taneous chemical processes, not involving enzyme reactions. Although most investigators have focused their attention on the ability of the cytochromes P450 to bioactivate thalidomide, Wells and colleagues[7] demonstrated that thalidomide could be bioactivated by prostaglandin H synthase or lipoxygenase to a reactive intermediate; this free radical intermediate caused the oxidation of DNA (increased amounts of 8-hydroxy-2'-deoxyguanosine, an oxidized adduct of DNA) and glutathione (increased oxidation of GSH to GSSG). In their report on page 582, Wells and colleagues investigate the species specificity of thalidomide teratogenicity by treating a susceptible species, rabbit, and an insensitive species, mouse, with thalidomide and comparing DNA oxidation and teratogenicity in the absence and presence of a free-radical scavenger[5]. They report that in rabbits, but not mice, embryonic DNA oxidation and thalidomide teratogenicity are abolished by pre-treatment with alpha-phenyl-N-t-butylnitrone (PBN), a free radical spin trapping agent. These data provide the first direct evidence that free radical-mediated oxidative damage to embryonic macromolecules is required to mediate the teratogenic effects of thalidomide.

It is unlikely that the resistance of mice to thalidomide teratogenicity is due to a decreased ability to catalyze metabolic activation. Rabbit and mouse embryos may differ in their abilities to detoxify free radicals, or to repair oxidative DNA damage. At least in rodents, enzymes involved in defense against oxidative stress, such as superoxide dismutase, GSH peroxidase, and the GSH-transferases, are present in relatively low concentrations in the embryo[8]. The depletion of GSH, by inhibition of its synthesis with buthionine sulfoximine, alters the teratogenicity of some drugs but not others, whereas exposure to high concentrations of buthionine sulfoximine (≥1.0 mM) during organogenesis causes growth retardation and increased abnormalities[9].

Thalidomide is not toxic to the mother, yet DNA oxidation in maternal organs can be as much as tenfold higher than embryonic DNA oxidation. This observation suggests that it is not DNA oxidation itself that is responsible for thalidomide teratogenicity, but rather the consequences of oxidative stress during organogenesis. Reactive oxygen species may participate in normal and abnormal development. The addition of antioxidants to murine limbs in culture during organogenesis prevents digit individualization as well as interdigital cell death; many regions of the midgestation mouse embryo that undergo cell death have high levels of reactive oxygen species[10].

In addition to damaging DNA, oxidative stress affects gene expression, specifically altering the activities of transcription factors with redox-regulated cysteine residues in their DNA binding domains; these include activator protein-1 (AP-1), the tumor-suppressor protein, p53, and nuclear factor regulating expression of kappa light-chain immunoglobulin (NF-κB). In fact, thalidomide acts to reduce inflammation by selectively downregulating cytokine gene expression, notably TNF-α, by activated monocytes[11]. That the redox status of oxidant-sensitive transcription factors is essential in determining the response of the limb to insult with thalidomide is an attractive hypothesis. If it is true, it will be important to elucidate the roles of these transcription factors in mediating the desired immunomodulatory properties of thalidomide as well as the unwanted teratogenic effects. Further investigation of these mechanisms, and of the possibility that protection against oxidative stress with a free-radical scavenger may separate the therapeutic effects of thalidomide from its teratogenicity, is an urgent priority.

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P53 escape from P19ARF-trapped MDM2

Maintenance of steady-state levels of the tumor suppressor p53 is very dependent on its interaction with Mdm2. This multifunctional protein antagonizes p53 activity by inhibition of p53-dependent transcription, as well as by enforcement of p53 nuclear transport and cytoplasmic degradation. But while Mdm2 antagonizes p53, what controls Mdm2? Jason D. Weber and colleagues from the St. Jude's Children's Research Hospital and SUNY now report in the May issue of *Nature Cell Biology* that the nucleolar protein Arf, a product of the Ink4 locus, sequesters Mdm2 in the nucleoli after activation of the oncoprotein Myc. Similarly, while Arf and Mdm2 linger in the nucleoli, p53 takes action in the nuclei of senescent mouse fibroblasts. Thus, Arf takes the stage as an essential element in the control of p53 activation, raising questions about the *in vivo* tumor-promoting effect of tumor-associated Arf mutants with defective intracellular co-localization.

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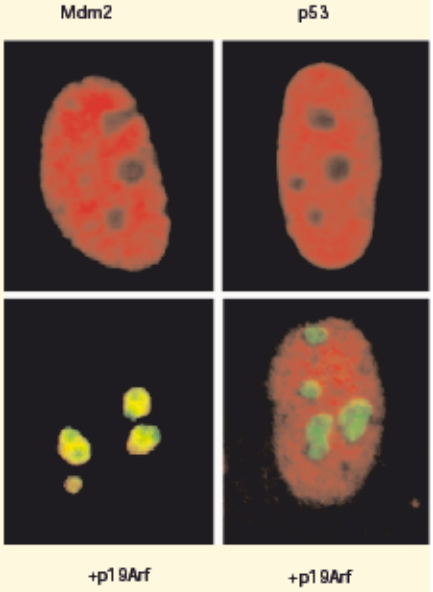

Fig. A newly discovered protein–protein interaction leads to p53 activation: after nucleolar trapping (yellow) of Mdm2 (red) by Arf (green), p53 is free to act.