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The novel partnership of L-GILZ and p53: a new affair in cancer?

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Abbreviations: DEX, dexamethasone; GC, glucocorticoid; L-Gilz, long glucocorticoid-induced leucine zipper; Mdm2, mouse double minute 2 homolog; NF-κB, nuclear factor-κB; Puma, p53 upregulated modulator of apoptosis.

A recent report from our laboratory reveals how long glucocorticoid-induced leucine zipper (L-Gilz) protein binds to p53 and mouse double minute 2 homolog (Mdm2), thus dissociating the p53/Mdm2 complex and activating p53 with subsequent activation of downstream genes p21 and p53 upregulated modulator of apoptosis (Puma). p53 activation appears to be the mechanism by which both basal and glucocorticoid (GC)-induced L-Gilz inhibits proliferation and induces antioncogenic activity in human cancer.

The transcription factor tumor protein p53 (TP53, best known as p53) is the main tumor suppressor regulating the expression of genes crucial for maintaining cellular homeostasis and ensuring genomic stability.[1] Upon activation by diverse oncogenic stress stimuli, p53 triggers cellular responses through regulation of its transcriptional targets to help repair or eliminate cells with damaged DNA, i.e., potential cancers.[2] Indeed, most cancer cells carry mutation(s) of TP53, thereby growing and metastasizing by escaping p53 regulation, whereas normal cells maintain low levels of p53.[3] Therefore, it is not surprising that p53 expression is tightly regulated through feedback mechanisms involving partner molecules that continuously monitor p53 expression/degradation to allow the appropriate biological responses.[4] The most prominent negative regulator of p53 is mouse double minute 2 homolog (Mdm2), which binds p53 and interferes with p53-mediated transcription, promotes p53 nuclear export, and induces ubiquitin-mediated proteasomal degradation.[5] p53 was discovered based on its antitumorigenic properties, although today it is known to exhibit a much broader spectrum of cellular functions. Since its discovery, enormous resources have been invested in basic research on the physiological and pharmacological regulation of p53, which has resulted in significant advances in cancer research (for a review see refs[6]).

Our recent paper in Cell Death and Differentiation reveals new details of the regulation of p53 activation.[7] Long glucocorticoid (GC)-induced leucine zipper (L-Gilz), a newly identified isoform of the better-characterized GILZ,[8] forms dimers with Mdm2 and p53 (although it has greater affinity for the former) and inhibits the p53/Mdm2 interaction. As a consequence of these events p53 is stabilized and activated, and Mdm2 expression is reduced. The ubiquitination/proteasome machinery appears to be involved in L-Gilz–induced activation of p53, as L-Gilz decreases ubiquitination of p53 and increases that of Mdm2 (**Fig. 1**). As expected, L-Gilz activation of p53 triggers the antiproliferative and apoptotic pathways of p53, which involve increased expression of p21 and p53 upregulated modulator of apoptosis (Puma) with consequent inhibition of cell proliferation *in vitro* and tumor growth *in vivo*. Accordingly, silencing of L-GILZ reverses the antiproliferative activity of dexamethasone (DEX).[7] Hence, this new player, L-Gilz, fits into the intricate network of signals activating p53 and pathways activated by p53 to further control cell fate. The mechanism of L-Gilz action has not yet been fully elucidated, but it resembles that of other p53 and/or Mdm2 molecular partners that regulate p53 activation by dissociating Mdm2/p53 complexes and/or by acting on the ubiquitination machinery. However, unlike other binding partners, L-GILZ is upregulated by DEX in breast cancer cells, and this offers one more intriguing avenue to explore. We will now review what we know as the basis for what we still need to discover. First, what is the molecular mechanism of L-Gilz–induced p53 activation? L-Gilz/p53 binding requires nuclear export of p53 and occurs in the cytoplasm, where L-Gilz/Mdm2 binding and L-Gilz-induced dissociation of the p53/Mdm2 complex also occur (**Fig. 1**). Despite these interesting findings, we do not yet know why L-Gilz binds preferentially to Mdm2, but also forms cytoplasmic dimers with p53. We also do

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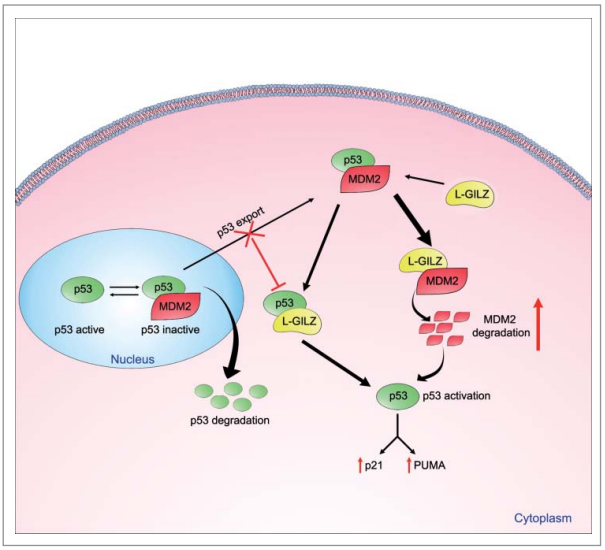

Figure 1. Mechanisms of p53 activation by L-GILZ. Long glucocorticoid-induced leucine zipper (L-Gilz) interacts directly with p53 and mouse double minute 2 homolog (Mdm2) in the cytosol, dissociating the p53/Mdm2 complex. The affinity of L-Gilz is greater for Mdm2 (large arrow) than for p53 (small arrow). L-Gilz/p53 dimer formation is prevented by inhibition of nuclear export. As a result of L-Gilz binding to p53 and Mdm2, ubiquitination of p53 is decreased and that of Mdm2 is increased, and p53 is activated with consequent activation of p21 and p53 upregulated modulator of apoptosis (Puma).

not know whether the binding of L-Gilz to p53 and/or Mdm2 is required for altered ubiquitination of p53 and Mdm2. We are aware that there could be mechanisms other than ubiquitination underlying L-Gilz–induced p53 activation. Other unexplored avenues are possible differences in binding of L-Gilz to p53 and/or Mdm2 under basal conditions and in the presence of stress stimuli that normally activate p53. If such differences exist, the diverse interactions of L-Gilz with p53/Mdm2 may assume functional significance, for example to maintain low expression levels or activate p53, depending on L-Gilz, p53, and Mdm2 expression levels. Understanding the molecular mechanism underlying p53 activation by L-Gilz is essential for planning pharmacological manipulation of L-Gilz when p53 activation is required.

Second, what is the role of L-GILZ in human cancers? By activating p53, L-Gilz suppresses the growth of xenografts in mice; therefore, a correlation between decreased expression/function of L-GILZ and hypofunction of p53 in human tumors is plausible. Clearly, tumors that express wild-type p53 and whose antitumorigenic function has been switched off, for example by MDM2 overexpression, may provide more attractive targets than tumors expressing mutated p53 for potential therapeutic strategies to enhance L-GILZ expression and restore p53 activity. In addition, DEX upregulated L-GILZ expression in a breast cancer cell line, and silencing of L-GILZ reversed DEX antiproliferative activity as well as expression of p53, p21, and PUMA. Thus, L-GILZ may represent a means of GC/p53 crosstalk[9] and in this way contribute to GC therapeutic efficacy. Many approaches should be taken to verify this intriguing hypothesis. In fact, recent demonstrations of the role of p53 in protection against sources of inflammatory stress such as reactive oxygen and nitrogen species, infectious agents, cytokines, and signaling pathways, for example the nuclear factor-κB (NF-κB) pathway,[10] suggest that, through p53 activation, L-GILZ may impact not only GC-responsive cancers, but also canonical GC–anti-inflammatory activity.

The chronic inflammatory response and stress pathways promoting carcinogenesis often recognize the same multitude of overlapping signals that are activated when tissue homeostasis is impaired by damaging stimuli and involve p53 responses to a large extent.[1-4] With the finding that L-GILZ activates p53, an intriguing new field of investigation has opened up that may link GCs, p53, inflammation, and cancer. These topics are already being extensively investigated, but this new common thread of L-GILZ could aid in the exploration of currently unknown underlying molecular mechanisms. The study of L-GILZ /p53 crosstalk has only just begun.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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