TP53

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TP53 tumor suppressor gene is a key player for cellular homeostasis.

hematological malignancies mutant P53

1. Introduction

The development of personalized therapies for cancer treatment has received considerable attention in recent years. Two main steps are mandatory to achieve an effective personalized therapy: first, the identification of a suitable target involved in one or several pathway(s) that is (are) impaired in a given cancer or in a group of cancers and, second, the identification of a drug that can specifically hit that target, thus reducing the undesired effects of its dysfunction.

One of the targets that best suites the first requirement is the P53 tumor suppressor protein, which is a key player in different pathways ranging from cell cycle regulation, DNA damage response, apoptosis, senescence, DNA repair and cell migration to those more recently identified, such as autophagy and metabolism. Under normal conditions, the intracellular P53 protein is kept at a low level by a negative-feedback loop with the MDM2 E3 ubiquitin ligase, which promotes its degradation in the absence of stress [1]. However, following different types of stress, P53 becomes activated, accumulates in the cell nuclei, and trans-activates a plethora of target genes that build up an appropriate cell response. To achieve these goals, P53 binds, as a tetrameric transcription factor, to conserved response elements (REs) located in the promoter regions of target genes, including *P21* and *GADD45A* for the cell cycle arrest, *BAX*, *PUMA* and *NOXA* for the induction of apoptosis, thus activating their expression and counteracting cancer onset and progression [2][3].

The occurrence of a *TP53* mutation may have important consequences on cell homeostasis: (i) the genes that are normally modulated by wild-type P53 are no longer activated, (ii) the mutant P53 protein is not able to participate in the negative-feedback loop with MDM2, leading to an accumulation of mutant P53 protein itself; (iii) the mutant protein can acquire new functions, the so-called gain of function (GOF) properties [4]. In general, these P53 dysfunctions represent detrimental events in cancer as they facilitate cell growth and prevent the response to therapy.

More than 50% of human tumors [5] show *TP53* mutations, although their frequency varies among different types of tumor ranging from 90% in ovary cancer, 50–80% in lung cancer, 40–60% in colorectal cancer to 10% in prostate cancer. The frequency of *TP53* mutations is also highly heterogeneous in the different types of leukemia and

lymphomas, being usually low at diagnosis and reaching values up to 60% at progression or at relapse [5]. Besides mutations, P53 dysfunctions may also be generated by the deletion of the *TP53* locus on the short arm of chromosome 17 [indicated as del(17p)] [6][7] as well as by the abnormally high expression of wild-type P53 negative regulators (e.g., MDM2/4) [8].

Because of its widespread functions in cancer origin and progression, the P53 protein has been considered a promising target for the development of new anticancer strategies. Nowadays, three main strategies are available, including (i) the restoration of wild-type P53 activity by inhibiting its binding with MDM2/4 proteins [9][10]; (ii) the reactivation of the wild-type function in the mutant P53 protein [11] and (iii) the elimination of the undesired GOF activities through degradation of the mutant P53 protein [12][13][14][15].

Based on the above-described general strategies, several molecules have been developed and tested in different tumor models. The appealing feature of these molecules is represented by their ability of inducing an efficient apoptotic response in cancer cells that are generally refractory to chemotherapy. Molecules, such as Nutlin and RITA, inhibit the binding of wild-type P53 to MDM2 and, although with different mechanisms, prevent the negative control of MDM2; this allows the P53 stabilization and the induction of a P53-dependent transcription of genes, which induce cell death [16][17]. Conversely, PRIMA-1 and its methylated derivative PRIMA-1^{Met} (from here on mentioned as APR246) have been isolated as small molecular weight molecules able to restore the DNA binding capacity of different mutant P53 proteins and to induce significant apoptosis in cancer cells carrying a mutant P53 protein [18]. The other interesting approach that may prevent the GOF activities of the mutant P53 and the chemoresistance that is consequent to it is based on mutant P53 deprivation. In cancer cells, mutant P53 is stabilized by the over-expression of the HSP90 protein [19]; therefore, several HSP90 inhibitors, such as 17-AAG or Ganetespib, have been tested for their ability to cause the degradation of mutant P53 and for their capacity of acting as anticancer molecules [20][21]. In addition, HDAC inhibitors, such as SAHA, can induce the degradation of mutant P53 and restrain the growth of mutant P53 expressing tumors [15][20]. Some of these molecules (i.e., nutlins, APR246, ganetespid) have reached an advanced level of preclinical experimentation, and clinical trials have been started [10][11][12].

2. *TP53* Mutations in Hematological Malignancies

The frequency of *TP53* mutations in hematological cancers is lower than in solid tumors (http://p53.free/.fr). In lymphomas, the incidence of *TP53* mutations varies significantly according to the histological subtype and also to the disease stage; generally, *TP53* mutations are relatively infrequent in low-grade non-Hodgkin lymphoma (NHL), whereas a higher incidence is reported in aggressive NHL subtypes [22]. Burkitt lymphoma (BL) has consistently been found to have a frequency of *TP53* mutations up to 33% of cases, as detected by the sequencing of exons 5–9 of the *TP53* gene [23]. *TP53* is mutated in 3–8% of the acute myeloid leukemia (AML) cases [24], in less than 3% of the acute lymphoblastic leukemia (ALL) cases [25], and in 10–12% of multiple myeloma (MM) cases [26][27]. As a general rule, *TP53* mutations in hematological malignancies are associated with a more aggressive disease course, resistance to therapies, and a dire outcome.

CLL represents approximately 30% of all adult leukemias [28] and is characterized by a clonal expansion of small, relatively monomorphic circulating B cells, which may infiltrate the bone marrow, the lymph nodes, and the spleen [29]. The clinical course is heterogeneous, ranging from a rapid disease progression, requiring early treatment, to decades of survival with minimal or no treatment [30][31].

More than 80% of CLL cases have genomic aberrations at diagnosis, the most frequent being partial deletions at 13q (~55%), 11q (~15%), 17p (~8%), and gain of chromosome 12 (~15%) [32]. The incidence of *TP53* mutations is approximately 5–7% at diagnosis [33][34], but it rises as the disease progresses, reaching approximately 40% in refractory CLL [35][36][37][38]. In general, global P53 dysfunctions [i.e., *TP53* mutations or (del 17p)] are associated with adverse outcomes due to the development of resistance to chemotherapy and chemo-immunotherapies. Therefore, their presence represents a key biomarker that guides the therapy decision [39]. Accordingly, the European Research Initiative on CLL (ERIC) group considers mandatory *TP53* mutational screening for all patients before the starting of any therapy [40]. This approach prevents the use of chemo-immunotherapy in favor of new therapies with BCR (B-Cell Receptor) inhibitors [41][42][43][44][45][46] or BCL-2 inhibitors [47][48] in patients with P53 dysfunctions [49]. In addition, a reassessment of *TP53* status before the initiation of any subsequent line of therapy is recommended to exclude the occurrence/expansion of mutant P53 clones during disease progression [33]. Finally, it should be pointed out that the presence of a P53 dysfunction determined as *TP53* mutation and/or del(17p) has a negative effect on the overall survival of patients treated with the new targeted therapies [50].

The presence of a P53 dysfunction may also influence CLL progression from the early disease stages, measured as time to first treatment (TTFT). In CLL, a large overlap between the presence of del(17p) and a *TP53* mutation at the single patient level is present since the majority of patients present both alterations. These patients generally have a shorter TTFT than patients with no *TP53* dysfunctions (i.e., mutations and/or deletions) [51]. Due to few patients with exclusively del(17p) in the various cohorts investigated, it has not been possible to determine whether the presence of the sole del(17p) confers a worse prognosis than the presence of both del(17p) and a *TP53* mutation; moreover, a note of caution should be suggested by the observation made by different groups that a number of patients with exclusively *TP53* mutations are characterized by the presence of IGHV mutations, which notoriously confers a good prognosis [52]. Thus, it is possible that this group of patients with mutated IGHV genes and *TP53* mutations represents a special subset of CLL that have the tendency to not progress since they are not present in cohorts of patients at later stages of the disease [52]. Very recently, the influence of *TP53* mutations on early disease progression has been investigated in CLL [51]. Since the presence of a *TP53* mutation does not necessarily imply a complete P53 inactivation [34], functional characterization of mutant P53 protein encoded by *TP53* mutations was also performed by using the O-CLL1 observational study (clinicaltrial.gov identifier NCT00917540) that recruited a cohort of clinically and molecularly well-characterized Binet stage A patients. The analyzed mutant P53 proteins appeared to be functionally heterogeneous, but such heterogeneity was not associated with differences in TTFT within the group of patients carrying only the *TP53* mutation without del(17p). Even though this study demonstrates that the occurrence of del(17p) significantly predicts TTFT, while that of a *TP53* mutation alone is unable of such prediction [51], further analysis in a larger cohort is needed to get insights on the impact of the functional heterogeneity of P53 mutants on CLL prognosis and therapy.

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