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Regulation of the cell fate by DNA damage and hypoxia

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Abstract

In order to provide the means for the design of novel rational anti-cancer drug therapies research efforts are concentrated on unravelling the molecular circuits which induce programmed cell death and block proliferation of cancer cells. Modern therapeutic strategies are based on the understanding of the complexity of physiological functions such as differentiation, development, immune responses, cell-cycle arrest, DNA damage repair, apoptosis, autophagy, energy metabolism, and senescence. It has become evident that this knowledge will provide the means to target the components of the pathways involved in these processes in a specific and selective manner thus paving the way for the development of effective and personalised anti-cancer therapies. Transcription is a crucial cellular process that regulates a multitude of physiological functions, which are essential in disease progression and cellular response to therapy. Transcription factors such as the p53 tumor suppressor and the hypoxia-inducible factor-α (HIF-α) are key players in carcinogenesis and cellular response to cancer therapies. Both of these transcription factors regulate gene expression of genes involved in cell death and proliferation, in some cases cooperating towards producing the same outcome and in some others mediating opposing effects. It is thus apparent that fine tuning of the activity of these transcription factors is essential to determine the cellular response to therapeutic regimens, in other words whether tumor cells will commit to apoptosis or evade engagement with the anti-proliferative effects of drugs leading to drug resistance. Our observations support the notion that the functional crosstalk between HIF-1α and p53 pathways and thus the fine tuning of their transcriptional activity is mediated by cofactors shared between the two transcription factors such as components of the p300 co-activator multiprotein complex. In particular, there is evidence to suggest that differential composition of the co-modulatory protein complexes associated with p53 and HIF-1α under diverse types of stress conditions differentially regulate the expression of distinct subsets of p53 and HIF-1α target genes involved in processes such as cell cycle arrest, apoptosis, chronic inflammation, and cellular energy metabolism thereby determining the cellular fate under particular types of micro-environmental stress.

Key words: Cancer; Transcription; Apoptosis; Inflammation; Tumor energy metabolism; Glycolysis; Oxidative phosphorylation; p53; Hypoxia-inducible factor; p300/CBP associated factors

Core tip: The results of our work endorse the notion that specific features determine targeting of transcription factors to distinct clusters of their target genes including the nature of the DNA binding sites found within the regulatory region of the promoter of each one of the target genes, the composition of the cofactor

network associated with different transcription factors under diverse types of stress conditions and the precise posttranslational modifications of each one of the transcription factors linking characteristic PTM codes with discrete types of micro-environmental stress. These features are essential considerations for the design of effective therapeutics and individualised cancer treatment.

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INTRODUCTION

The transcriptional regulation of gene expression is a crucial mechanism by which cells maintain homeostasis, differentiate, survive and proliferate, respond to internal signals as well as those they receive from their surroundings, and adjust to local environmental conditions[1]. The transcription process is regulated mainly at two levels. One encompassing transcription factors and the transcriptional machinery, and the other involving chromatin which is the packaging structure of the DNA and consists of the four histone proteins H2A, H2B, H3 and H4 forming the nucleosome[2,3]. The two levels of regulation are connected to each other since access of the transcription machinery to the DNA is regulated by molecular modifications of the chromatin structure executed by remodelling reactions such as phosphorylation, methylation, and acetylation[4] which control the binding between transcription factors and DNA thereby selectively and specifically modulating gene expression of their target genes[5,6]. These modifications represent the so called "histone code"[7], which is a type of encryption that indicates either open access (euchromatin structure) of transcription factors to the DNA and transcription initiation of the target genes or closed chromatin conformation (heterochromatin) and transcriptional repression[8,9]. In this respect transcriptional co-factors, which are proteins mediating histone modifications thus determining the open or closed chromatin conformation are of crucial importance in the activation or repression of gene expression and therefore for the cellular physiology[10-12].

The detailed understanding of the regulation of gene expression has provided the means to comprehend how aberrant regulation of the transcriptional events can lead to disease[13]. The role of DNA binding transcription factors and their modulators, of the non-coding RNAs, as well as the effects of epigenetic changes on the structure of the chromatin on transcription regulation and the impact of these events on the cellular physiology has been elucidated for many different diseases, for example diabetes[14] cardiovascular disease[15], neurological disorders[16], rheumatoid arthritis[17] cancer[18] and conditions such as obesity[19] and ageing[20]. Transcriptional regulation is not only important to understand the initiation, development, and prognosis of the disease but it is also imperative in predicting the cellular response to therapeutic modalities[21-24].

DNA DAMAGE RESPONSE: THE ROLE OF THE p53 TUMOR SUPPRESSOR

A characteristic example of the importance of the transcription process in the outcome of the disease and the cellular response to drug treatment has been demonstrated by the function of the transcription factor and tumor suppressor protein p53[25]. p53 is a transcription factor responding alternatively to diverse types of stress conveying different signals in a manner dependent on the type of stress[26] by modulating gene expression of specific subsets of its target genes involved in vital and sometimes contradicting cellular functions such as cell cycle control[27], apoptosis[28], senescence[29,30], autophagy[31], DNA damage repair[32,33], and tumor energy metabolism[34]. It is worth noting that more than 90% of p53 mutations in human cancers occur in its DNA binding domain[35] hampering the ability of this transcription factor to bind to DNA and transactivate its transcription target genes and emphasising the importance of transcription in oncogenesis[36]. Under mild stress conditions p53 facilitates cell survival by activating a set of genes involved in cell cycle arrest and DNA damage repair[37]. In prolonged stress or irreversible DNA damage p53 activates programmed cell death[38]. Post-translational modifications of p53 including ubiquitination, phosphorylation, methylation and acetylation are also very important in the regulation of its protein stability and transcription target selectivity[39].

HYPOXIA-INDUCIBLE FACTOR-1α MEDIATED RESPONSE TO HYPOXIA

Hypoxia is an important pathophysiological state found mainly in solid tumors since the rapid growth of cancer tissues is associated with vascularisation deficiency, and therefore low oxygen availability which reaches levels below 5%[40]. Hypoxic conditions give rise to the expression of genes encoding proteins which promote angiogenesis, invasion and metastasis, and enhanced glycolytic metabolism[41-45]. Major contributing factors to the cellular and systemic adaptation in response to hypoxic conditions are primarily the hypoxia-inducible factors (HIFs)[45,46]. HIF-1 is a transcription factor that regulates the induction of various genes facilitating adaptation and survival of cells in low oxygen conditions such as erythropoietin[47] vascular endothelial growth factor[48] glucose transporters, and glycolytic enzymes[49,50].

CROSSTALK BETWEEN p53 AND HIF-1

The functional crosstalk between HIF-1α and p53 pathways at several levels has been extensively studied[51-53]

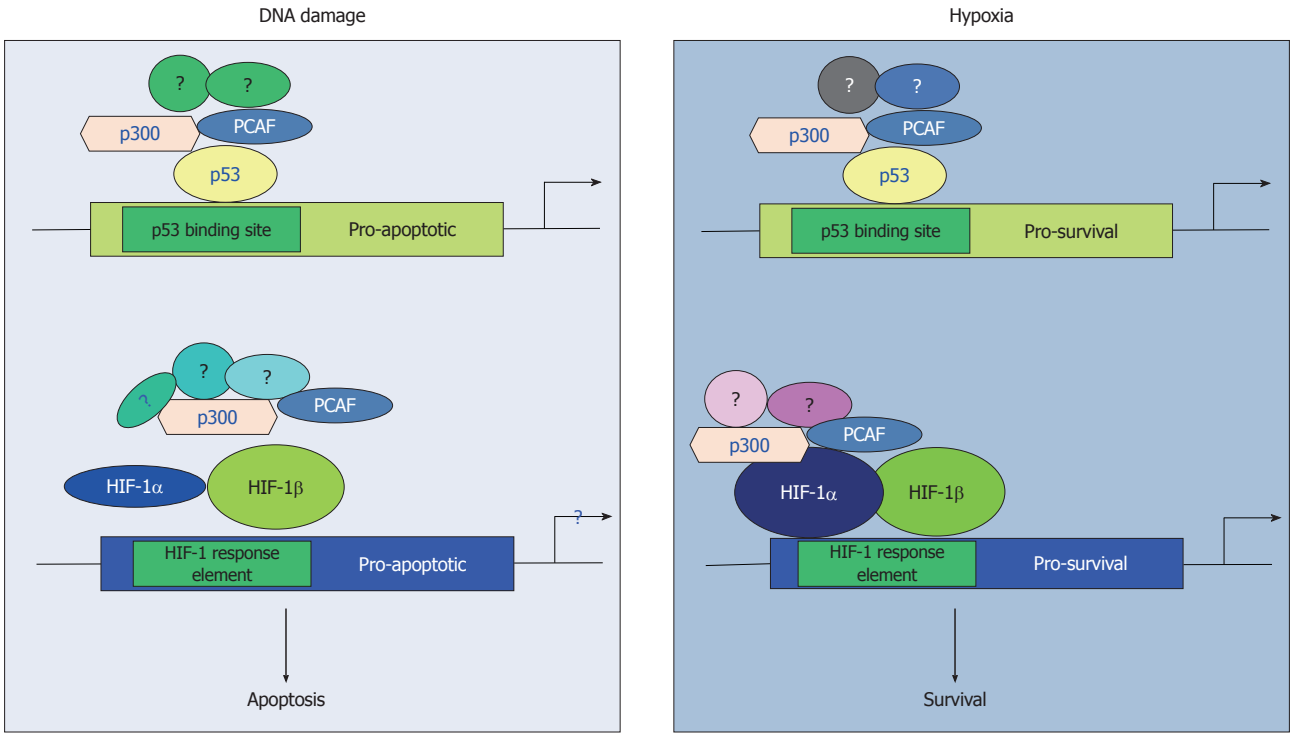

Figure 1 p300/CBP associated factor mediates p53 and hypoxia inducible factor-1α transcription target selectivity in a manner dependent on the type of stress. In DNA damage conditions the p300/CBP associated factor (PCAF) is recruited to the promoters of pro-apoptotic gene targets thus inducing p53 mediated cell death, whereas in conditions of low oxygen availability PCAF mediates p53 and hypoxia inducible factor 1α (HIF-1α) post-translational modifications that selectively target both transcription factors to a subset of their transcription target genes with pro-survival activity thereby inducing cell proliferation.

and indicated that under certain conditions p53 and HIF-1α co-operate in inducing apoptosis whereas they exert opposing functions in G1 cell cycle arrest[54,55]. p53 has also been shown to be stabilized in hypoxia mimicking conditions in a HIF-1α dependent manner[56] although its transcriptional activity is attenuated in hypoxia since it is incapable to induce the expression of its transcription targets including pro-apoptotic members of the Bcl-2 family under these conditions[57]. Although the molecular mechanisms involved have not yet been clearly elucidated, it appears that both p53 and HIF-1α regulate cellular energy production pathways by modulating the gene expression of glucose transporters and enzymes involved in glycolysis and oxidative phosphorylation. In particular, the glucose transporter GLUT-1 is downregulated by p53 and upregulated by HIF-1α[58-60] and similarly hexokinase 2 is upregulated by mutated p53[61,62], and induced by HIF-1α[63]. These contradicting observations are due at least in part to the differential interactions of p53 and HIF-1α with their common co-activators or co-repressors[64-67].

ROLE OF THE COFACTORS SHARED BETWEEN p53 AND HIF-1α

The p300/CBP transcriptional coactivator assembles a number of diverse cofactor proteins into multicomponent complexes[68] and is itself involved in the regulation of the transcriptional activity of both HIF-1 and p53[69,70]. The steroid receptor coactivator 1 is a component of the p300/CBP complex[71] and another common cofactor shared between HIF-1[72] and p53[73]. In addition, the nuclear receptor coactivator TIF2 interacts with HIF-1 to potentiate its transcriptional activity[74], although it inhibits p53 transcription potential when fused with the acetyltransferase MOZ associated with acute myeloid leukaemia[75].

Our studies investigating the crosstalk between p53 and HIF-1α[64,65,76] have elucidated an additional molecular mechanism explaining the inability of p53 to activate its pro-apoptotic targets in hypoxia and implicate p300/CBP associated factor (PCAF) in the fine-tuning of the transcriptional activity and protein stability of both p53 and HIF-1α in DNA damage and hypoxic conditions. PCAF is a common cofactor for both p53 and HIF-1α[64,67] and is recruited to the transcriptional complex of the one or the other transcription factor in a tissue and type of stress dependent manner (Figure 1) determining the pathway of energy production (Figure 2) and the cellular fate under diverse stress conditions[64,65] providing an additional evidence for the importance of the co-activator function in determining the cell fate under hypoxia by modulating both p53 and HIF-1α responses.

IMPLICATIONS ON THE EFFICACY OF ANTI-CANCER THERAPIES

The therapeutic activity of many anti-cancer agents depends on their ability to specifically and selectively induce apoptotic pathways in cancer cells. Radioactivity and

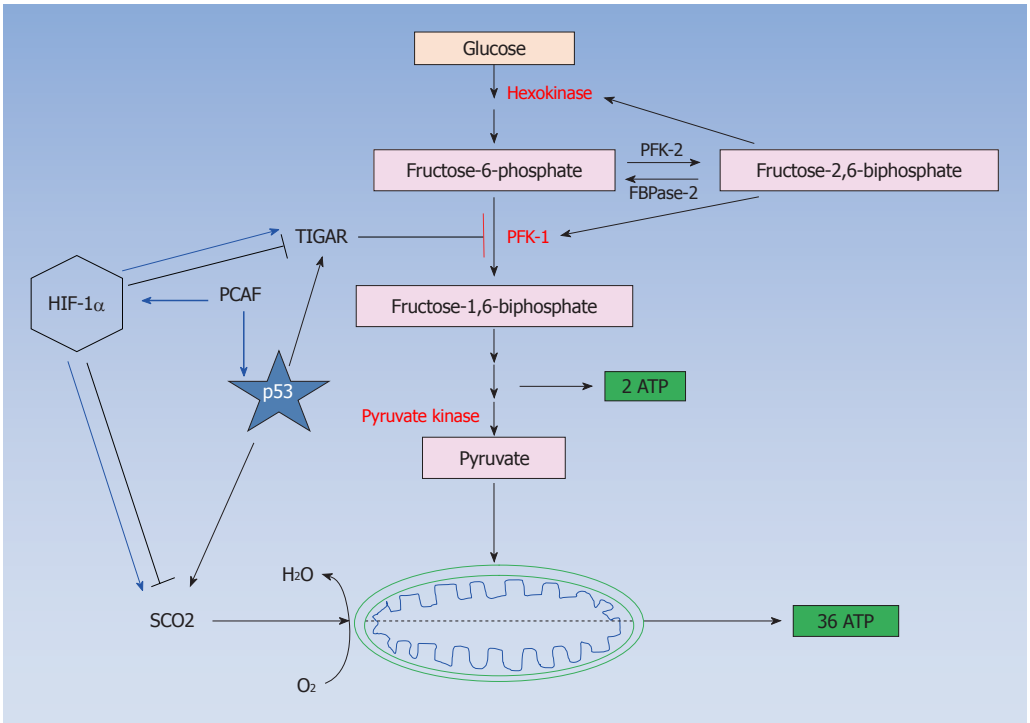

Figure 2 p300/CBP associated factor determines cellular energy metabolism pathways under diverse types of stress. Differential post-translational modifications of p53 and hypoxia inducible factor 1α (HIF-1α) mediated by p300/CBP associated factor (PCAF), distinctly modulate cellular energy metabolism pathways by activating or repressing the expression of their target genes Tp53 induced glycolysis and apoptosis regulator (TIGAR) and synthesis of cytochrome c oxidase 2 (SCO2). PFK: Phosphofructokinase.

chemotherapeutic drugs mediate their pro-apoptotic effects through the induction of pro-apoptotic pathways regulated by transcription factors such as the tumor suppressor protein p53. The tumor suppressor p53 signalling pathway is a highly regulated process involving a cascade of events, mediated among other pathways by various transcriptional co-factors such as the p300, and other p300 associated factors such as the tetratricopeptide domain 5 and PCAF[77,78]. These co-factors regulate the p53 transcriptional activity and protein stability by acetylating different lysine residues in its C-terminal region and in this way they contribute to the p53 mediated cellular adaptation to diverse types of stress[79,80]. In addition, it has become clear from the studies investigating the molecular mechanisms of the regulation of HIF-1α protein stability and transcriptional activity that p300 is required for the trans-activation of HIF-1α and that there is competition for limiting amounts of this cofactor in hypoxia between HIF-1α and p53[69,81-83].

Poor response or resistance to anti-cancer chemotherapeutics by hypoxic tumors has been evidenced and it is attributed to the lack of vascular system that would allow efficient drug delivery to these tumors[84]. Likewise, radiation therapy requires oxygen radicals for efficient production of DNA strand breaks, and thus hypoxic tumor microenvironment contributes to radioresistance[44,84]. Furthermore, repression of the p53 transcriptional activity and inability of this transcription factor to induce its pro-apoptotic targets in hypoxic conditions is an additional mechanism conferring drug resistance to hypoxic tumors[85].

CONCLUSION AND FUTURE DIRECTIONS

Our observations have provided evidence supporting the view that distinct subpopulations of transcription co-activator complexes as well as differential posttranslational modifications determine the transcriptional target selectivity of both p53 and HIF-1α under diverse micro-environmental conditions[64,65,76] resulting in the expression of distinct subsets of genes, which carry out different functions, in a type of stress dependent manner. This distinction in the transcriptional cofactors' function can be interpreted in a variety of ways. Firstly, transcription cofactors might facilitate the recruitment of different transcription factors to distinct regions of the genome[86] thus allowing different transcription factors to carry out specialised functions determining the cellular fate (survival or apoptosis) (Figure 1). Secondly, differences in the structure of the promoter between the different targets of various transcription factors could be responsible for preferential binding of particular subsets of these targets by alternatively posttranslationally modified transcription factors. For example, PCAF dependent acetylation of either p53 or HIF-1α is a mechanism by which these transcription factors distinguish between their pro-survival or pro-apoptotic target promoters[64] or glycolytic or oxidative phosphorylation inducers (Figure 2)[65,87-89].

To substantiate this hypothesis we are currently using genome wide ChIP-seq approaches to uncover the spe-

cific transcriptional circuitries that determine the specificity and target selectivity of several transcription factors including p53, glucocorticoid receptor, estrogen receptor, HIF-1α and NF-κB which play very important roles in carcinogenesis. The ultimate aim of this investigation is to acquire essential knowledge that will guide the identification of new transcriptional targets in the DNA damage response and low oxygen availability networks and thus facilitate the development of selective therapeutics for potential personalized cancer therapeutics.

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