contact with B cells and expression of both the signaling adaptor SAP and the transcription factor Bcl-6. This is consistent with other recent studies indicating that T_{reg} cells acquire characteristics of specific $CD4^+$ effector T cell subsets (such as T helper types 1, 2 or 17) to colocalize with them and regulate their responses[12].

However, although the two studies identify and characterize similar populations of T_{FR} cells, they differ in their conclusions regarding how these cells influence the germinal center reaction. Linterman *et al.*[10] used a mixed bone marrow chimera strategy to selectively disrupt the development of T_{FR} cells and found that this resulted in enhanced accumulation of T_{FH} and germinal center B cells and impaired affinity maturation. Although at first glance this result seems somewhat contradictory, increasing T_{FH} cell numbers would probably decrease the stringency of T_{FH} cell–mediated selection of high-affinity B cells, and, indeed, the authors found that survival of non–antigen-specific B cells increased in the absence of T_{FR} cells[10]. By contrast, in the study by Chung *et al.*[11], mice lacking T_{FR} cells had only a modest increase in T_{FH} cells but generated more antibody-secreting cells, and, unlike the mice in the Linterman *et al.*[10] study, showed increased production of high affinity antibodies.

Although the reasons for the divergent functional results of these studies are not readily apparent, they probably relate to the different experimental systems used. To prevent T_{FR} cell development, Linterman *et al.*[10] used T_{reg} cells from SAP knockout (*Sh2d1a*$^{-/-}$) mice, whereas the T_{reg} cells used by Chung *et al.*[11] were from *Cxcr5*$^{-/-}$ or *Bcl6*$^{-/-}$ mice.

Although loss of any of these molecules blocks T_{FR} cell function, it's likely that there are subtle differences in the phenotypes of the different knockout cells. For instance, SAP can also modulate T cell–T cell interactions[13], and this may account for the larger expansion of T_{FH} cells in mice carrying SAP-knockout T_{reg} cells. Additionally, Chung *et al.*[11] used adoptive transfer into T cell–deficient mice to study T_{FR} deficiency, and lymphopenia-induced expansion may therefore have masked the function of T_{FR} cells in regulating the abundance of T_{FH} cells.

Despite these differences, the identification of a specialized population of T_{reg} cells in germinal centers raises many interesting questions regarding their mechanisms of action and their roles in preventing autoantibody production and enforcing self tolerance after somatic hypermutation. Of particular interest will be determining whether these T_{FR} cells are defective in people with autoantibody-mediated autoimmunity and whether T_{FR} cells modulate germinal center responses solely through inhibition of T_{FH} cells or also through direct interaction with germinal center B cells (**Fig. 1**). In either case, these two studies clearly show that T_{reg} cells help shape the antibody response and provide new insights into how order is maintained in one of the immune system's roughest neighborhoods.

COMPETING FINANCIAL INTERESTS
The authors declare no competing financial interests.

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A ribosomal tactic to halt cancer

Hua Lu

The ribosomal protein RPL11 can block cell growth by boosting function of the tumor suppressor p53 in response to ribosomal stress, but the connection of this role with cancer has been obscure. New findings show that the nucleolar protein PICT1 can sequester RPL11, impairing p53 activation and favoring tumor growth (pages 944–951).

Studies over the past decades have shown a number of ribosome-independent functions for individual ribosomal proteins[1]. One of these functions is to regulate the stability and activity of p53, the most important tumor suppressor in mammals, in response to nucleolar or ribosomal stress, which usually happens when ribosomal biogenesis is disrupted[2].

Three large 60S ribosome subunits, including RPL11 and RPL5, were initially reported to activate p53 by directly associating with its physiological repressor MDM2 and inhibiting its E3 ubiquitin ligase activity toward p53 upon ribosomal stress[3–6]. Rapidly accumulating evidence has revealed more ribosomal proteins that possess similar p53-activating activity and has bolstered a previously underappreciated ribosomal stress–MDM2-p53 pathway[2].

In this issue of *Nature Medicine*, Sasaki *et al.*[7] show that PITC1 (protein-interacting with the C terminus 1), a protein whose expression is altered in numerous cancers, inhibits p53 responses to stress via MDM2 by sequestering RPL11 in the nucleolus, promoting tumor growth. *PITC1*-deficient mice showed p53 accumulation and slow tumor growth, and reduced PITC1 expression was associated with better prognosis in individuals with cancer. Disrupting the interaction of PITC1 with RPL11 may open new avenues for preventing cancer development.

Previous genetic studies emphasized the biological role of the ribosomal protein–MDM2-p53 pathway. Abnormally activated p53 in response to ribosomal stress caused by haploinsufficiency (with only one functional copy of a gene) of the *Rps14* gene was shown to cause bone marrow defects in a human 5q syndrome–like mouse model[8]. Another study showed that mice harboring a MDM2 mutant protein that is unable to bind RPL11 and RPL5 fail to activate p53 in response to ribosomal stress. When these MDM2 mutant mice are crossed with mice that constitutively express the oncogene *Myc* in B cells under the control of the Eμ immunoglobulin heavy chain enhancer (Eμ-c-Myc mice) they develop lymphomas more frequently and earlier than Eμ-c-Myc transgenic mice[9]. However, the role of individual MDM2-interacting ribosomal proteins in cancer remained largely unclear.

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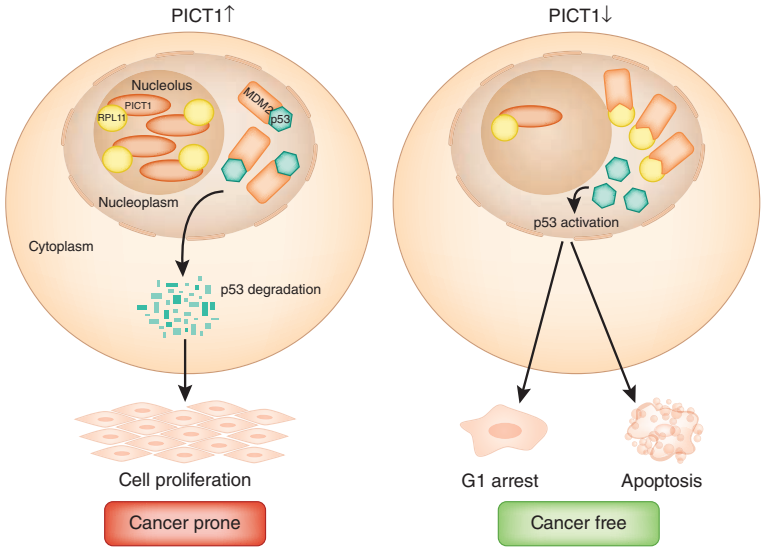

Figure 1 The imbalance of nucleolar PICT1 abundance modifies the oncogenic potential by controlling the RPL11-MDM2-p53 pathway. When PICT1 levels are high or abnormally high, PICT1 binds RPL11 in the nucleolus, preventing it from binding nucleoplasmic MDM2, a protein that associates with p53 and mediates its ubiquitination and degradation (left). Consequently, increased PICT1 leads to p53 inactivation, favoring tumor growth. But when PICT1 abundance is decreased, RPL11 flees from PICT1 binding and diffuses to the nucleoplasm, where it interacts with MDM2, inhibiting MDM2-mediated p53 ubiquitination (right). The resulting induction of p53 leads to p53-dependent G1 arrest and apoptosis, hindering the growth of cancerous cells.

The above findings by Sasaki *et al.*[7] stem from another surprising result. They found that the nucleolar protein PICT1 actually possesses an oncogenic potential by inactivating p53 (ref. 7), instead of acting as a tumor suppressor as previously proposed[10]. The *PICT1* gene resides in human chromosome 19q13.32, which is often altered in human tumors[11]. Furthermore, overexpression of foreign PICT1 in human glioma cells led to stabilization of another well-reputed tumor suppressor, PTEN, and induced apoptosis[10], suggesting a putative tumor suppressor function. But other studies[12] have been inconsistent with this hypothesis, as lower levels of PICT1 were paradoxically correlated with a better prognosis for oligodendrogliomas[12].

To clarify this controversy, the authors deleted the *Pict1* gene in mice and found that PICT1 was essential for mouse embryogenesis, as *Pict1*-null mice died during embryogenesis at day 3.5 (E3.5)[7]. Additionally, PICT1 levels were inversely proportional to those of p53 in mouse *Pict1*$^{-/-}$ embryonic stem (ES) cells carrying an inducible foreign *PICT1* gene, suggesting that PICT1 might downregulate p53. Surprisingly, chemical carcinogen–induced skin tumors grew more slowly in *Pict1*$^{+/-}$ than in wild-type mice. Humans with colon or esophageal cancers that harbor wild-type p53 and low expression of PICT1 showed better five-year survival compared to those with high levels of PICT[7]. These lines of evidence indicate that PICT1 is a potential tumor promoter rather than a tumor suppressor, at least in wild-type p53–containing cancers.

PICT1's tumor-promoting activity seems to act through p53 inactivation[7]. After ruling out some potential tumor suppressor contenders acting in the p53 pathway, such as PTEN or ARF[7], the authors narrowed the suspects down to the MDM2-binding ribosomal proteins, given that PICT1 and ribosomal proteins are in the nucleus. Although PICT1 associates with ribosomal proteins within the nucleolus, knocking down only RPL11, but not RPL5, RPL23 or RPS7, impaired the induction of p53 levels after PITC1 loss[7]. Consistently, reducing PICT1 expression resulted in diffusion of only RPL11 from the nucleolus to the nucleoplasm. The nucleoplasmic RPL11 then bound nucleoplasmic MDM2, inhibiting its E3 ubiquitin ligase activity toward p53 and leading to p53 stabilization and activation (**Fig. 1**). This finding suggests that individual MDM2-binding ribosomal proteins could act independently of each other, perhaps in a signal-dependent fashion. Yet it remains to be determined whether RPL11 might work with other unidentified MDM2-binding ribosomal proteins in response to low PICT1 levels. This new molecular mechanism explains why skin tumors grew much more slowly in *Pict1*$^{+/-}$ mice and why humans with colon or esophageal cancers that contain functional p53 and lower levels of PICT1 showed improved survival.

The study by Suzuki *et al.*[7] suggests that RPL11 may be crucial for preventing cancer development by activating p53 under ribosomal stress caused by PICT1 reduction or other agents[7], but it also poses some questions. How can the decrease of PICT1 levels release specifically RPL11 into the nucleoplasm, even though PICT1 binds all MDM2-interacting ribosomal proteins? Does RPL11 act alone under such circumstances? Another open question is why MDM2 levels were not induced when p53 was significantly elevated, given that MDM2 is also its transcriptional target.

The modulation of the p53-MDM2 pathway by PICT1 (ref. 7) resembles the regulation of this pathway by another nucleolar protein, nucleostemin[13]. Its loss activates p53 by inducing interactions between RPL11, RPL5 and MDM2 but nucleostemin can also bind MDM2 directly, thus inactivating it. It may be possible that decreasing PICT1 levels might turn off other yet unknown mechanisms required for MDM2 expression at post-transcriptional levels. This could then explain why knockdown of PICT1 fails to induce MDM2 expression, regardless of p53 activation. Moreover, it remains to be shown whether PICT1 has any p53-independent role in ribosomal biogenesis, given that deletion of the *Trp53* gene could not fully rescue the embryonic death of PICT1-null mice[7].

Describing the PICT1-RPL11 interaction might offer valuable information for the future discovery of anticancer drugs. It will be necessary to further investigate whether RPL11-MDM2 complexes and p53 concentrations in the nucleoplasm are induced in *Pict1*$^{+/-}$ mouse skin tumor tissues or human colon or esophageal cancers with functional p53 and low expression of PICT1. Nonetheless, this enticing study by Sasaki *et al.*[7] places ribosomal proteins, particularly RPL11, firmly in the hub of cancer research as potential tumor suppressors. The field is expecting more mechanistic and biological insights into their role in regulating the p53-MDM2 pathway and in the development of cancer or other bone marrow genetic disorders in the foreseeable future.

COMPETING FINANCIAL INTERESTS
The author declares no competing financial interests.

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