tinctions and population declines in Hawaii, for example, have been caused by the introduction of exotic species. Throughout the United States, impoundments, river dredging, and other riverine development projects combined with the introduction of exotic species like the sea lamprey (*Petromyzon marinus*), the grass carp (*Ctenopharyngodon idella*), the Asian clam (*Corbicula fluminea*), and the zebra mussel (*Dreissena polymorpha*) may be responsible for the endangerment of hundreds of fish, mollusks, and other aquatic species.

Although many species continue to decline in number and some are threatened with extinction, the news about endangered species is not all bad. Some species have recovered and have been removed from the endangered species list or "downgraded" from endangered to threatened status, and others are well on their way to recovery. Continued progress toward recovery will require the application of good science to natural resource policy and management decisions.

Sound scientific information about the status and trends of biological resources and reliable information about the causes of species endangerment must be the foundation of our efforts to conserve biological diversity. The recovery of the bald eagle (*Haliaeetus leucocephalus*), leading to its recent downgrading from endangered to threatened status, would not have been possible without scientific documentation of the effects of dichlorodiphenyltrichloroethane (DDT) on its reproduction and the subsequent banning of that pesticide nationwide. In a growing number of cases, ranging from the burrowing owl (*Athene cunicularia*) in California to pitcher plants (*Sarracenia* spp.) in Alabama, better scientific information about the habitat requirements of species has led to cooperative management plans involving state, federal, and private partners that provide hope for the recovery of endangered species with relatively little negative impact on economic activities.

In addition to knowing more about the specific factors responsible for the decline of individual species, we need to expand our general understanding of what kinds of species are prone to extinction and incorporate this information into proactive, multiple species protection plans. Dobson *et al.* discuss the vulnerability of endemic species, but are all geographically restricted species necessarily at greater risk? For example, biogeographers often distinguish between paleoendemics, which are relict species left by the extinction of their close relatives, and neoendemics, which are newly evolved taxa often restricted to a small area (*3*). Are neoendemics rare only by virtue of their recent emergence and, therefore, less likely to go extinct than paleoendemics? Or does the very longevity of paleoendemics suggest that they are less likely to go extinct in the future because of their success in the past?

We must also improve our understanding of what human activities are most harmful to species and under what circumstances organisms can tolerate or even benefit from human activities. Species that do well in early successional habitats—such as the endangered Kirtland's warbler (*Dendroica kirtlandii*) in the jack-pine forests of Michigan and Bachman's sparrow (*Aimophila aestivalis*) in southeastern pine forests—sometimes benefit from both controlled fire and limited clear-cutting when these activities create appropriate forest openings. Many early successional species are adapted to living in a mosaic of shifting habitat patches. Can we use our growing knowledge of metapopulation dynamics to devise forest management plans that allow for both the viability of native plant and animal populations and profitable forest harvest (*4*)?

And finally, how can we use our general knowledge of the distribution of rare and threatened species to maximize the protection of species at the least cost and inconvenience to the public? As Dobson *et al.* point out, many threatened and endangered species are aggregated in relatively small areas, and "a large proportion of endangered species can be protected on a small proportion of land." If we improve our knowledge of the distribution and co-occurrence of species, then we can provide a sounder scientific basis for ecosystem-based habitat conservation plans (HCPs), cooperative agreements that protect many species under a single plan. When properly designed, on the basis of a thorough understanding of species distribution and habitat requirements, and implemented with the cooperation of local authorities and landowners, such plans provide protection for currently endangered species. Also, by providing habitat protection for many other species, HCPs provide a proactive mechanism for preventing the future endangerment of additional species.

An enhanced version of this Perspective, with live links, can be seen in *Science* Online on the Web at http://www.sciencemag.org/

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TRANSLATION

eIF4G: A Multipurpose Ribosome Adapter?

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To be joined as partners in protein synthesis, mRNAs and ribosomes must be presented to each other in the ritual of translation initiation. Protein-mRNA interactions precede the engagement of the small ribosomal subunit (40S) with the mRNA. This rate-limiting step is followed by the joining of the large (60S) subunit at the translation initiation codon of the mRNA and the beginning of protein synthesis (*1*). Recent data from several laboratories have implicated a long-known translation initiation factor—eIF4G (formerly p220 or eIF-4γ)—as a critical link between mRNAs and 40S subunits during the initial engagement process.

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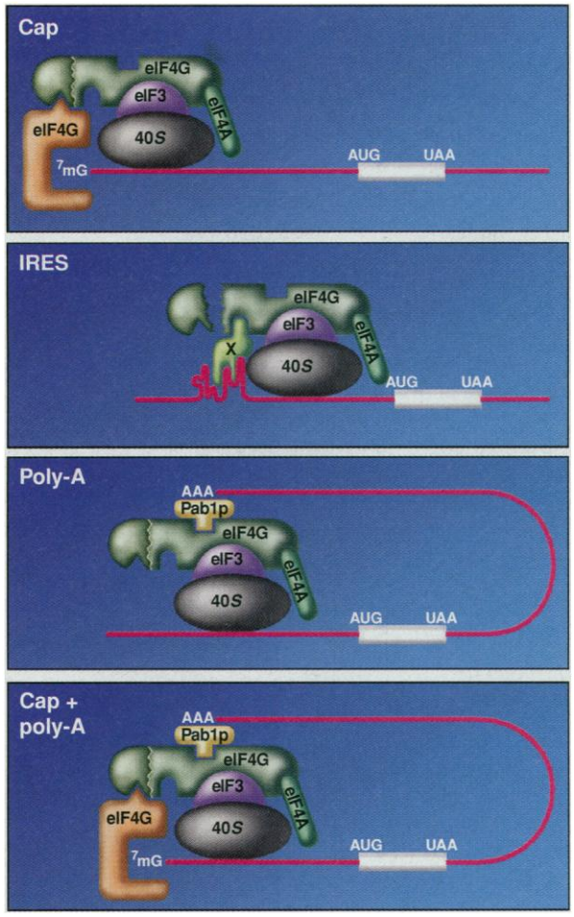
Cellular mRNAs receive a 5′ cap structure (^{7}mGpppN) and a 3′ polyadenylated [poly(A)$^+$] tail as a nuclear dowry before their export into the cytoplasm as mature mRNAs. Both these moieties activate translation initiation in concert with cytoplasmic binding proteins, the cap-binding protein eIF4E, and the poly(A)$^+$ binding protein (Pab1p in yeast). However, some picornaviral RNAs and a few cellular mRNAs have specialized sequences within their 5′ untranslated regions that directly promote ribosome binding independent of a cap structure. These are the internal ribosome entry sequences (IRES) (*2*). How can all these different modes of connecting mRNAs and 40S ribosomal subunits be used for translation initiation? The cell's answer may resemble the solution found by avid international travelers for the difficulties of using electrical appliances in foreign

countries: the use of an adapter.

Picornaviruses such as poliovirus or foot-and-mouth-disease virus encode proteases that specifically clip the NH_2-terminal third off eIF4G to inhibit the cap-dependent translation of cellular mRNAs (*3*). The viral RNAs escape this inhibition by virtue of their IRES (*2*), indicating that the integrity of eIF4G is important for cap-dependent, but not for IRES-mediated, translation initiation. The cap-binding protein, eIF4E, can directly plug into the NH_2-terminal third of eIF4G (*4*, *5*), while the central third associates with eIF3, a multimeric complex that is bound to the 40*S* subunit (*5*) (see figure). Therefore, eIF4G forms a bridge between the cap structure (via eIF4E) and the 40S subunit (involving eIF3) that is broken by the picornaviral proteases. The proteolytic clip kills two birds with one stone, because it not only uncouples the cap from eIF4G, but the liberated COOH-terminal cleavage product actively supports IRES-mediated translation (*6*). Similar to the cap in conjunction with eIF4E, the IRES might also be connected with eIF4G, perhaps by means of IRES-binding proteins (X in the figure). Recent data suggest that, at least in some instances, X could be part of eIF4G itself (*7*). The central domain of eIF4G binds strongly and specifically to a structural element within the encephalomyocarditis virus IRES upstream of the initiation codon. Thus, eIF4G can also build a molecular bridge between this IRES and the ribosome.



More than gadgetry. Several ways of engaging the small ribosomal subunit (40*S*) with mRNAs (red line) are mediated by the adapter protein eIF4G. For clarity, only translation initiation factors mentioned in the text are shown.

Once bound, the 40S subunit scans the mRNA in a 3′ direction to identify the initiation codon (*1*). The directionality of the scanning process suggests that 40S subunits should contact the mRNAs 5′ of the initiation codon, a requirement that the locations of both the cap structure and IRES help to meet.

Studies in cell-free translation extracts from yeast indicated that the poly(A)$^+$ tail stimulates 40S subunit recruitment to the mRNA (*8*). This recruitment is mediated by Pab1p. Pab1p acts synergistically with the cap structure, but can function independently as well. Once more, eIF4G is the responsible molecular adapter (*9*): Pab1p can bind to a region of <120 amino acids that is conserved between the two yeast homologs of eIF4G (see figure). Mutations that disrupt Pab1p binding affect poly(A)$^+$ tail–stimulated translation in vitro, with little effect on cap-mediated protein synthesis. Interestingly, Pab1p and eIF4G interact only in the presence of RNA, perhaps to selectively favor Pab1p that is bound to the poly(A)$^+$ tail. eIF4G thus integrates the functions of the cap and the poly(A)$^+$ tail in translation. Somehow the 3′ end of the mRNA must bend over backwards to deliver 40S subunits 5′ of the translation initiation codon. A simultaneous interaction of eIF4G with the cap-binding protein eIF4E and the poly(A)$^+$ binding protein Pab1p could be one mechanism to accomplish this and would effectively circularize the mRNA (see figure). It will be important to determine whether the mammalian poly(A)$^+$ binding protein and eIF4G also interact to activate translation.

A role as a multipurpose adapter between mRNAs and ribosomes would make eIF4G an ideal target for translational control. The cellular protein DAP-5/p97 is a candidate for such a function (*10*, *11*). To a first approximation, DAP-5/p97 resembles the larger of the cleavage products generated by picornaviral proteases and is homologous to the COOH-terminal two-thirds of eIF4G. It binds to eIF3 and eIF4A (a translation initiation factor with RNA-dependent helicase activity that is required for both cap- and IRES-dependent translation), but lacks the domain that binds the cap-binding protein eIF4E (*10*). Whether IRESs exist that can bind DAP-5/p97 remains to be determined, but transfection experiments have suggested that DAP-5/p97 suppresses both cap-dependent and encephalomyocarditis virus IRES-mediated translation (*10*), probably by forming a translationally inactive protein complex that includes eIF3 and eIF4A but excludes eIF4E. If DAP-5/p97 could bind to (currently unrecognized) specific mRNA sequences, it may act as a positive translation factor for these mRNAs (*11*). Although DAP-5/p97 appears to be involved in modulating interferon-γ–induced programmed cell death (*11*), the physiological targets and mode of action are still enigmatic.

Within a short while, these new, primarily biochemical data have changed eIF4G from an unknown entity to a center-stage player during translation initiation. eIF4G may also unlock some of the mysteries of how regulatory elements in the 3′ untranslated regions of mRNAs and their binding proteins can control ribosome binding at the 5′ end of mRNA. Such regulatory mechanisms underlie numerous genetic switches during early embryonic development and in cell differentiation (*12*). Much work still needs to be done to rigorously test whether, when, and how eIF4G serves as a multipurpose adapter for ribosomes. Nonetheless, eIF4G function already offers a conceptual framework for a better understanding of the initiation rites between mRNAs and ribosomes.

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