to clinical studies

Md Entaz Bahar[1], Hyun Joon Kim[2] and Deok Ryong Kim[1]✉

Metastatic dissemination of solid tumors, a leading cause of cancer-related mortality, underscores the urgent need for enhanced insights into the molecular and cellular mechanisms underlying metastasis, chemoresistance, and the mechanistic backgrounds of individuals whose cancers are prone to migration. The most prevalent signaling cascade governed by multi-kinase inhibitors is the mitogen-activated protein kinase (MAPK) pathway, encompassing the RAS–RAF–MAPK kinase (MEK)–extracellular signal-related kinase (ERK) pathway. RAF kinase is a primary mediator of the MAPK pathway, responsible for the sequential activation of downstream targets, such as MEK and the transcription factor ERK, which control numerous cellular and physiological processes, including organism development, cell cycle control, cell proliferation and differentiation, cell survival, and death. Defects in this signaling cascade are associated with diseases such as cancer. RAF inhibitors (RAFi) combined with MEK blockers represent an FDA-approved therapeutic strategy for numerous *RAF*-mutant cancers, including melanoma, non-small cell lung carcinoma, and thyroid cancer. However, the development of therapy resistance by cancer cells remains an important barrier. Autophagy, an intracellular lysosome-dependent catabolic recycling process, plays a critical role in the development of RAFi resistance in cancer. Thus, targeting RAF and autophagy could be novel treatment strategies for *RAF*-mutant cancers. In this review, we delve deeper into the mechanistic insights surrounding RAF kinase signaling in tumorigenesis and RAFi-resistance. Furthermore, we explore and discuss the ongoing development of next-generation RAF inhibitors with enhanced therapeutic profiles. Additionally, this review sheds light on the functional interplay between RAF-targeted therapies and autophagy in cancer.

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Symposium on Genodermatoses: Review Article

RASopathies: Evolving Concepts in Pathogenetics, Clinical Features, and Management

Abstract

RASopathies refers to the group of disorders which are caused by a mutation in various genes of the RAS/MAPK (RAT sarcoma virus/Mitogen activated protein kinase) pathway. It includes many genes with varied functions, which are responsible for cell cycle regulation. As the mutation in one gene affects the entire pathway, there are many overlapping features among the various syndromes which are included under an umbrella term "RASopathies." However, neuroectodermal involvement is a unifying feature among these syndromes, which are caused by germline mutations affecting genes along this pathway. Recently, many other RASopathies have been described to involve blood vessels, lymphatics, and immune system. Also, many cutaneous mosaic disorders have been found to have mutations in the concerned pathway. The purpose of this article is to briefly review the pathogenesis of RASopathies with cutaneous manifestations, and summarise the features that can be helpful as diagnostic clues to dermatologists. As we understand more about the pathogenesis of the pathway at the cellular level, the research on genotype-phenotype correlation and therapeutic options broadens. Targeted therapy is in the clinical and preclinical trial phase, which may brighten the future of many patients.

Keywords: *Newer drugs, pathogenetics, RASopathies*

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REVIEW

SPECIAL ISSUE
TRANSLATING MULTISCALE RESEARCH IN RARE DISEASE

RASopathies – what they reveal about RAS/MAPK signaling in skeletal muscle development

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ABSTRACT

RASopathies are rare developmental genetic syndromes caused by germline pathogenic variants in genes that encode components of the RAS/mitogen-activated protein kinase (MAPK) signal transduction pathway. Although the incidence of each RASopathy syndrome is rare, collectively, they represent one of the largest groups of multiple congenital anomaly syndromes and have severe developmental consequences. Here, we review our understanding of how RAS/MAPK dysregulation in RASopathies impacts skeletal muscle development and the importance of RAS/MAPK pathway regulation for embryonic myogenesis. We also discuss the complex interactions of this pathway with other intracellular signaling pathways in the regulation of skeletal muscle development and growth, and the opportunities that RASopathy animal models provide for exploring the use of pathway inhibitors, typically used for cancer treatment, to correct the unique

RAS is perhaps the best studied signal transducer as it is somatically mutated in approximately 20% of human cancers (Prior et al., 2020). Variants in the canonical RAS genes (*HRAS*, *KRAS* and *NRAS*) often activate RAS signaling, resulting in the dysregulation of the cell cycle and many other vital cellular processes. So, the notion that critical components of the oncogenic RAS pathway can be mutated and activated during development is surprising as its dysregulation during development was thought to be embryonically lethal (Castel et al., 2020). Given this, RASopathies afford us an opportunity to study specific RAS/MAPK pathway-activating gene variants that are present in individuals with a single, germline pathogenic variant. By contrast, in somatic cancers, individuals typically harbor multiple oncogenic variants, not only in RAS, but in many other genes as well. Thus, RASopathies provide us with a unique opportunity to study the role of the RAS/MAPK pathway in normal development and to investigate how its dysregulation impacts specific developmental processes.

In this Review, we focus on how RAS/MAPK dysregulation in RASopathies affects mammalian skeletal muscle development. Many earlier studies into the role of the RAS/MAPK pathway in

ANNUAL REVIEWS

Annual Review of Biochemistry

Signaling from RAS to RAF: The Molecules and Their Mechanisms

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Keywords

International Journal of *Molecular Sciences*

MDPI

Review

Biomarker Landscape in RASopathies

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