Cancer and Metastasis Reviews
https://doi.org/10.1007/s10555-022-10057-z

NON-THEMATIC REVIEW

p73 isoforms meet evolution of metastasis

Stella Logotheti[1] · Athanasia Pavlopoulou[2,3] · Stephan Marquardt[4] · Işıl Takan[2,3] · Alexandros G. Georgakilas[1] · Thorsten Stiewe[5,6,7]

Received: 10 May 2022 / Accepted: 30 July 2022

Abstract
Cancer largely adheres to Darwinian selection. Evolutionary forces are prominent during metastasis, the final and incurable disease stage, where cells acquire combinations of advantageous phenotypic features and interact with a dynamically changing microenvironment, in order to overcome the metastatic bottlenecks, while therapy exerts additional selective pressures. As a strategy to increase their fitness, tumors often co-opt developmental and tissue-homeostasis programs. Herein, 25 years after its discovery, we review *TP73*, a sibling of the cardinal tumor-suppressor *TP53*, through the lens of cancer evolution. The *TP73* gene regulates a wide range of processes in embryonic development, tissue homeostasis and cancer via an overwhelming number of functionally divergent isoforms. We suggest that *TP73* neither merely mimics *TP53* via its p53-like tumor-suppressive functions, nor has black-or-white-type effects, as inferred by the antagonism between several of its isoforms in processes like apoptosis and DNA damage response. Rather, under dynamic conditions of selective pressure, the various p73 isoforms which are often co-expressed within the same cancer cells may work towards a common goal by simultaneously activating isoform-specific transcriptional and non-transcriptional programs. Combinatorial co-option of these programs offers selective advantages that overall increase the likelihood for successfully surpassing the barriers of the metastatic cascade. The p73 functional pleiotropy-based capabilities might be present in subclonal populations and expressed dynamically under changing microenvironmental conditions, thereby supporting clonal expansion and propelling evolution of metastasis. Deciphering the critical p73 isoform patterns along the spatiotemporal axes of tumor evolution could identify strategies to target *TP73* for prevention and therapy of cancer metastasis.

Keywords Cancer evolution · Metastasis · Co-option · Developmental and tissue homeostasis programs · p73 isoforms · Tumor evolutionary trajectories

✉ Stella Logotheti
stella_logotheti@mail.ntua.gr

1 DNA Damage Laboratory, Physics Department, School of Applied Mathematical and Physical Sciences, National Technical University of Athens (NTUA), 15780 Zografou, Greece

2 Izmir Biomedicine and Genome Center (IBG), 35340 Balcova, Izmir, Turkey

3 Izmir International Biomedicine and Genome Institute, Dokuz Eylül University, 35340 Balcova, Izmir, Turkey

4 Institute of Translational Medicine for Health Care Systems, Medical School Berlin, Hochschule Für Gesundheit Und Medizin, 14197 Berlin, Germany

5 Institute of Molecular Oncology, Universities of Giessen and Marburg Lung Center (UGMLC), Philipps-University, Marburg, Germany

6 Institute of Lung Health, Giessen, Germany

7 German Center for Lung Research (DZL), Philipps-University, Marburg, Germany

1 Introduction

The famous tumor-suppressor *TP53* is the most frequently mutated gene in cancer. For decades, the restoration of the pathways governed by this key transcription factor has posed as the "Holy Grail" of anticancer targeting. More than two decades ago, the discovery of its two siblings, namely *TP63* and *TP73*, led to a new challenge in p53-based therapeutics. The transcription factors encoded by these genes show a remarkable structural resemblance with the archetypical family member regarding three main functional domains, mainly the N-terminal transactivation domain (TA), the core DNA binding domain (DBD), and the C-terminal oligomerization domain (OD); thus, it was initially anticipated that they act similarly to *TP53*. Surprisingly, it was soon realized that, unlike *TP53*, they are rarely mutated in cancers and play major roles in embryonic development. Still, they participate, at least in part, in oncogenesis and affect

Published online: 11 August 2022

p53-mediated tumor-suppressive pathways, not only because they share common target genes and overlapping transcriptional profiles with wild-type *TP53* [1–4], but also because they physically interact with p53 mutants [5].

Intriguingly, *TP73* has been frequently viewed as a *TP53* "copycatter" because it potently transactivates many p53 apoptotic targets and mimics or substitutes for p53 oncosuppressive pathways, especially in response to DNA damage [6]. Shortly after its discovery though, it was recognized that *TP73* plays a controversial role in tumorigenesis. This attribute was largely associated with its ability to synthesize two main classes of protein isoforms: the TA isoforms that bear an intact and functional transactivation domain, and the N-terminally truncated DN isoforms that lack either part of or the entire TA. The DNs act as dominant negative inhibitors of TAp73 and p53 and, depending on the mechanism through which truncation of the transactivation domain occurs, they are further subdivided into the ΔN and the ΔTA subclasses (presented in detail in Sect. 4) [7–11]. An important milestone for understanding the contributions of these isoform classes in cancer has been the generation of TA or ΔN knockout (KO) mice. According to these models, TAp73s regulate genomic stability, thereby opposing tumor formation, while ΔNp73s act as oncogenes, by inhibiting the DNA damage response [12, 13]. Similar to ΔNp73s, the ΔTAs function in a consistently oncogenic manner [14, 15]. Given that TAs and DNs are frequently overexpressed across cancer types, it was initially proposed that the net effect of p73 gene on the disease outcome is determined by the TA/DN ratio. On the one hand, TAp73 isoforms directly transactivate several p53/p73-responsive apoptotic genes, ultimately leading to an anti-oncogenic phenotype. On the other hand, abundant DNp73 isoforms block gene transactivation, either by competing for p53/p73 binding sites or by forming transcriptionally inactive TAp73/DNp73 hetero-oligomers, thereby favoring oncogenesis [11]. In view of these findings, manipulation of the TA/DN equilibrium towards apoptosis appeared to hold promise for anticancer targeting [4, 16].

Nonetheless, in several instances, some TAp73 isoforms demonstrate a "janus" behavior in specific cancer-related processes, a fact that is neither consistent with their *bona fide* tumor-suppressive role nor adequately explained by the TA/DN ratio concept. A representative example of this controversy has been the role of p73 in tumor angiogenesis. On the one hand, TAp73 suppresses this important cancer hallmark by promoting degradation of the hypoxia-inducible factor 1α (HIF-1α) [17], as well as by repressing proangiogenic cytokines and HIF-1α activity [18]. On the other hand, hypoxia-inducible TAp73 supports tumorigenesis by regulating the angiogenic transcriptome [19]. Although these conflicting data may, at least in part, arise from cell context-dependent differences, the lack of a clear understanding of the effects of p73 in some cancer processes complicates its exploitation as a potential therapeutic target. Furthermore, recent comparative high-throughput transcriptome analyses of CRISPR/Cas9-based KO of ΔNp73 or TAp73 in mouse embryonic stem cells revealed that there are not only target genes which are controlled inversely by TA and ΔN, but also genes that are regulated by TA and ΔN in the same direction or by only one class of isoforms [20]. These data imply that TA and ΔN do not always antagonize each other, but rather have a more complicated affair.

In the present article, for the first time, to the best of our knowledge, we address *TP73* in the context of evolution of metastasis. First, we summarize metastasis as an evolutionary process, whereby cancer cells frequently co-opt several physiological processes to recapitulate traits that increase their fitness and propensity to metastasize. Then, we set forth a novel model of p73 isoform interplay, whereby DN-induced oncogenic pathways are combined with a variety of non-oncogenic pathways controlled by the co-expressed TAs. Products of *TP53* and *TP63* can further shape the intricate interplay of DN and TA isoforms, adding an extra level of sophistication to this model. We thus propose an evolution-driven rationale that could explain the existing controversies and suggest strategies to optimize p73-based targeting towards improving the therapeutic management of metastasis.

2 Acquisition of metastatic potential as an evolutionary process

Metastasis is the final stage of the multistep process of cancer development, following initiation, promotion, and progression. Dissemination takes place through multiple routes and in different directions, and is characterized by complex spatiotemporal patterns and trajectories [21]. Metastasis largely adheres to the Darwinian principles, driven by evolutionary and ecological forces [22]. A neoplasm is a highly versatile and heterogeneous population of cells carrying genetic and epigenetic alterations, which arise constantly due to genomic instability [23]. This mosaic of diversified cell variants expands or contracts in the neoplasm, according to changes in their external microenvironment. The fittest, or "evolutionarily successful," cell variants are those acquiring capabilities that offer selective advantages under specific microenvironmental changes. This highly dynamic process enables tumors to adapt quickly to new conditions and evade therapeutic targeting [22].

Metastasis is an inherently insufficient procedure, since the vast majority of migrating cells perish in the blood circulation, while only a small subset of those manages to reach distant sites and acquire macrometastatic features [24]. In this context, cancer cells concomitantly and quickly undergo several key adaptations that increase the likelihood for acquiring attributes that are essential for overcoming evolutionary barriers and gaining metastatic potential. Bypassing bottlenecks of the metastatic cascade requires a combination of traits, such as motility, immune evasion,

and ability to survive in circulation and proliferate at distant sites, rather than a single specific attribute. Henceforth, the term "metastatic potential" refers to any combination of cancer phenotypes that enable cell dissemination and increase the probability of metastasis [24]. Overall, the evolution of metastasis is shaped by combinations of phenotypic features acquired by the cancer cells and their interactions with the host microenvironment and immune system [25, 26].

3 Co-option of developmental and/or tissue homeostasis programs increases metastatic potential

While at early stages cancer cells accumulate driver mutations, at advanced stages, they do not acquire additional, metastasis-specific mutations [27], but rather hijack programs of tissue-homeostasis and normal embryonic development and reactivate them in an unusual place, at the wrong time [28]. It has been suggested that genetically-activated oncogenic pathways driving tumor initiation could support metastasis through their interplay with physiological programs co-opted from stem cells, as well as developmental and regenerative processes [29] (Fig. 1). The most comprehensively studied example is epithelial—mesenchymal transition, the embryonic developmental program that controls, for example, the neural crest, and is frequently reactivated to support metastasis across most cancer types [30]. Besides, several other paradigms advocate that expression of genes and/or pathways in the wrong place and at the wrong time is a common mechanistic pattern that enhances metastatic potential [27]. For example, these can be genes with tissue-restricted expression [31, 32], pathways supporting placenta formation [33], programs of jaw [34] and neuronal

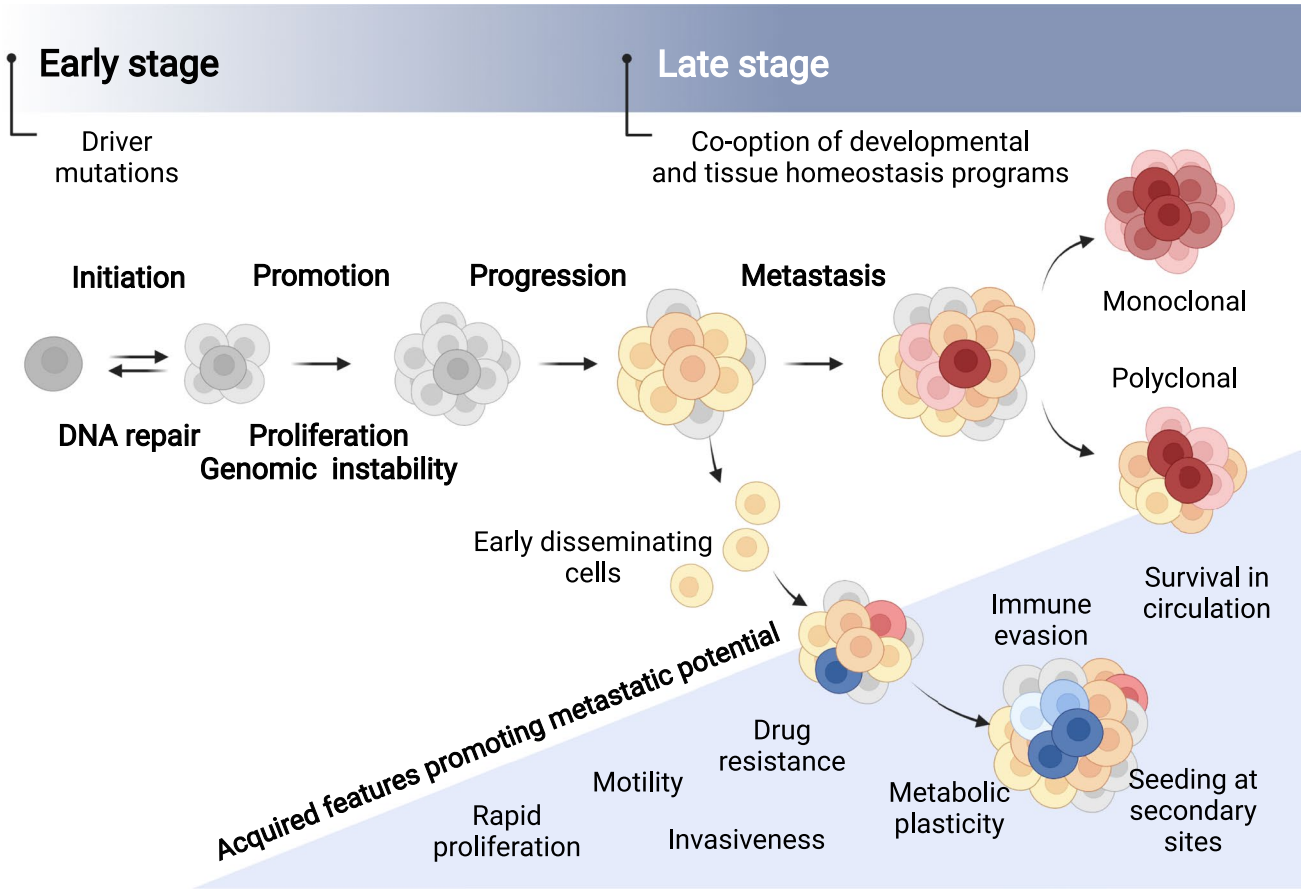

Fig. 1 Co-option of developmental and/or tissue-homeostasis programs offers selective advantages that increase metastatic potential. Driver mutations at initiation stages increase genetic instability and uncontrolled cell proliferation, supporting clonal heterogeneity along the spatiotemporal axis. Microenvironmental changes select for the fittest cancer cell subpopulations, allowing them to expand at the expense of others. During this process, pathways underlying sophisticated programs of development and/or tissue homeostasis are co-opted to recapitulate various selectable traits. Accumulation of advantageous traits (such as motility, invasiveness, immune evasion, survival in circulation, resilience to intravascular shear forces, rapid proliferation, ability to seed at secondary sites, drug resistance, metabolic plasticity) creates combinations of phenotypes that increase the propensity of specific clones to overcome the barriers of the metastatic cascade following a variety of evolutionary trajectories

development [28, 35], or key regulators of angiogenesis [36]. Interestingly, the same developmental programs that catalyzed vertebrate evolution are also important for tumor evolution [34].

By co-opting entire programs at once, cancer cells may acquire phenotypic traits needed to overcome multiple bottlenecks during the metastatic process faster than by mere accumulation of single mutations. Importantly, off-context expression of genes/mechanisms appears not only to enhance the migratory and invasive capabilities of cancer cells, but also to reprogram tumor interactions with other cellular components in the TME or with the host stroma. By secreting key neuronal, angiogenic, or immunomodulatory factors, tumors can dynamically modify the interplay among several cell types in the TME and express receptors to these cues [37, 38], such as nervous and immune cells, fibroblasts, endothelial, and bone-marrow-derived cells. In turn, these cells can orchestrate tumor growth and enhance the metastatic properties of cancer cells [37]. Overall, co-option emerges as a recurrent, prevalent, and conserved mechanism which supports acquisition and augmentation of metastatic propensity.

4 The pleiotropic functions of p73 are recapitulated in tumors

The *TP73* gene can encode more than 20 isoforms, the largest number among the p53 family members. The p73 isoforms are generated via differential splicing and alternative promoter usage. First, use of a canonical (P1) and an alternative internal promoter (P2) at the 5′ end leads to the generation of the TA and Δ*N* classes of isoforms. Then, alternative splicing at the 3′ end spawns several C-terminal splice variants (α, β, γ, δ, ε, ζ, η, and θ) [41]. Finally, in some cancer types, an additional type of N-terminal truncation has been described, that is, the ΔTA isoforms (mainly ΔEx2p73 and ΔEx2/3p73), derived by aberrant alternative splicing at the 5′ end (Fig. 2a). The ΔTAs are slightly different from the P2-derived ΔN variants: while in the ΔTAs the transactivation domain, encoded by exon 2 and 3, is partly or entirely cropped out, the ΔNs start with 13 unique residues derived from exon 3' which, together with the N-terminal PXXP motifs, constitutes a cryptic transactivation region with the potential to induce some specific target genes [42]. This ΔN-specific transactivation domain is essentially missing from ΔTAs. Nevertheless, as a general rule, both P2-derived ΔNs and P1-derived ΔTAs function as dominant-negative inhibitors of TAp73. For this review, we therefore summarize ΔNs and ΔTAs with the collective term "DN" when referring to p73 isoforms lacking the typical TA domain. As far as their expression is concerned, TA and ΔN have been found in a variety of normal and tumor tissues, whereas ΔTA are tumor-specific and highly expressed in certain cancer types, such as melanoma [15, 43], lung [44], and hepatocellular carcinomas [45]. The overwhelming number of isoforms is generated from several combinations of N-terminal heads and C-terminal tails with different functional domains and residues which, in turn, are correlated with divergent functions [46]. The C-terminus is particularly enriched in motifs and residues that mediate protein–protein interactions including several modulators of p73 transcriptional activity (Fig. 2b). Through its unique combination of interacting surfaces, each p73 isoform can establish protein–protein interactions in a highly selective manner. The targets regulated by each isoform depend on the presence of a N-terminal TA domain, as well as on the interaction partners in the cell milieu which are recognized by respective surfaces in the p73 C-terminus [41, 47]. Furthermore, the organization of the p73 target gene promoters can be selective for specific C-terminal variants [48]. Notably, interactions between p73 isoforms and their repertoire of protein binding partners do not take place exclusively in the nucleus, but also in several subcellular compartments outside of the nucleus, pointing to non-transcriptional modes of p73 isoform function [47].

The mechanistic pleiotropy of *TP73* leads to a high degree of functional diversity in multifaceted processes during embryonic development, tissue homeostasis, and cancer. Therefore, p73 isoforms display an expanding repertoire of physiological roles across normal tissues, including, but not limited to, the nervous system, the male and female reproductive organs, the respiratory epithelium, the vascular network, and the immune system [47]. In cancer tissues, the common consensus is that DNp73s are consistently oncogenic [49]. The TAp73 isoforms are traditionally anti-oncogenic [41], although some TAp73 splice variants show a janus behavior, depending on the cellular context. For example, TAp73α can inhibit apoptosis induced by a range of death stimuli [50] or even oppose the antiproliferative and apoptotic effects of TAp73β [51]. Moreover, TAp73 activates anabolic pathways, compatible with proliferation and promotion of cancer cells, and cooperates with AP-1 transcription factors to sustain cell proliferation [51–55].

Intriguingly, analogies emerge between several physiological and cancer processes regulated by *TP73*, raising the possibility that transcriptional programs activated by p73 isoforms may be hijacked within the cancer cell context. The p73-regulated targets that are reactivated off-context in cancer cells are discussed in detail in the following subsections and summarized in Fig. 3a.

4.1 Normal vasculogenesis and tumor angiogenesis

p73 regulates VEGF and TGFβ signaling and is required *in vivo* for endothelial cell differentiation, migration, and the formation of vascular networks. Differential p73-isoform

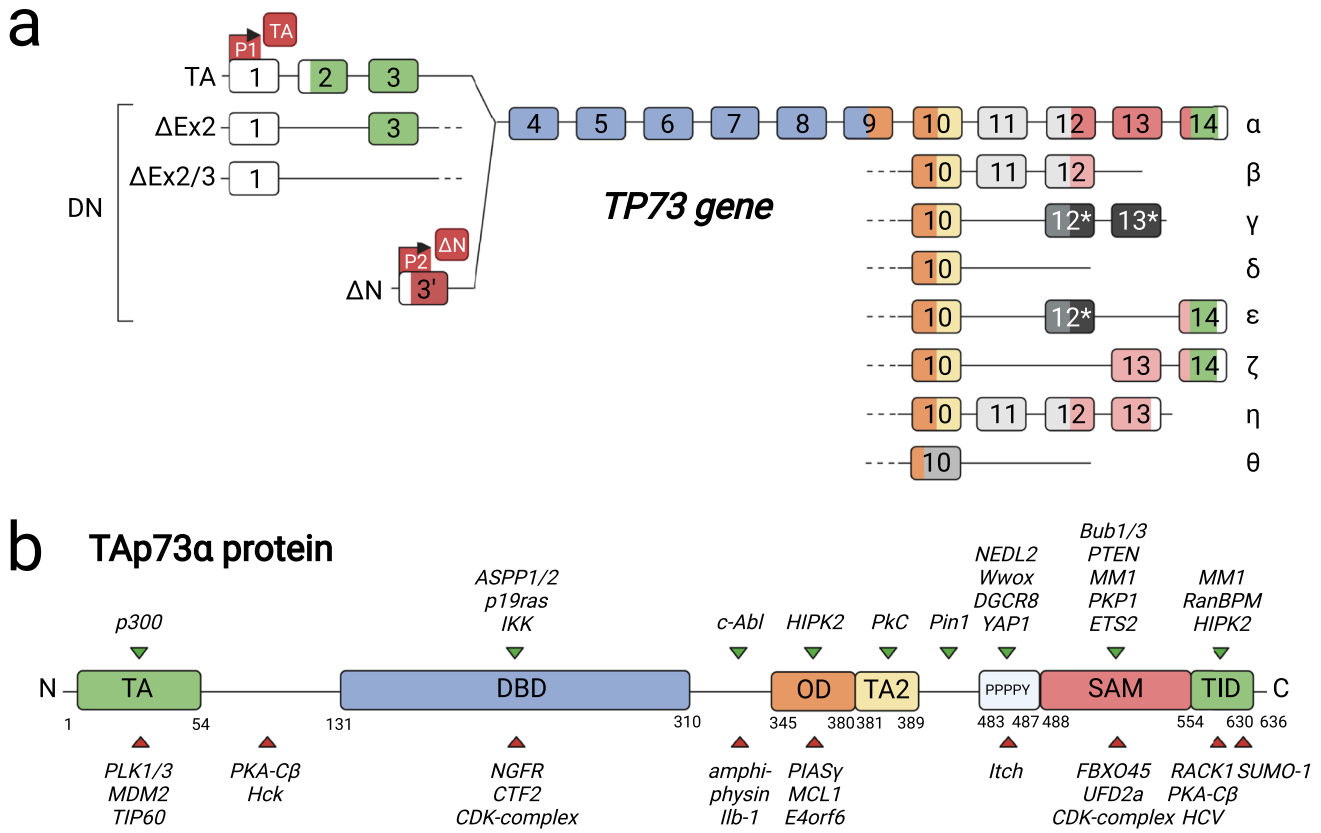

Fig. 2 The p73 gene synthesizes an overwhelming number of functionally divergent isoforms that act through transcriptional and non-transcriptional modes of action. **a** Diagram depicting synthesis of p73 isoforms by the use of an external (P1) and alternative internal promoter (P2) in the 5′ end (TA and ΔN isoforms), alternative splicing in the 5′ end (ΔTA isoforms: ΔEx2p73, ΔEx2/3p73), and alternative splicing in the 3′ end (C-terminal splice variants α-θ). All isoforms contain the invariant core DNA-binding domain. ΔN and ΔTAs are collectively referred to as "DN" isoforms. Different combinations of the N-terminal heads and C-terminal tails give rise to functionally divergent isoforms that control a range of physiological and cancer-related processes. **b** Protein-binding motifs and crucial amino acid residues span the p73 protein products and are recognized by an increasing repertoire of modifying enzymes, co-regulators, and other protein interactors. Green and red arrows denote activating or inhibitory effects of the protein interactors, correspondingly. Each p73 isoform has a unique combination of these motifs and residues, reflecting an own set of PPIs. Abbreviations: TA, transactivation domain; DBD, DNA-binding domain; OD, oligomerization domain; SAM, sterile alpha motif; TID, transcription-inhibitory domain; 2TA, second transactivation domain; PPPPY, conserved proline-rich motif (adapted from [41, 47]). The exons encoding each functional domain are color-matched between **a** and **b**. The α splice variants have an intact SAM domain (represented in dark color), while β, ε, ζ, and η synthesize only parts of it (light-colored). The γ and ε bear a frameshift from the original reading frame (black exons with asterisks) leading to C-termini that differ completely or partially, correspondingly, from the tail of the full-length α variant

regulation is necessary for physiological vasculogenesis and angiogenesis [57]. In analogy, the VEGF pathway is responsive to overexpression of several p73 isoforms in cancer tissues. Tumor-intrinsic activation of the p73-VEGF axis regulates formation of new blood vessels around the tumor, whereby DNp73 has proangiogenic capacity and clearly promotes this phenomenon, while TAp73 exerts both a positive and a negative effect mediated by the differential regulation of VEGFA [58]. Intriguingly, under hypoxic conditions, both DNp73 and TAp73 induce VEGFA expression and tumor angiogenesis, implying that these isoforms do not counteract each other, consistent with their traditional roles, but, under specific environmental conditions, may affect the same pro-metastatic processes in a concerted manner [59].

4.2 Liver metabolism and deregulated tumor energetics

TP73 influences hepatocellular lipid metabolism, glutathione homeostasis, and the pentose phosphate pathway, via transcriptionally regulating metabolic enzymes, such as cytochrome c oxidase subunit IV isoform 1, glucose 6-phosphate dehydrogenase, and glutaminase-2 (GLS2). Depletion of all p73 isoforms results in altered lysine metabolism and glycolysis, distinct patterns for glutathione synthesis, and Krebs cycle, as well as an augmented pentose phosphate pathway and abnormal lipid accumulation [60]. These effects are reminiscent of the p73-mediated deregulation of cellular energetics in tumors. TAp73-expressing cancer cells show

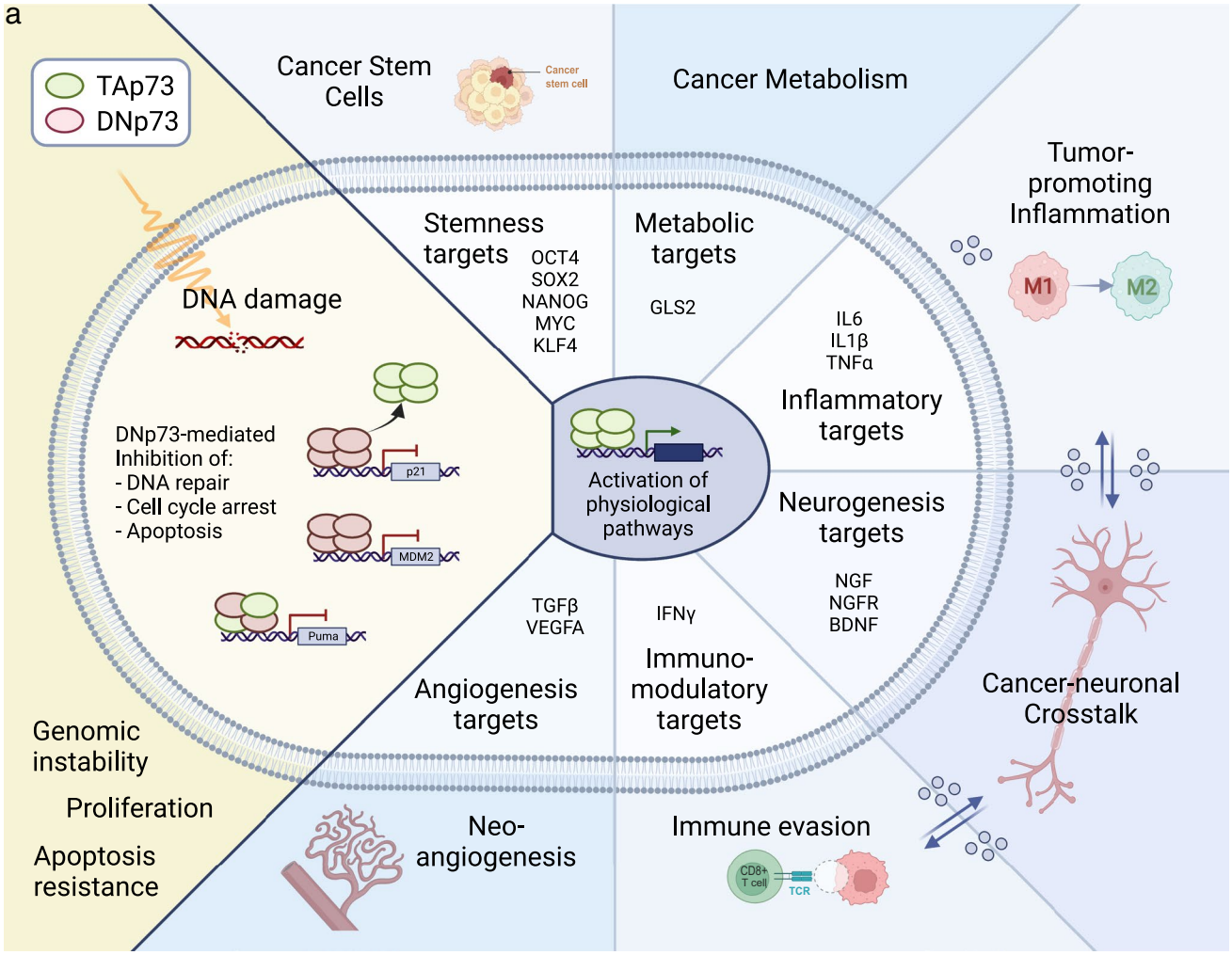

Fig. 3 Model of enhancement of metastatic potential by an interplay of oncogenic p53 family members with TAp73-regulated physiological programs**. a** *Oncogenic pathways controlled by DNs are combined with concomitantly expressed non-oncogenic pathways regulated by TAs:* high DNp73 levels suppress TAp73-induced cell cycle arrest, DNA repair, and apoptosis via antagonistic binding of DNp73 homo-oligomers or by formation of TA/DNp73 hetero-oligomers that are transcriptionally inactive at their particular targets. Co-expressed TAs retain residual transcriptional and non-transcriptional programs of immune evasion, inflammation, angiogenesis, metabolism, stemness, and/or neurogenesis. Notably, some TAp73-induced secreted molecules are commonly recognized by immune, neuronal, and/or endothelial cells in the TME; hence, their co-option might support inter-related TME-relevant processes or simultaneously regulate more than one cell types. **b** *Co-expression of oncogenic p53 and p63 isoforms reinforces the prometastatic co-option of TA-regulated programs*: DNp63 and mutp53 enhance the DNp73 oncogenic programs, by blocking tumor-suppressive effects of TAp73 isoforms. In parallel, crucial processes such as tumor metabolism, cancer stemness, immune evasion, neoangiogenesis, and tumor inflammatory pathways are positively regulated by gain-of-function mutp53 [118–122], and DNp63 [123–125], so that co-expression of these p53 family members reinforces programs co-opted by the TAp73 isoforms

an increased rate of glycolysis, higher amino acid uptake, and increased levels and biosynthesis of acetyl-CoA [61]. In addition, TAp73 activates serine biosynthesis, thereby augmenting intracellular levels of serine and glycine; it is also associated with the accumulation of glutamate, anaplerotic tricarboxylic acid (TCA) cycle intermediates, and glutathione. This is achieved through the transcriptional control of GLS2, which converts glutamine into glutamate and thereby fuels the serine biosynthetic pathway. TAp73 depletion inhibits cancer cell proliferation capacity upon serine/glycine-deprivation, implying that p73 supports cancer cell survival under metabolic stress [54]. Hence, TAp73 isoforms can regulate metabolic plasticity by activating the transcription of metabolic enzymes, such as GLS2, both in normal and cancer tissues.

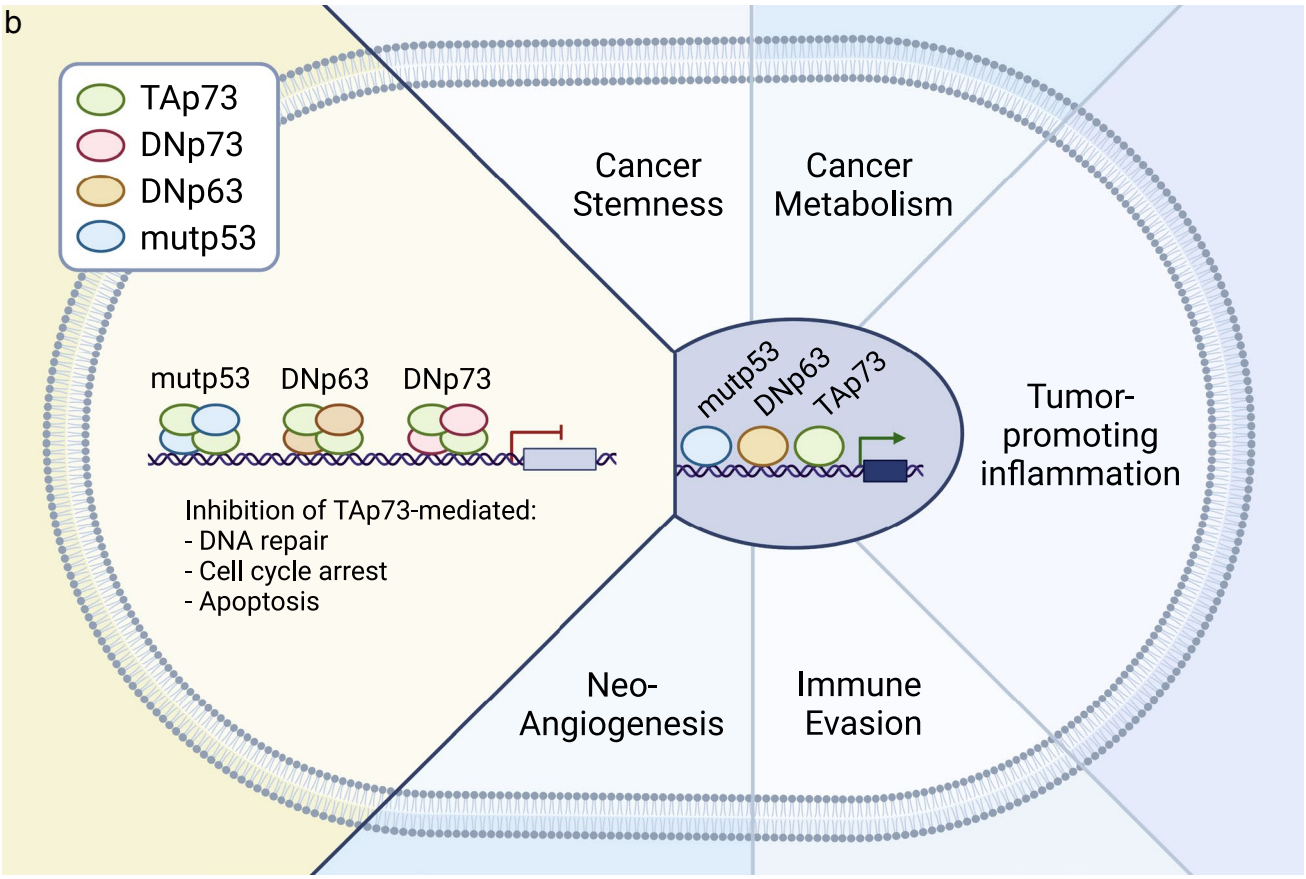

Fig. 3 (continued)

4.3 Inflammation resolution and tumor-promoting inflammation

Compelling evidence from *TP73* knockout mice and chronic inflammatory skin conditions pinpoints p73 isoforms as key regulators of inflammatory cascades. In particular, pan-p73 KO mice manifest severe rhinitis and purulent otitis media, with massive neutrophil infiltration and a pathogenic microbiome, resulting from inappropriate or hyperactive epithelial responses and constitutive inflammatory signals [62]. Studies in TAp73 KO mice have further demonstrated that TAp73 isoforms are required for macrophage-mediated innate immunity and the resolution of the inflammatory response via a M1-to-M2 effector phenotype switch. These effects are associated with TAp73-dependent regulation of proinflammatory cytokines and immunomodulatory molecules, such as tumor necrosis factor alpha (TNF-α), interleukin-6 (IL-6), and major histocompatibility complex class II [63]. Moreover, in palmoplantar pistulosis, the SAM domain-containing protein products of the *TP73* gene enhance IL-6 production from the reticular crypt epithelial cells that surround lymphoid follicles [64], while in atopic dermatitis, ΔNp73 abundantly expressed in keratinocytes increases, via NF-κB activation, the release of the thymic stromal lymphopoietin (TSLP), a cytokine that induces differentiation and activation of Th2 cells and innate lymphoid cells [65]. By analogy, in the context of cancer, TAp73 isoforms regulate cytokine expression and immunomodulatory molecules, resulting in both positive and negative modulation of the TME and tumor progression. For example, in breast cancer, TAp73 upregulates IL-1β [66], which on the one hand resolves acute inflammation and initiates adaptive anti-tumor responses, and on the other hand promotes tumor development over the course of chronic inflammation [67]. Again in breast cancer, TAp73 isoforms control macrophage accumulation and M1-to-M2 phenotype switch through inhibition of the NF-κB pathway. In particular, loss of TAp73 induces a NF-κB–regulated inflammatory signature in breast cancers, including *CCL2*, a known chemoattractant for monocytes and macrophages, while TAp73 expression in patient samples is inversely correlated with accumulation of pro-tumoral macrophages [68]. Although the specific effect of each p73 isoform on components of the innate immune system is yet to be clarified and might differ significantly among the several C-terminal variants, the aforementioned studies clearly indicate that products of

the *TP73* gene modulate the cancer-macrophage cell interactions via co-opting their ability to regulate proinflammatory molecules. Comprehensive cytokine profiling of cells with different p73 isoform contexts as well as identification of p73 isoform-specific secretomes could shed more light on the relative programs and their involvement in sustaining a proinflammatory TME [69].

4.4 Adaptive immunity and tumor immune evasion

The immune system, both innate and adaptive, can recognize and destroy cancer cells [40]; hence, the ability to evade immune destruction is a major selective advantage for tumor survival and seeding at a secondary site. Importantly, *TP73* gene products are negative regulators of the Th1-mediated immune response, and p73 isoform(s) dysregulation appears to be implicated in host susceptibility to autoimmune diseases [70]. Although the p73 levels are very low in naive CD4 + T cells, they increase in differentiated Th1 cells. Both TAp73 and DNp73 negatively control the Th1 immune response via transrepression of IFN-γ transcription and downregulation of IFN-γ production, a cytokine important for Th1 differentiation [70]. Hence, p73-induced regulation of the same key targets within cancer cells, for example IFN-γ, may suppress the differentiation of immune cells in the TME and/or modify cancer-immune cell interactions, thereby influencing tumor immune evasion either negatively or positively [69, 70]. Given that state-of-the-art immunotherapeutic strategies, such as checkpoint inhibitor and Chimaeric Antigen Receptor (CAR) T-cell therapies, target the interactions between tumor and T cells [40], future experiments directed towards elucidating how p73 isoforms recapitulate their immunomodulatory capabilities within tumors to influence T cells and support an immunosuppressive TME could provide a means for optimization of immunotherapeutics.

4.5 Neurodevelopment and cancer-neuronal crosstalk

p73 isoforms are indispensable for neuronal development. Neurodevelopmental abnormalities represent a recurrent and predominant phenotype in mice with selective KO of (i) all p73 isoforms, (ii) the TAp73s, (iii) the ΔNp73s, and (iv) the C-terminus of the p73α isoform, causing an α-to-β isoform shift, with a persistent effect in hippocampus formation. TAp73 isoforms modulate the expression of the neurotrophin receptor p75 (p75NTR, also known as NGFR) in post-synaptic neurons, a central factor in axonal growth and dendritic arborization [71]. Activation of tumor-intrinsic neurotrophin signalling in cancer cells is indicative of a "dangerous liaison" between tumors and the nervous system [72], which largely influences tumor aggressiveness, drug response, and/or therapy-induced neuronal toxicities [73]. Intriguingly, TAp73α, TAp73β, DNp73α, and DNp73β can all, to varying extent, activate NGFR in melanoma cells, along with additional neurotrophic factors, such as nerve growth factor (NGF) and brain-derived neurotrophic factor BDNF [28]. It appears that co-option of p73-regulated neurodevelopmental networks, as evidenced by recapitulation of p73-neurotrophin axes in tumors, could perhaps reprogram cancer-neuronal cell interactions during metastatic progression [47]. Furthermore, given that immune cells also respond to neuronal cues [37], it is possible that p73-induced activation of neurodevelopmental programs may sustain a neuromodulatory secretome that favors a complex cancer-neuronal-immune cell crosstalk in the TME. Currently, it remains unknown whether p73-activated neuronal factors may affect disease progression and response to immunotherapies, which are becoming standard care modalities in a growing number of cancer types [40]. Identification of the p73-relevant co-opted neurodevelopmental programs that possibly underlie these complex interactions could identify novel strategies to prevent metastasis and improve immunotherapy.

4.6 Neuronal tissue stemness and cancer stemness

Stemness is a dynamic cellular property enabling tissue self-renewal and homeostasis. Many somatic tissues retain a small percentage of stem cells to ensure regeneration during adulthood, while a constant versatility is established between differentiated and multipotent cells [74]. In an analogous manner, a solid tumor is made up of heterogenous cell subpopulations, which are generated and sustained by a small subpopulation within the tumor, defined as "cancer stem cells" (CSCs), while a bidirectional conversion between CSCs (pluripotent cells) and non-CSCs (less dedifferentiated cells) generates a dynamic state between these cell subpopulations [75]. In neuronal tissues, *TP73* affects stemness across all differentiation stages, from neural stem cells to postmitotic neurons [76–79]. In general, TAp73 is required for neuronal differentiation and maintenance of neural stem cells, while ΔNp73 is required for neuronal cell survival [80]. In melanoma cells, DNp73 increases stemness and self-renewal capacity [81], while addition of either TAp73 or DNp73 isoforms co-elevates a panel of stemness factors (Nanog, CD133, Oct4, Sox2, c-myc, KLF4) along with the neurotrophic factors NGF, NGFR, and BDNF [28]. The fact that p73-mediated stemness is, at the same time, accompanied by expression of key neurotrophins within the same tumor cell context suggests that the ability of p73 isoforms to toggle between stemness and neurodifferentiation cell fates may be hijacked by p73-expressing tumors to advance metastasis.

Collectively, the reported roles of p73 isoforms on cancer phenotypes are not independent from their physiological functions, but pinpoint to recapitulation of p73-governed pathways and/or transcriptional modules in a cancer cell context, in line with the emerging importance of co-option of physiological programs as a prevalent mechanism of metastatic competence. Obviously, the more functions the p73 gene controls through its many diverse isoforms, the more p73-driven regulatory programs are available to a cancer cell that can be abused upon *TP73* deregulation and isoform overexpression. If such non-oncogenic programs are activated "off-context" in a combinatorial manner within the cancer cell context, they can theoretically offer a suite of selective advantages in the course of metastasis.

5 Tumor selective forces and p53 intrafamily crosstalk can turn DNp73 and TAp73 isoforms from eternal rivals to "brothers in arms"

In this section, we put forth a model, whereby p73 isoforms that traditionally antagonize each other collaborate under selective pressures in the tumor microenvironment (TME) to surpass bottlenecks of metastatic evolution (Fig. 3a). This model of conditional cooperation between TAp73 and DNp73 isoforms can be further shaped by an interplay with the two other members of the p53 family which are often co-expressed in the same tumor context (Fig. 3b). We propose that tumor subclones with co-expression of TA and DNp73 might bear selective advantages over DNp73-only–expressing clones which enable their progression across several tumor evolutionary trajectories (Fig. 4).

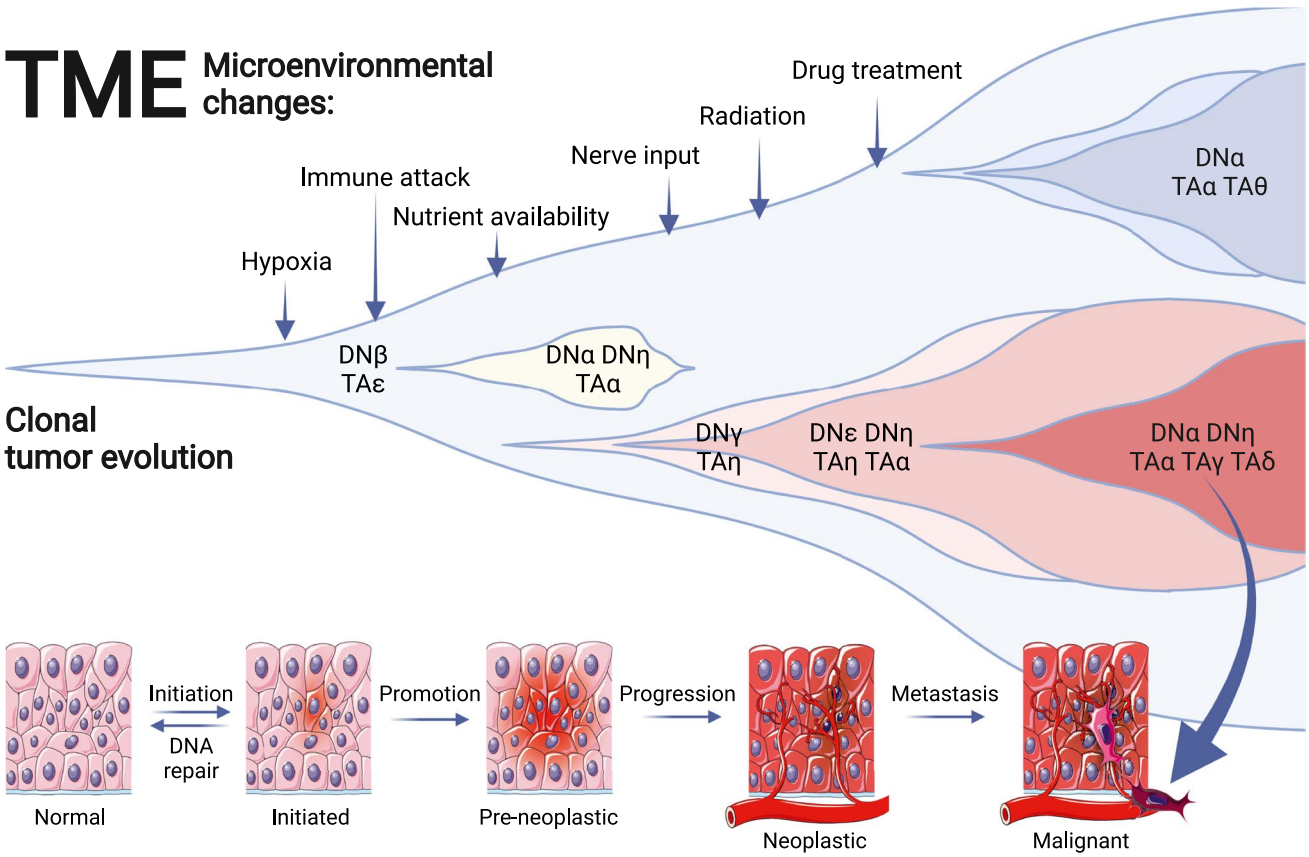

Fig. 4 Microenvironmental pressures select for highly metastatic subclones with co-opted TAp73 isoform-regulated programs. Tumor heterogeneity generates DNp73-only and TA/DNp73-coexpressing subclones, in which DNp73 promotes proliferation by inhibiting DNA repair, cell cycle arrest, and apoptosis. In the TA/DNp73-coexpressing subclones, DNp73 keeps pro-apoptotic TAp73 activities in check, allowing tumor cells to tolerate TAp73 isoform expression and profit from the co-option of TAp73-regulated programs involved in metabolic plasticity, cancer stemness, or tumor interactions with neuronal, endothelial, and immune cells in the TME

5.1 Evolution-driven model of TAp73 and DNp73 cooperation

DNp73s consistently promote tumorigenesis, whereas TAp73s traditionally oppose these effects, typically via hetero-oligomerization and competition for binding to common target genes. However, there are instances where TAp73 isoforms display both positive and negative effects on cancer-related processes [69]. The tumor-suppressive effects of TAp73s are clear in genomic stability, cell-cycle arrest, apoptosis, and response to DNA damaging agents, where they activate DNp73-repressed target genes, such as p21, PUMA, and BAX. TAp73s also exert, in many cancer types, well-defined tumor-protective roles regarding inhibition of cancer cell migration and EMT [69, 82]. Notwithstanding, in TME-related processes, especially in interactions of cancer cells with immune and endothelial cells, TAp73 isoforms act as a double-edged sword, where they not only inhibit but also promote an immunosuppressive environment and tumor angiogenesis [69]. The two-faced behavior of TAp73s is further evidenced by their positive effects on cancer metabolism, stemness, and prometastatic neurotrophin secretion in the TME [47]. Intriguingly, these processes are supported by co-option of non-oncogenic TAp73-induced pathways. Hence, the variety of non-oncogenic programs activated "off-context" in tumors by TAp73 isoforms along with their p53-like tumor-suppressive functions can theoretically offer a suite of selective advantages for interactions of tumors with their TME, which can eventually undermine the *bona fide* TAp73 activities.

Deregulation of the *TP73* gene in cancer cells leads to overexpression of more than one p73 isoforms, and in many cases, TAs are co-overexpressed with DNs. For example, non-small cell lung cancer cells express both TA and DN isoforms [83], while it appears that of all TAp73 isoforms, TAp73γ is more commonly expressed [84]. In a similar manner, TAp73α is co-expressed with DNp73 isoforms in aggressive melanoma [85] and in hepatocellular carcinoma cells [86]. Given the limitations of the currently available experimental tools for p73 isoform detection, the number of isoforms co-expressed in cancer cells might have even been underestimated and actually be higher than the already known. For example, most p73 antibodies discriminate mainly between TA *versus* ΔN isoforms, while tools to discriminate specific variants at high resolution are still missing. Even use of a pan-p73 antibody which recognizes all p73 isoforms cannot accurately discriminate between the ones with similar molecular weights. Moreover, post-translational modifications alter the apparent molecular weight and prevent unambiguous identification of protein isoforms based on Western blots. The p73 isoform expression patterns are therefore often inferred only indirectly from mRNA based on isoform-specific reverse transcription PCR. Hence, the variety of expressed p73 isoforms in a cancer cell, and consequently the corresponding isoform-specific programs that can be potentially affected, might be even higher. Overall, a tumor simultaneously overexpresses p73 isoforms which can regulate a wide range of, both common and unique, functions. This is translated into an increased potential for co-option of isoform-specific protein interactions and/or transcriptional modules.

The co-expression of the p73 isoforms and co-option of non-oncogenic programs are the two key parameters of a model which we hereby put forth to explain how TAp73s can, in some instances, turn from rivals to accomplices of the malignant DNp73s (Fig. 3a). In particular, according to the TA/DN equilibrium "rule-of-thumb," cancer cells lose their ability for genomic stability or apoptosis when DNs prevail over TAs. In this case, TAp73 isoforms have failed to counteract the abundantly expressed DNs with regard to the regulation of common targets that are affected in opposite ways by DNs and TAs, such as inducers of apoptosis, cell cycle arrest, and DNA damage response. However, the persistent expression of TAs, often in high levels, along with the DNs in the cancer cells, implies that tumor cells might benefit from their co-expression. Herein, we suggest that TAs are not mere inert bystanders in cancer cells, but rather retain some ability to bind to their own sets of gene targets and interact with protein co-regulators leading to residual transcriptional and non-transcriptional programs that underlie TAp73-specific functions. Under these conditions, DNp73-induced suppression of genomic stability and apoptosis is combined with co-opted programs of immune evasion, angiogenesis, metabolism, stemness, and/or neurogenesis that are engaged by the co-expressed TAp73 isoforms. Although these co-opted programs might not counteract apoptosis directly, they offer selective advantages for the cancer cells under evolutionary pressures exerted by the spatiotemporally changing TME. The DNp73-mediated increase of genomic instability can lead to genomic and clonal heterogeneity. Co-option of TAp73-regulated traits along with DNp73-enhanced genomic instability could provide a fertile ground for creating combinations of cancer phenotypes that overall enhance metastatic potential. The co-opted p73-based capabilities might not be manifested at all instances, but upon conditional cues from the TME. For example, if TAp73α is co-expressed with DNp73s, as is the case in melanoma or hepatocellular cancer cells [85, 86], the excessive TAp73α might not be able to displace DNp73 from their common apoptotic targets so as to resurrect apoptosis; however, it may still activate metabolism-related target genes that potentially offer metabolic plasticity upon changes of nutrient availability in the TME. In this case, clonal subpopulations that co-express TAp73α and DNp73s might be selected over those that express only DNp73s and expand in the presence of metabolic stress. In a similar manner,

DNp73-positive subpopulations which co-express TAp73 isoforms with the potential to activate immunomodulatory cytokines might have survival advantages under conditions of strong evolutionary pressure imposed by immunotherapy. In support of our model, two other traditional rivals, p53 and ΔNp63, can achieve mutually beneficial cooperation [87], thereby indicating that such collaborative patterns may be a common theme among the p53 family members.

5.2 Oncogenic p53 and p63 isoforms can shape the prometastatic co-option of TAp73-regulated programs

The p73 isoforms interact not only with each other but also with the two other family members, i.e., *TP53* and *TP63*, which are often co-expressed in many different cancer types. As the structure of the p73 oligomerization domain is very similar to that of p63, the two proteins efficiently hetero-oligomerize. Intriguingly, mixed p63/p73 tetramers were even found to be thermodynamically more stable than homotetramers [88–90]. Oligomerization with various p63 isoforms therefore expands the repertoire of p73-complexes and enables further functional diversification. For example, DNp63α inhibits TAp73β-mediated transactivation of pro-apoptotic genes, such as p21 and BAX, and this was found to be critical for survival of squamous cell carcinomas of the head and neck [90, 91]. Despite efficient p63/p73 hetero-oligomerization, however, TAp73β-inhibition by DNp63α was found to be due primarily to promoter squelching rather than direct interaction [90].

Although structural differences between the p73 and p53 oligomerization domains do not allow formation of stable tetrameric complexes, p73 isoforms were nevertheless shown to interact physically with several missense mutants of p53 that are commonly found in cancer cells. This interaction is mediated by the DNA-binding core domain and modulated by the common p53 codon 46 polymorphism and the mutation class [92, 93]. The so-called "structural" p53 missense mutations (such as p53R175H) that affect protein conformation and destabilize the DBD show strong binding to p63 and p73, whereas p53 "contact" mutants that only mildly affect the conformation (such as p53R273H) bind less efficiently [93, 94]. The interaction between the destabilized mutant p53 DBD does not require the p63/p73 DBDs, but instead involves contacts with the C-termini of p63/p73 isoforms [94, 95]. The TID domain within the α-isoform-specific C termini of p63 and p73 was found essential for binding to p53R175H [95]. It has been demonstrated that although binding is decreased in TAp63β, TAp63γ, and TAp73β, it is efficient for the C terminus of TAp73γ, indicating that the same p53 mutant differentially associates with C-terminal variants of p63/p73, with potential consequences for tumor development [94]. Last but not least, it remains questionable if these interactions represent complexes of defined stoichiometry and geometry or if they are better described as soluble aggregates which would also provide a mechanistical explanation for the inhibition of p63/p73 transcriptional activity by aggregating p53 mutants [95–98].

Of note, alternative N- and C-terminal isoforms of wild-type p53, which are also found to be expressed in different cancer contexts [99], were described to bind and modulate the transcriptional activity of p73 isoforms as an additional layer of crosstalk [95, 100]. However, the involved domains and modes of interaction have not yet been thoroughly elucidated.

Besides their direct hetero-oligomer-based mode of interaction, p73 isoforms crosstalk with other p53 family members indirectly. For example, although p73 isoforms fail to hetero-oligomerize with wild-type p53, p73 and p53 bind to an overlapping set of response elements and compete with one another for DNA binding at the promoters of target genes [7, 8]. In a similar note, it was recently reported that mutant p53R270H forms a complex with Notch1 and antagonizes p63/p73-mediated suppression of HES1 and ECM1 genes [101]. Moreover, the *TP73* P2 promoter contains a p53 response element through which transactivating family members can induce ΔNp73 expression [8, 10], establishing a negative regulatory feedback loop. Furthermore, p73 protein stability is inversely correlated with transactivation potential as p73 degradation involves the N-terminal TA domain [102]. Binding of TAp73 to dominant-negative isoforms and family members therefore inhibits transactivation, but simultaneously stabilizes the TAp73 protein [102]. This could potentially result in a scenario where TAp73 stabilization by low-level expression of DNp73 induces target gene expression to a higher degree than TAp73 alone. Notably, DN-induced stabilization TAp73 could likewise boost non-transcriptional TAp73 functions which are not controlled by the dominant-negative isoforms.

The complex p53 intrafamily crosstalk that takes place across human cancers [103] adds an extra layer of sophistication in the proposed model and further shapes cooperation of TAp73 and DNp73 towards enhancing selective advantages for overcoming the barriers of metastatic cascades (Fig. 3b). We propose that the large variety of intrafamily interactions can combinatorially modulate the p73-associated evolutionary fitness of the cancer cell. In particular, the more isoforms of the p53 family are co-expressed, the more opportunities for a cancer cell to co-opt isoform-specific functions of the fellow p53 family members and/or benefit from the interference of TAp73-regulated programs by p63 or p53 mutants. On the one hand, DNp63 and p53 mutants could help tumors to profit from pro-metastatic TAp73 functions by reinforcing inhibition of apoptosis, in a similar manner as the one described for DNp73. On the other hand, complexes between p73 and either p63 isoforms or p53 mutants may

lead to different cistromes and interactomes, creating a stunning layer of intricacy, which can be hijacked to accumulate metastatic capabilities.

5.3 Cancer clones co-expressing TAp73 and DN73 isoforms can evolve across several trajectories

Due to their potential for co-option of the vestigial physiological programs, TA/DNp73 co-expressing subclones might have increased fitness as compared to only-DNp73-expressing ones when confronted with a variety of microenvironmental pressures, such as metabolic stress, hypoxia, radiation therapy, drug treatment, or changes in the immune contexture (Fig. 4). The expression dynamics of p73 isoforms relative to each other, as well as to other interacting p53 family members, across the temporal axis of tumor evolution could likely reflect to the model of tumor progression. For example, overexpression of DNp73 isoforms in all clones along with TAp73 in heterogeneous patterns within a tumor would indicate that expression of DN-regulated antiapoptotic traits occurs at early stages, followed by expression of TA-regulated physiological programs in the selected subclonal populations. Hence, depending on their spatial and temporal co-expression, as well as the p53/p63 context, DNp73 and TAp73 co-expressed in tumor subclones may cooperate to offer a wide range of selective advantages within a dynamically changing TME. This eventually allows survival, clonal expansion, and dissemination via multiple trajectories that reflect respective co-option of a variety of distinct physiological programs.

6 Future perspectives for p73-based targeting of evolution of metastasis

Tumor evolution represents a therapeutic target of immense interest, with the potential to catalyze a paradigm shift in personalized cancer patient management [26]. The recently recognized functional divergence of *TP73* propels this dynamic process, since the many shared and distinct functions of its several splice variants which are co-expressed in the same cancer content may, under certain conditions, be hijacked to enhance the metastatic potential of tumor subpopulations within a constantly changing TME. In response to conditional cues from the TME, those subclones bearing combinations of p73 isoforms that support traits compatible with their survival under the new conditions would plausibly get selected and expanded. Consequently, beyond their typical antagonistic functions, TA and DNp73 isoforms might surprisingly work together toward a common goal, that is, the increase of metastatic potential. Identifying the conditions under which p73 isoforms act as either collaborators or competitors may provide a blueprint for better understanding p73-mediated regulation of metastasis.

The mechanism(s) by which isoform-specific transcriptional modules are activated simultaneously to support cooperativity of TA- and DN-controlled functions in shaping evolutionary trajectories remains a *terra incognita*. One possibility would be the formation of TA/DN hetero-oligomers which combinatorially regulate distinct subsets of targets, perhaps different from the targets of each homo-oligomer. Such a scenario would be analogous to hetero-oligomers between wild-type and mutant p53: mutp53 by itself cannot bind to wtp53 target genes but can block wtp53 in a dominant-negative manner. However, this dominant-negative effect is often incomplete, and more pronounced on low-affinity binding sites in pro-apoptotic promoters but less at high-affinity binding sites such as p21 [108–110]. Inhibition of TA by DNp73 could be similarly incomplete and preferentially block some tumor-suppressive but not other pro-metastatic activities in metabolism, immunomodulation, neurogenesis, and/or stemness. Currently, not much is known about the transcriptional programs and/or the protein interactomes of different TAp73/DNp73 hetero-oligomers *versus* the homo-oligomers. This is attributed, at least in part, to experimental limitations. Such experiments would typically require overexpression of several combinations of TAp73 and DNp73 isoforms in cell lines, in specific ratios, followed by high throughput cistrome and transcriptome analyses. However, thus far, p73 isoform overexpression experiments have posed a risk for technical artifacts, while at the endogenous level, the lack of p73 isoform-specific antibodies suitable for ChIP-Seq analyses has prevented such studies. Nowadays, an increasingly enriched arsenal of sophisticated tools, such as mice engineered to preferentially express specific C-terminal p73 variants [111, 112] and cell line models with selective CRISPR/Cas9-based knockout of TA or DN isoforms [20], may allow us to revisit these ideas and characterize cooperative and antagonistic roles of p73 isoforms in a higher resolution.

Another possible mechanism could be that p73 isoforms activate specific traits via establishing relevant interactions with epigenetic regulators, such as chromatin-modifying enzymes and/or long non-coding RNAs. The multitude of phenotypes required for metastases would be hard to achieve in a microevolutionary stepwise manner (i.e., through small-scale genomic alterations, such as single nucleotide substitutions and small indels affecting single genes). Instead, it is conceivable that macroevolutionary leaps, which are frequently associated with large-scale genome alterations, can catalyze these steps [25]. For example, the pro-metastatic activity of NFIB in lung cancer metastasis is linked to a widespread increase in chromatin accessibility indicative of global genome reprogramming during metastatic progression [113]. In view of this, we hypothesize that gene

activations required for the recapitulation of whole tissue programs co-opted in cancer cells may be achieved more efficiently within a narrow time frame by epigenetic reprogramming than by individual mutations. In this respect, p73 isoforms might reprogram the epigenetic landscape by, for instance, interacting with tissue-specific epigenetic modifiers that would eventually allow for extensive de-suppression of spatiotemporally restricted transcriptional modules that specify a function which is hijacked by cancer cells. Moreover, given that metastasis is frequently characterized by large-scale genomic alterations, such as copy number changes or structural chromosomal rearrangements manifested as chromosomal instability and chromothripsis [25], a topic for fruitful research would be to investigate for any correlations between macroevolutionary leaps and p73-induced epigenetic reprogramming.

In-depth understanding of the spatially heterogeneous expression of p73 isoforms along the temporal axis of tumor evolution could be informative to develop and optimize therapeutic targeting approaches. Suitable next-generation high-throughput methods are already in place and can be employed to describe the spatiotemporal heterogeneity of p73 isoforms in tumors, measure their involvement in models of tumor evolution, and elucidate how they shape tumor evolutionary trajectories. Single-cell RNA-Seq analysis combined with spatial transcriptomics methods [114] might be able to discriminate in a higher resolution p73 isoforms that are expressed in several parts of the tumor. Moreover, lineage tracing approaches, such as genetic barcoding, could be applied to track a p73-expressing cell introduced into a tumor and identify its progeny, both spatially and temporally [21]. These findings could enable tailoring p73-based therapies according to the stage of cancer and the given model of tumor evolution. For example, assuming a linear model of evolution of metastasis, induction of TAp73 isoforms with potent apoptotic properties at early stages might counteract the antiapoptotic effects of DNp73 [115]. On the contrary, late stages might be treated optimally via a pan-p73 inhibition strategy, where deletion of all co-expressed p73 isoforms would suppress simultaneously all p73-dependent traits that cooperatively increase the metastatic potential in a "two-birds-with-one-stone" manner. In tumor types where immunological agents are the first-line therapy, thus inevitably adding strong pressure for tumor immune evasion [116], early inhibition of p73 isoforms that regulate immune evasion traits could provide an evolutionary disadvantage and delay the development of resistance to immunotherapy.

Last but not least, mutations in oncogenic drivers are conserved in metastatic tumors, and mutations of the p53 gene are among the most persistent and prevalent in metastatic tumors [105, 117]. This indicates that p53 mutants in paternal clones offer major survival advantages and are therefore selected. Given that p73 interacts with mutp53, it would be worthwhile to investigate if metastatic trajectories are created through crosstalk of the p53 mutants with co-opted p73 isoform-specific programs. Molecular mechanisms that determine how specific oncogenic drivers interact with various physiological programs, and what triggers their activation in support of metastasis, are gaining increasing attention [29]. Detailed insight into this interplay is likely to open new avenues for the development of p53/p73-based therapeutic interventions at different stages of metastatic progression.

Acknowledgements All figures presented in this work were created using BioRender (biorender.com). AGG acknowledges Deutscher Akademischer Austauschdienst "Hochschulpartnerschaften mit Griechenland" (No. 57513880) and "DNA Damage and Repair and Their Relevance to Carcinogenesis" (No. 57339330).

Funding This work was supported by Deutsche Forschungsgemeinschaft, TRR81/3 109546710 Project A10 to TS.

Declarations

Conflict of interest The authors declare no competing interests.

References

1. Yang, A., & McKeon, F. (2000). P63 and P73: P53 mimics, menaces and more. *Nature Reviews Molecular Cell Biology, 1*(3), 199–207. https://doi.org/10.1038/35043127
2. Graziano, V., & De Laurenzi, V. (2011). Role of p63 in cancer development. *Biochimica et Biophysica Acta, 1816*(1), 57–66. https://doi.org/10.1016/j.bbcan.2011.04.002
3. Su, X., Chakravarti, D., & Flores, E. R. (2013). p63 steps into the limelight: Crucial roles in the suppression of tumorigenesis and metastasis. *Nature Reviews Cancer, 13*(2), 136–143. https://doi.org/10.1038/nrc3446
4. Stiewe, T. (2007). The p53 family in differentiation and tumorigenesis. *Nature Reviews Cancer, 7*(3), 165–168. https://doi.org/10.1038/nrc2072
5. Li, Y., & Prives, C. (2007). Are interactions with p63 and p73 involved in mutant p53 gain of oncogenic function? *Oncogene, 26*(15), 2220–2225. https://doi.org/10.1038/sj.onc.1210311
6. Ramos, H., Raimundo, L., & Saraiva, L. (2020). p73: From the p53 shadow to a major pharmacological target in anticancer therapy. *Pharmacological Research, 162*, 105245. https://doi.org/10.1016/j.phrs.2020.105245
7. Stiewe, T., Theseling, C. C., & Pützer, B. M. (2002). Transactivation-deficient Delta TA-p73 inhibits p53 by direct competition for DNA binding: Implications for tumorigenesis. *Journal of Biological Chemistry, 277*(16), 14177–14185. https://doi.org/10.1074/jbc.M200480200
8. Kartasheva, N. N., Contente, A., Lenz-Stöppler, C., Roth, J., & Dobbelstein, M. (2002). p53 induces the expression of its antagonist p73 Delta N, establishing an autoregulatory feedback loop. *Oncogene, 21*(31), 4715–4727. https://doi.org/10.1038/sj.onc.1205584
9. Zaika, A. I., Slade, N., Erster, S. H., Sansome, C., Joseph, T. W., Pearl, M., et al. (2002). DeltaNp73, a dominant-negative inhibitor of wild-type p53 and TAp73, is up-regulated in human tumors. *Journal of Experimental Medicine, 196*(6), 765–780. https://doi.org/10.1084/jem.20020179

10. Grob, T. J., Novak, U., Maisse, C., Barcaroli, D., Lüthi, A. U., Pirnia, F., et al. (2001). Human delta Np73 regulates a dominant negative feedback loop for TAp73 and p53. *Cell Death and Differentiation, 8*(12), 1213–1223. https://doi.org/10.1038/sj.cdd.4400962
11. Marabese, M., Vikhanskaya, F., & Broggini, M. (2007). p73: A chiaroscuro gene in cancer. *European Journal of Cancer, 43*(9), 1361–1372. https://doi.org/10.1016/j.ejca.2007.01.042
12. Tomasini, R., Tsuchihara, K., Wilhelm, M., Fujitani, M., Rufini, A., Cheung, C. C., et al. (2008). TAp73 knockout shows genomic instability with infertility and tumor suppressor functions. *Genes and Development, 22*(19), 2677–2691. https://doi.org/10.1101/gad.1695308
13. Wilhelm, M. T., Rufini, A., Wetzel, M. K., Tsuchihara, K., Inoue, S., Tomasini, R., et al. (2010). Isoform-specific p73 knockout mice reveal a novel role for delta Np73 in the DNA damage response pathway. *Genes and Development, 24*(6), 549–560. https://doi.org/10.1101/gad.1873910
14. Stiewe, T., Zimmermann, S., Frilling, A., Esche, H., & Pützer, B. M. (2002). Transactivation-deficient DeltaTA-p73 acts as an oncogene. *Cancer Research, 62*(13), 3598–3602.
15. Steder, M., Alla, V., Meier, C., Spitschak, A., Pahnke, J., Fürst, K., et al. (2013). DNp73 exerts function in metastasis initiation by disconnecting the inhibitory role of EPLIN on IGF1R-AKT/STAT3 signaling. *Cancer Cell, 24*(4), 512–527. https://doi.org/10.1016/j.ccr.2013.08.023
16. Lunghi, P., Costanzo, A., Mazzera, L., Rizzoli, V., Levrero, M., & Bonati, A. (2009). The p53 family protein p73 provides new insights into cancer chemosensitivity and targeting. *Clinical Cancer Research, 15*(21), 6495–6502. https://doi.org/10.1158/1078-0432.CCR-09-1229
17. Amelio, I., Inoue, S., Markert, E. K., Levine, A. J., Knight, R. A., Mak, T. W., et al. (2015). TAp73 opposes tumor angiogenesis by promoting hypoxia-inducible factor 1α degradation. *Proc Natl Acad Sci U S A, 112*(1), 226–231. https://doi.org/10.1073/pnas.1410609111
18. Stantic, M., Sakil, H. A., Zirath, H., Fang, T., Sanz, G., Fernandez-Woodbridge, A., et al. (2015). TAp73 suppresses tumor angiogenesis through repression of proangiogenic cytokines and HIF-1α activity. *Proc Natl Acad Sci U S A, 112*(1), 220–225. https://doi.org/10.1073/pnas.1421697112
19. Dulloo, I., Phang, B. H., Othman, R., Tan, S. Y., Vijayaraghavan, A., Goh, L. K., et al. (2015). Hypoxia-inducible TAp73 supports tumorigenesis by regulating the angiogenic transcriptome. *Nature Cell Biology, 17*(4), 511–523. https://doi.org/10.1038/ncb3130
20. López-Ferreras, L., Martínez-García, N., Maeso-Alonso, L., Martín-López, M., Díez-Matilla, Á., Villoch-Fernandez, J., et al. (2021). Deciphering the Nature of Trp73 Isoforms in Mouse Embryonic Stem Cell Models: Generation of Isoform-Specific. *Cancers (Basel), 13*, 13. https://doi.org/10.3390/cancers13133182
21. Gui, P., & Bivona, T. G. (2022). Evolution of metastasis: New tools and insights. *Trends Cancer, 8*(2), 98–109. https://doi.org/10.1016/j.trecan.2021.11.002
22. Merlo, L. M., Pepper, J. W., Reid, B. J., & Maley, C. C. (2006). Cancer as an evolutionary and ecological process. *Nature Reviews Cancer, 6*(12), 924–935. https://doi.org/10.1038/nrc2013
23. McGranahan, N., & Swanton, C. (2017). Clonal heterogeneity and tumor evolution: Past, present, and the future. *Cell, 168*(4), 613–628. https://doi.org/10.1016/j.cell.2017.01.018
24. Birkbak, N. J., & McGranahan, N. (2020). Cancer genome evolutionary trajectories in metastasis. *Cancer Cell, 37*(1), 8–19. https://doi.org/10.1016/j.ccell.2019.12.004
25. Turajlic, S., & Swanton, C. (2016). Metastasis as an evolutionary process. *Science, 352*(6282), 169–175. https://doi.org/10.1126/science.aaf2784
26. Amirouchene-Angelozzi, N., Swanton, C., & Bardelli, A. (2017). Tumor evolution as a therapeutic target. *Cancer Discov*, https://doi.org/10.1158/2159-8290.Cd-17-0343
27. Rodrigues, P., Patel, S. A., Harewood, L., Olan, I., Vojtasova, E., Syafruddin, S. E., et al. (2018). NF-κB-dependent lymphoid enhancer co-option promotes renal carcinoma metastasis. *Cancer Discovery, 8*(7), 850–865. https://doi.org/10.1158/2159-8290.Cd-17-1211
28. Logotheti, S., Marquardt, S., Richter, C., Sophie Hain, R., Murr, N., Takan, I., et al. (2020). Neural networks recapitulation by cancer cells promotes disease progression: a novel role of p73 isoforms in cancer-neuronal crosstalk. *Cancers, 12*, 12. https://doi.org/10.3390/cancers12123789
29. Patel, S. A., Rodrigues, P., Wesolowski, L., & Vanharanta, S. (2021). Genomic control of metastasis. *British Journal of Cancer, 124*(1), 3–12. https://doi.org/10.1038/s41416-020-01127-6
30. Kerosuo, L., & Bronner-Fraser, M. (2012). What is bad in cancer is good in the embryo: Importance of EMT in neural crest development. *Seminars in Cell & Developmental Biology, 23*(3), 320–332. https://doi.org/10.1016/j.semcdb.2012.03.010
31. Rousseaux, S., Debernardi, A., Jacquiau, B., Vitte, A. L., Vesin, A., Nagy-Mignotte, H., et al. (2013). Ectopic activation of germline and placental genes identifies aggressive metastasis-prone lung cancers. *Sci Transl Med, 5*(186), 186ra166. https://doi.org/10.1126/scitranslmed.3005723
32. Richter, C., Marquardt, S., Li, F., Spitschak, A., Murr, N., Edelhäuser, B. A. H., et al. (2019). Rewiring E2F1 with classical NHEJ via APLF suppression promotes bladder cancer invasiveness. *Journal of Experimental & Clinical Cancer Research, 38*(1), 292. https://doi.org/10.1186/s13046-019-1286-9
33. Costanzo, V., Bardelli, A., Siena, S., & Abrignani, S. (2018). Exploring the links between cancer and placenta development. *Open Biol, 8*, 6. https://doi.org/10.1098/rsob.180081
34. Marquardt, S., Pavlopoulou, A., Takan, I., Dhar, P., Pützer, B. M., & Logotheti, S. (2021). A systems-based key innovation-driven approach infers co-option of jaw developmental programs during cancer progression. *Front Cell Dev Biol, 9*, 682619. https://doi.org/10.3389/fcell.2021.682619
35. Yılmaz, H., Toy, H. I., Marquardt, S., Karakülah, G., Küçük, C., Kontou, P. I., et al. (2021). In silico methods for the identification of diagnostic and favorable prognostic markers in acute myeloid leukemia. *International Journal of Molecular Sciences, 22*, 17. https://doi.org/10.3390/ijms22179601
36. Kerbel, R. S. (2000). Tumor angiogenesis: Past, present and the near future. *Carcinogenesis, 21*(3), 505–515. https://doi.org/10.1093/carcin/21.3.505
37. Cervantes-Villagrana, R. D., Albores-García, D., Cervantes-Villagrana, A. R., & García-Acevez, S. J. (2020). Tumor-induced neurogenesis and immune evasion as targets of innovative anticancer therapies. *Signal Transduction and Targeted Therapy, 5*(1), 99. https://doi.org/10.1038/s41392-020-0205-z
38. Mravec, B. (2022). Neurobiology of cancer: Definition, historical overview, and clinical implications. *Cancer Medicine, 11*(4), 903–921. https://doi.org/10.1002/cam4.4488
39. Martik, M. L., & Bronner, M. E. (2017). Regulatory logic underlying diversification of the neural crest. *Trends in Genetics, 33*(10), 715–727. https://doi.org/10.1016/j.tig.2017.07.015
40. Logotheti, S., & Pützer, B. M. (2019). STAT3 and STAT5 targeting for simultaneous management of melanoma and autoimmune diseases. *Cancers (Basel), 11*, 10. https://doi.org/10.3390/cancers11101448
41. Logotheti, S., Pavlopoulou, A., Galtsidis, S., Vojtesek, B., & Zoumpourlis, V. (2013). Functions, divergence and clinical value

of TAp73 isoforms in cancer. *Cancer and Metastasis Reviews, 32*(3–4), 511–534. https://doi.org/10.1007/s10555-013-9424-x
42. Liu, G., Nozell, S., Xiao, H., & Chen, X. (2004). DeltaNp73beta is active in transactivation and growth suppression. *Molecular and Cellular Biology, 24*(2), 487–501. https://doi.org/10.1128/MCB.24.2.487-501.2004
43. Sakil, H. A. M., Stantic, M., Wolfsberger, J., Brage, S. E., Hansson, J., & Wilhelm, M. T. (2017). ΔNp73 regulates the expression of the multidrug-resistance genes ABCB1 and ABCB5 in breast cancer and melanoma cells - a short report. *Cell Oncol (Dordr)*.https://doi.org/10.1007/s13402-017-0340-x
44. George, J., Lim, J. S., Jang, S. J., Cun, Y., Ozretić, L., Kong, G., et al. (2015). Comprehensive genomic profiles of small cell lung cancer. *Nature, 524*(7563), 47–53. https://doi.org/10.1038/nature14664
45. Stiewe, T., Tuve, S., Peter, M., Tannapfel, A., Elmaagacli, A. H., & Pützer, B. M. (2004). Quantitative TP73 transcript analysis in hepatocellular carcinomas. *Clinical Cancer Research, 10*(2), 626–633. https://doi.org/10.1158/1078-0432.ccr-0153-03
46. Osterburg, C., & Dötsch, V. (2022). Structural diversity of p63 and p73 isoforms. *Cell Death and Differentiation*. https://doi.org/10.1038/s41418-022-00975-4
47. Logotheti, S., Richter, C., Murr, N., Spitschak, A., Marquardt, S., & Putzer, B. M. (2021). Mechanisms of functional pleiotropy of p73 in cancer and beyond. *Front Cell Dev Biol, 9*, 737735. https://doi.org/10.3389/fcell.2021.737735
48. Koeppel, M., van Heeringen, S. J., Kramer, D., Smeenk, L., Janssen-Megens, E., Hartmann, M., et al. (2011). Crosstalk between c-Jun and TAp73alpha/beta contributes to the apoptosis-survival balance. *Nucleic Acids Research, 39*(14), 6069–6085. https://doi.org/10.1093/nar/gkr028
49. Oswald, C., & Stiewe, T. (2008). In good times and bad: P73 in cancer. *Cell Cycle, 7*(12), 1726–1731. https://doi.org/10.4161/cc.7.12.6148
50. Muppani, N., Nyman, U., & Joseph, B. (2011). TAp73alpha protects small cell lung carcinoma cells from caspase-2 induced mitochondrial mediated apoptotic cell death. *Oncotarget, 2*(12), 1145–1154. https://doi.org/10.18632/oncotarget.391
51. Cheng, C., Feng, S., Jiao, J., Huang, W., Huang, J., Wang, L., et al. (2018). DLC2 inhibits development of glioma through regulating the expression ratio of TAp73α/TAp73β. *American Journal of Cancer Research, 8*(7), 1200–1213.
52. Jiang, P., Du, W., & Yang, X. (2013). A critical role of glucose-6-phosphate dehydrogenase in TAp73-mediated cell proliferation. *Cell Cycle, 12*(24), 3720–3726. https://doi.org/10.4161/cc.27267
53. Velletri, T., Romeo, F., Tucci, P., Peschiaroli, A., Annicchiarico-Petruzzelli, M., Niklison-Chirou, M. V., et al. (2013). GLS2 is transcriptionally regulated by p73 and contributes to neuronal differentiation. *Cell Cycle, 12*(22), 3564–3573. https://doi.org/10.4161/cc.26771
54. Amelio, I., Markert, E. K., Rufini, A., Antonov, A. V., Sayan, B. S., Tucci, P., et al. (2014). p73 regulates serine biosynthesis in cancer. *Oncogene, 33*(42), 5039–5046. https://doi.org/10.1038/onc.2013.456
55. Subramanian, D., Bunjobpol, W., & Sabapathy, K. (2015). Interplay between TAp73 protein and selected activator protein-1 (AP-1) family members promotes AP-1 target gene activation and cellular Growth. *Journal of Biological Chemistry, 290*(30), 18636–18649. https://doi.org/10.1074/jbc.M115.636548
56. Nemajerova, A., & Moll, U. M. (2019). Tissue-specific roles of p73 in development and homeostasis. *Journal of Cell Science, 132*, 19. https://doi.org/10.1242/jcs.233338
57. Fernandez-Alonso, R., Martin-Lopez, M., Gonzalez-Cano, L., Garcia, S., Castrillo, F., Diez-Prieto, I., et al. (2015). p73 is required for endothelial cell differentiation, migration and the formation of vascular networks regulating VEGF and TGFβ signaling. *Cell Death and Differentiation, 22*(8), 1287–1299. https://doi.org/10.1038/cdd.2014.214
58. Sabapathy, K. (2015). p73: A positive or negative regulator of angiogenesis, or both? *Molecular and Cellular Biology, 36*(6), 848–854. https://doi.org/10.1128/MCB.00929-15
59. Dulloo, I., Hooi, P. B., & Sabapathy, K. (2015). Hypoxia-induced DNp73 stabilization regulates Vegf-A expression and tumor angiogenesis similar to TAp73. *Cell Cycle, 14*(22), 3533–3539. https://doi.org/10.1080/15384101.2015.1078038
60. He, Z., Agostini, M., Liu, H., Melino, G., & Simon, H. U. (2015). p73 regulates basal and starvation-induced liver metabolism *in vivo*. *Oncotarget, 6*(32), 33178–33190. https://doi.org/10.18632/oncotarget.5090
61. Amelio, I., Antonov, A. A., Catani, M. V., Massoud, R., Bernassola, F., Knight, R. A., et al. (2014). TAp73 promotes anabolism. *Oncotarget, 5*(24), 12820–12934. https://doi.org/10.18632/oncotarget.2667
62. Yang, A., Walker, N., Bronson, R., Kaghad, M., Oosterwegel, M., Bonnin, J., et al. (2000). p73-Deficient mice have neurological, pheromonal and inflammatory defects but lack spontaneous tumours. *Nature, 404*(6773), 99–103. https://doi.org/10.1038/35003607
63. Tomasini, R., Secq, V., Pouyet, L., Thakur, A. K., Wilhelm, M., Nigri, J., et al. (2013). TAp73 is required for macrophage-mediated innate immunity and the resolution of inflammatory responses. *Cell Death and Differentiation, 20*(2), 293–301. https://doi.org/10.1038/cdd.2012.123
64. Koshiba, S., Ichimiya, S., Nagashima, T., Tonooka, A., Kubo, T., Kikuchi, T., et al. (2008). Tonsillar crypt epithelium of palmoplantar pustulosis secretes interleukin-6 to support B-cell development via p63/p73 transcription factors. *The Journal of Pathology, 214*(1), 75–84. https://doi.org/10.1002/path.2266
65. Kumagai, A., Kubo, T., Kawata, K., Kamekura, R., Yamashita, K., Jitsukawa, S., et al. (2017). Keratinocytes in atopic dermatitis express abundant ΔNp73 regulating thymic stromal lymphopoietin production via NF-κB. *Journal of Dermatological Science, 88*(2), 175–183. https://doi.org/10.1016/j.jdermsci.2017.06.017
66. Vikhreva, P., Petrova, V., Gokbulut, T., Pestlikis, I., Mancini, M., Di Daniele, N., et al. (2017). TAp73 upregulates IL-1β in cancer cells: Potential biomarker in lung and breast cancer? *Biochemical and Biophysical Research Communications, 482*(3), 498–505. https://doi.org/10.1016/j.bbrc.2016.10.085
67. Bent, R., Moll, L., Grabbe, S., & Bros, M. (2018). Interleukin-1 Beta-A friend or foe in malignancies? *International Journal of Molecular Sciences, 19*, 8. https://doi.org/10.3390/ijms19082155
68. Wolfsberger, J., Sakil, H. A. M., Zhou, L., van Bree, N., Baldisseri, E., de Souza Ferreira, S., et al. (2021). TAp73 represses NF-κB-mediated recruitment of tumor-associated macrophages in breast cancer. *Proceedings of the National Academy of Sciences, 118*, 10. https://doi.org/10.1073/pnas.2017089118
69. Rozenberg, J. M., Zvereva, S., Dalina, A., Blatov, I., Zubarev, I., Luppov, D., et al. (2021). Dual role of p73 in cancer microenvironment and dna damage response. *Cells, 10*, 12. https://doi.org/10.3390/cells10123516
70. Ren, M., Kazemian, M., Zheng, M., He, J., Li, P., Oh, J., et al. (2020). Transcription factor p73 regulates Th1 differentiation. *Nature Communications, 11*(1), 1475. https://doi.org/10.1038/s41467-020-15172-5
71. Niklison-Chirou, M. V., Agostini, M., Amelio, I., & Melino, G. (2020). Regulation of adult neurogenesis in mammalian brain. *International Journal of Molecular Sciences, 21*, 14. https://doi.org/10.3390/ijms21144869
72. Griffin, N., Faulkner, S., Jobling, P., & Hondermarck, H. (2018). Targeting neurotrophin signaling in cancer: The renaissance.

Pharmacological Research, 135, 12–17. https://doi.org/10.1016/j.phrs.2018.07.019
73. Monje, M., Borniger, J. C., D'Silva, N. J., Deneen, B., Dirks, P. B., Fattahi, F., et al. (2020). Roadmap for the emerging field of cancer neuroscience. *Cell, 181*(2), 219–222. https://doi.org/10.1016/j.cell.2020.03.034
74. Friedmann-Morvinski, D., & Verma, I. M. (2014). Dedifferentiation and reprogramming: Origins of cancer stem cells. *EMBO Reports, 15*(3), 244–253. https://doi.org/10.1002/embr.201338254
75. Batlle, E., & Clevers, H. (2017). Cancer stem cells revisited. *Nature Medicine, 23*(10), 1124–1134. https://doi.org/10.1038/nm.4409
76. Talos, F., Abraham, A., Vaseva, A. V., Holembowski, L., Tsirka, S. E., Scheel, A., et al. (2010). p73 is an essential regulator of neural stem cell maintenance in embryonal and adult CNS neurogenesis. *Cell Death and Differentiation, 17*(12), 1816–1829. https://doi.org/10.1038/cdd.2010.131
77. Fujitani, M., Cancino, G. I., Dugani, C. B., Weaver, I. C., Gauthier-Fisher, A., Paquin, A., et al. (2010). TAp73 acts via the bHLH Hey2 to promote long-term maintenance of neural precursors. *Current Biology, 20*(22), 2058–2065. https://doi.org/10.1016/j.cub.2010.10.029
78. Gonzalez-Cano, L., Herreros-Villanueva, M., Fernandez-Alonso, R., Ayuso-Sacido, A., Meyer, G., Garcia-Verdugo, J. M., et al. (2010). p73 deficiency results in impaired self renewal and premature neuronal differentiation of mouse neural progenitors independently of p53. *Cell Death & Disease, 1*, e109. https://doi.org/10.1038/cddis.2010.87
79. Agostini, M., Tucci, P., Chen, H., Knight, R. A., Bano, D., Nicotera, P., et al. (2010). p73 regulates maintenance of neural stem cell. *Biochemical and Biophysical Research Communications, 403*(1), 13–17. https://doi.org/10.1016/j.bbrc.2010.10.087
80. Killick, R., Niklison-Chirou, M., Tomasini, R., Bano, D., Rufini, A., Grespi, F., et al. (2011). p73: A multifunctional protein in neurobiology. *Molecular Neurobiology, 43*(2), 139–146. https://doi.org/10.1007/s12035-011-8172-6
81. Meier, C., Hardtstock, P., Joost, S., Alla, V., & Pützer, B. M. (2016). p73 and IGF1R regulate emergence of aggressive cancer stem-like features via miR-885-5p control. *Cancer Research, 76*(2), 197–205. https://doi.org/10.1158/0008-5472.CAN-15-1228
82. Galtsidis, S., Logotheti, S., Pavlopoulou, A., Zampetidis, C. P., Papachristopoulou, G., Scorilas, A., et al. (2017). Unravelling a p73-regulated network: The role of a novel p73-dependent target, MIR3158, in cancer cell migration and invasiveness. *Cancer Letters, 388*, 96–106. https://doi.org/10.1016/j.canlet.2016.11.036
83. Daskalos, A., Logotheti, S., Markopoulou, S., Xinarianos, G., Gosney, J. R., Kastania, A. N., et al. (2011). Global DNA hypomethylation-induced ΔNp73 transcriptional activation in non-small cell lung cancer. *Cancer Letters, 300*(1), 79–86. https://doi.org/10.1016/j.canlet.2010.09.009
84. Logotheti, S., Michalopoulos, I., Sideridou, M., Daskalos, A., Kossida, S., Spandidos, D. A., et al. (2010). Sp1 binds to the external promoter of the p73 gene and induces the expression of TAp73gamma in lung cancer. *FEBS Journal, 277*(14), 3014–3027. https://doi.org/10.1111/j.1742-4658.2010.07710.x
85. Fürst, K., Steder, M., Logotheti, S., Angerilli, A., Spitschak, A., Marquardt, S., et al. (2019). DNp73-induced degradation of tyrosinase links depigmentation with EMT-driven melanoma progression. *Cancer Letters, 442*, 299–309. https://doi.org/10.1016/j.canlet.2018.11.009
86. Sayan, A. E., Sayan, B. S., Findikli, N., & Ozturk, M. (2001). Acquired expression of transcriptionally active p73 in hepatocellular carcinoma cells. *Oncogene, 20*(37), 5111–5117. https://doi.org/10.1038/sj.onc.1204669
87. Woodstock, D. L., Sammons, M. A., & Fischer, M. (2021). p63 and p53: Collaborative partners or dueling rivals? *Front Cell Dev Biol, 9*, 701986. https://doi.org/10.3389/fcell.2021.701986
88. Coutandin, D., Löhr, F., Niesen, F. H., Ikeya, T., Weber, T. A., Schäfer, B., et al. (2009). Conformational stability and activity of p73 require a second helix in the tetramerization domain. *Cell Death and Differentiation, 16*(12), 1582–1589. https://doi.org/10.1038/cdd.2009.139
89. Joerger, A. C., Rajagopalan, S., Natan, E., Veprintsev, D. B., Robinson, C. V., & Fersht, A. R. (2009). Structural evolution of p53, p63, and p73: Implication for heterotetramer formation. *Proc Natl Acad Sci U S A, 106*(42), 17705–17710. https://doi.org/10.1073/pnas.0905867106
90. Gebel, J., Luh, L. M., Coutandin, D., Osterburg, C., Löhr, F., Schäfer, B., et al. (2016). Mechanism of TAp73 inhibition by ΔNp63 and structural basis of p63/p73 hetero-tetramerization. *Cell Death and Differentiation, 23*(12), 1930–1940. https://doi.org/10.1038/cdd.2016.83
91. Rocco, J. W., Leong, C. O., Kuperwasser, N., DeYoung, M. P., & Ellisen, L. W. (2006). p63 mediates survival in squamous cell carcinoma by suppression of p73-dependent apoptosis. *Cancer Cell, 9*(1), 45–56. https://doi.org/10.1016/j.ccr.2005.12.013
92. Marin, M. C., Jost, C. A., Brooks, L. A., Irwin, M. S., O'Nions, J., Tidy, J. A., et al. (2000). A common polymorphism acts as an intragenic modifier of mutant p53 behaviour. *Nature Genetics, 25*(1), 47–54. https://doi.org/10.1038/75586
93. Gaiddon, C., Lokshin, M., Ahn, J., Zhang, T., & Prives, C. (2001). A subset of tumor-derived mutant forms of p53 down-regulate p63 and p73 through a direct interaction with the p53 core domain. *Molecular and Cellular Biology, 21*(5), 1874–1887. https://doi.org/10.1128/MCB.21.5.1874-1887.2001
94. Stindt, M. H., Muller, P. A., Ludwig, R. L., Kehrloesser, S., Dötsch, V., & Vousden, K. H. (2015). Functional interplay between MDM2, p63/p73 and mutant p53. *Oncogene, 34*(33), 4300–4310. https://doi.org/10.1038/onc.2014.359
95. Kehrloesser, S., Osterburg, C., Tuppi, M., Schäfer, B., Vousden, K. H., & Dötsch, V. (2016). Intrinsic aggregation propensity of the p63 and p73 TI domains correlates with p53R175H interaction and suggests further significance of aggregation events in the p53 family. *Cell Death and Differentiation, 23*(12), 1952–1960. https://doi.org/10.1038/cdd.2016.75
96. Xu, J., Reumers, J., Couceiro, J. R., De Smet, F., Gallardo, R., Rudyak, S., et al. (2011). Gain of function of mutant p53 by coaggregation with multiple tumor suppressors. *Nature Chemical Biology, 7*(5), 285–295. https://doi.org/10.1038/nchembio.546
97. Petronilho, E. C., Pedrote, M. M., Marques, M. A., Passos, Y. M., Mota, M. F., Jakobus, B., et al. (2021). Phase separation of p53 precedes aggregation and is affected by oncogenic mutations and ligands. *Chemical Science, 12*(21), 7334–7349. https://doi.org/10.1039/d1sc01739j
98. Wang, G., & Fersht, A. R. (2017). Multisite aggregation of p53 and implications for drug rescue. *Proc Natl Acad Sci U S A, 114*(13), E2634–E2643. https://doi.org/10.1073/pnas.1700308114
99. Anbarasan, T., & Bourdon, J. C. (2019). The emerging landscape of p53 isoforms in physiology, cancer and degenerative diseases. *International Journal of Molecular Sciences, 20*, 24. https://doi.org/10.3390/ijms20246257
100. Zorić, A., Horvat, A., & Slade, N. (2013). Differential effects of diverse p53 isoforms on TAp73 transcriptional activity and apoptosis. *Carcinogenesis, 34*(3), 522–529. https://doi.org/10.1093/carcin/bgs370
101. Zhang, J., Sun, W., Kong, X., Zhang, Y., Yang, H. J., Ren, C., et al. (2019). Mutant p53 antagonizes p63/p73-mediated tumor suppression via Notch1. *Proceedings of the National Academy of*

Sciences of the United States of America, 116(48), 24259–24267. https://doi.org/10.1073/pnas.1913919116
102. Slade, N., Zaika, A. I., Erster, S., & Moll, U. M. (2004). DeltaNp73 stabilises TAp73 proteins but compromises their function due to inhibitory hetero-oligomer formation. *Cell Death and Differentiation, 11*(3), 357–360. https://doi.org/10.1038/sj.cdd.4401335
103. Ferraiuolo, M., Di Agostino, S., Blandino, G., & Strano, S. (2016). Oncogenic intra-p53 family member interactions in human cancers. *Frontiers in Oncology, 6*, 77. https://doi.org/10.3389/fonc.2016.00077
104. Nemajerova, A., Amelio, I., Gebel, J., Dötsch, V., Melino, G., & Moll, U. M. (2018). Non-oncogenic roles of TAp73: From multiciliogenesis to metabolism. *Cell Death and Differentiation, 25*(1), 144–153. https://doi.org/10.1038/cdd.2017.178
105. Tang, Q., Su, Z., Gu, W., & Rustgi, A. K. (2020). Mutant p53 on the path to metastasis. *Trends Cancer, 6*(1), 62–73. https://doi.org/10.1016/j.trecan.2019.11.004
106. Carroll, D. K., Carroll, J. S., Leong, C. O., Cheng, F., Brown, M., Mills, A. A., et al. (2006). p63 regulates an adhesion programme and cell survival in epithelial cells. *Nature Cell Biology, 8*(6), 551–561. https://doi.org/10.1038/ncb1420
107. Barbieri, C. E., Tang, L. J., Brown, K. A., & Pietenpol, J. A. (2006). Loss of p63 leads to increased cell migration and up-regulation of genes involved in invasion and metastasis. *Cancer Research, 66*(15), 7589–7597. https://doi.org/10.1158/0008-5472.CAN-06-2020
108. Olive, K. P., Tuveson, D. A., Ruhe, Z. C., Yin, B., Willis, N. A., Bronson, R. T., et al. (2004). Mutant p53 gain of function in two mouse models of Li-Fraumeni syndrome. *Cell, 119*(6), 847–860. https://doi.org/10.1016/j.cell.2004.11.004
109. Lang, G. A., Iwakuma, T., Suh, Y. A., Liu, G., Rao, V. A., Parant, J. M., et al. (2004). Gain of function of a p53 hot spot mutation in a mouse model of Li-Fraumeni syndrome. *Cell, 119*(6), 861–872. https://doi.org/10.1016/j.cell.2004.11.006
110. Aubrey, B. J., Janic, A., Chen, Y., Chang, C., Lieschke, E. C., Diepstraten, S. T., et al. (2018). Mutant TRP53 exerts a target gene-selective dominant-negative effect to drive tumor development. *Genes and Development, 32*(21–22), 1420–1429. https://doi.org/10.1101/gad.314286.118
111. Amelio, I., Panatta, E., Niklison-Chirou, M. V., Steinert, J. R., Agostini, M., Morone, N., et al. (2020). The C terminus of p73 is essential for hippocampal development. *Proc Natl Acad Sci U S A, 117*(27), 15694–15701. https://doi.org/10.1073/pnas.2000917117
112. Laubach, K. N., Yan, W., Kong, X., Sun, W., Chen, M., Zhang, J., et al. (2022). p73α1, a p73 C-terminal isoform, regulates tumor suppression and the inflammatory response via Notch1. *Proc Natl Acad Sci U S A, 119*(22), e2123202119. https://doi.org/10.1073/pnas.2123202119
113. Denny, S. K., Yang, D., Chuang, C. H., Brady, J. J., Lim, J. S., Grüner, B. M., et al. (2016). Nfib promotes metastasis through a widespread increase in chromatin accessibility. *Cell, 166*(2), 328–342. https://doi.org/10.1016/j.cell.2016.05.052
114. Baccin, C., Al-Sabah, J., Velten, L., Helbling, P. M., Grünschläger, F., Hernández-Malmierca, P., et al. (2020). Combined single-cell and spatial transcriptomics reveal the molecular, cellular and spatial bone marrow niche organization. *Nature Cell Biology, 22*(1), 38–48. https://doi.org/10.1038/s41556-019-0439-6
115. Das, S., & Somasundaram, K. (2006). Therapeutic potential of an adenovirus expressing p73 beta, a p53 homologue, against human papilloma virus positive cervical cancer *in vitro* and *in vivo*. *Cancer Biology & Therapy, 5*(2), 210–217. https://doi.org/10.4161/cbt.5.2.2402
116. Andrews, M. C., & Wargo, J. A. (2017). Cancer evolution during immunotherapy. *Cell, 171*(4), 740–742. https://doi.org/10.1016/j.cell.2017.10.027
117. Zehir, A., Benayed, R., Shah, R. H., Syed, A., Middha, S., Kim, H. R., et al. (2017). Mutational landscape of metastatic cancer revealed from prospective clinical sequencing of 10,000 patients. *Nature Medicine, 23*(6), 703–713. https://doi.org/10.1038/nm.4333
118. Ghatak, D., Das Ghosh, D., & Roychoudhury, S. (2020). Cancer stemness: P53 at the wheel. *Frontiers in Oncology, 10*, 604124. https://doi.org/10.3389/fonc.2020.604124
119. Liu, J., Zhang, C., Hu, W., & Feng, Z. (2015). Tumor suppressor p53 and its mutants in cancer metabolism. *Cancer Letters, 356*(2 Pt A), 197–203. https://doi.org/10.1016/j.canlet.2013.12.025
120. Ghosh, M., Saha, S., Bettke, J., Nagar, R., Parrales, A., Iwakuma, T., et al. (2021). Mutant p53 suppresses innate immune signaling to promote tumorigenesis. *Cancer Cell, 39*(4), 494-508.e495. https://doi.org/10.1016/j.ccell.2021.01.003
121. Cooks, T., Pateras, I. S., Tarcic, O., Solomon, H., Schetter, A. J., Wilder, S., et al. (2013). Mutant p53 prolongs NF-κB activation and promotes chronic inflammation and inflammation-associated colorectal cancer. *Cancer Cell, 23*(5), 634–646. https://doi.org/10.1016/j.ccr.2013.03.022
122. Alvarado-Ortiz, E., de la Cruz-López, K. G., Becerril-Rico, J., Sarabia-Sánchez, M. A., Ortiz-Sánchez, E., & García-Carrancá, A. (2020). Mutant p53 gain-of-function: Role in cancer development, progression, and therapeutic approaches. *Front Cell Dev Biol, 8*, 607670. https://doi.org/10.3389/fcell.2020.607670
123. Moses, M. A., George, A. L., Sakakibara, N., Mahmood, K., Ponnamperuma, R. M., King, K. E., et al. (2019). Molecular mechanisms of p63-mediated squamous cancer pathogenesis. *International Journal of Molecular Sciences, 20*, 14. https://doi.org/10.3390/ijms20143590
124. Bid, H. K., Roberts, R. D., Cam, M., Audino, A., Kurmasheva, R. T., Lin, J., et al. (2014). ΔNp63 promotes pediatric neuroblastoma and osteosarcoma by regulating tumor angiogenesis. *Cancer Research, 74*(1), 320–329. https://doi.org/10.1158/0008-5472.CAN-13-0894
125. Gatti, V., Fierro, C., Annicchiarico-Petruzzelli, M., Melino, G., & Peschiaroli, A. (2019). ΔNp63 in squamous cell carcinoma: Defining the oncogenic routes affecting epigenetic landscape and tumour microenvironment. *Molecular Oncology, 13*(5), 981–1001. https://doi.org/10.1002/1878-0261.12473