

affinity may require multiple interactions that can also be attained by tandem insertions of a single sequence.

Many questions remain about the specific nature of this X chromosome rendezvous. In addition to identifying all the sequences required for pairing, we still need to know what the X chromosomes then do, how they do it, and what happens afterward, to ensure inactivation of just one of the pair. At X chromosome pairing, what process enables them to distinguish one from the other to achieve mutually exclusive choice? With so many questions left to answer, the future for this new relationship appears quite promising.

Chromosome cross-talk clearly adds a new dimension to the complex regulatory events at the initial stages of random X chromosome inactivation. Pairing is not unique to this inactivation process, as it coordinates monoallelic expression between other sites in the genome (12, 13). Chromosome courtship may be a relatively common way to orchestrate gene regulation, and it will be important to see whether this coupling occurs in the same fashion as on the X chromosomes.

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PALEONTOLOGY

Early Mammalian Evolutionary Experiments

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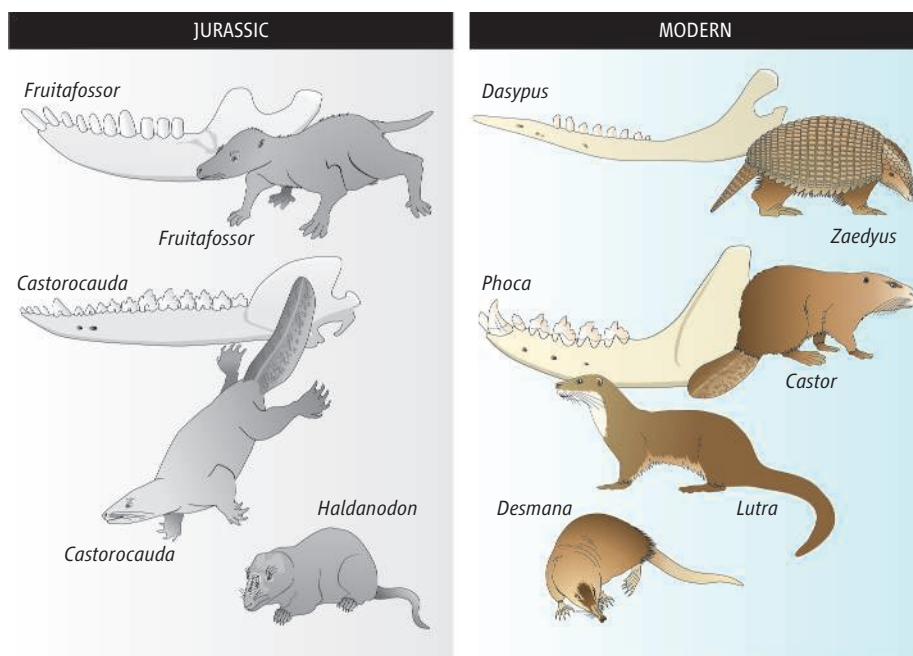
Mammals of the Mesozoic era (248 to 65 million years ago) generally are considered to be primitive, shrew-like creatures living in the shadow of the dinosaurs (1). Only after the extinction of the dinosaurs at the end of the Cretaceous era (144 to 65 million years ago) did they have a chance to explore a greater variety of ecological niches. During the adaptive radiation that began about 65 million years ago, mammals were able to invade all kinds of terrestrial environments, even the aquatic and aerial realms. Pushing back the mammalian conquest of the waters by more than 100 million years, Ji *et al.* (2) report on page 1123 of this issue a Middle Jurassic, 164-million-year-old skeleton with a beaverlike tail and seal-like teeth perfectly adapted for an aquatic life-style. This exciting fossil is a further jigsaw-puzzle piece in a series of recent discoveries, demonstrating that the diversity and early evolutionary history of mammals were much more complex than perceived less than a decade ago. It also impressively contradicts the widely held view that early stem representatives of modern crown groups (groups of organisms with living representatives) are generally primitive and unspecialized.

Until the mid-1970s, Mesozoic mammals were merely known by teeth and jaws that are informative for a systematic assignment but provide only limited insight into their paleobiology. The available fossil record drew a

picture of most Mesozoic mammals as primitive and generalized insectivorous animals with no particular adaptations (3–6). The initial discoveries of more complete specimens with skeletons resembling that of the living opossum *Monodelphis* and cheek teeth with

Before the extinction of the dinosaurs, most early mammals were thought to be small, nocturnal, and terrestrial. A new large Middle Jurassic fossil with fur and a beaverlike tail suggests that some were aquatic.

pointed cusps that are typical for insectivory supported this scenario (7, 8). The only clue that the known fossil record might be just the tip of the iceberg of Mesozoic mammalian ecomorphological diversity (see the figure) was an incomplete skeleton of the Late



Unexpected diversity. The Late Jurassic docodont *Haldanodon* shows strong skeletal adaptations to a semi-fossorial life-style (9–11) similar to those of modern *Desmana* (water mole). The basal mammal *Fruitafossor* exhibits dental and skeletal convergences to modern digging xenarthran placentals (12) such as armadillos (*Dasyurus*, *Zaedyus*). The new Middle Jurassic docodont *Castorocauda* (2) from Inner Mongolia possesses striking features for an aquatic life-style and combines skeletal, dental, and softpart characters of modern aquatic placentals such as beavers (*Castor*), river otters (*Lutra*), and seals (*Phoca*) [fossils and reconstructions redrawn from (2, 10, 12); note: figure not to scale].

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Jurassic stem mammal *Haldanodon* from Portugal with striking similarities to that of modern digging and semiaquatic desmans (water moles) (9–11). However, fossoriality apparently was not uncommon among Jurassic mammals, as is indicated by the recently discovered enigmatic *Fruitafossor* from the Morrison Formation in Colorado (12). This stem mammal of uncertain ordinal assignment not only possesses a postcranial skeleton very similar to that of Australia's semifossorial echidna, but also perfectly imitates two extreme specializations that previously were thought to be unique to the South American xenarthrans (anteaters, armadillos, and sloths). These are peglike and rootless dentine teeth lacking enamel and a lumbar vertebral column that is stabilized by additional articulation facets (xenarthry), both adaptations for digging up and feeding on colonial insects (for example, termites).

The discovery made by Ji *et al.* enriches this growing Mesozoic mammalian zoo by adding a semiaquatic swimmer and fish-eater. Most striking among the features of *Castorocauda* is the dorsoventrally flattened tail covered by small horn scales, remarkably like the modern beaver tail. Moreover, the exquisitely preserved fossil even presents other parts of the soft body such

as hair and webbing of the hindfeet. Additional support for the aquatic adaptation comes from the anterior cheek tooth dentition, which closely resembles that of fish-eating seals. Interestingly, an aquatic life-style and fish diet were previously postulated for Early Cretaceous triconodonts from Morocco based on the shape of isolated teeth (13).

These exciting discoveries may just be a glimpse of what is to come. They dramatically demonstrate how many gaps remain in our knowledge of Mesozoic mammalian diversity. New fossils are essential to fill these gaps in the understanding of the evolutionary history of life that obviously was much more complex than perceived a decade ago. The potential of fossil-rich deposits like the Jehol group in Liaoning Province in China or the Jiulongshan Formation in Inner Mongolia is only just beginning to be exploited. So far only fragmentary, but all the more tantalizing, mammalian fossils have come to light from the Jurassic and Early Cretaceous of Gondwana (southern continents) (14–16), making these days an exciting time for mammalian evolutionary biologists. We stand at the threshold of a dramatic change in the picture of mammalian evolutionary history, and many chapters (17) of it will soon need rewriting.

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CELL BIOLOGY

The Stress of Finding NEMO

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To survive, all living organisms must cope with the adverse effects of “genotoxic stress,” insults that constantly threaten the integrity and function of our genes. Such attacks come from environmental agents such as radiation, cigarette smoke, or chemical pollutants, and from the enemy within: the cell's own metabolic products that cause diverse lesions in the DNA. To deal with both the external and internal DNA-damaging agents, organisms have evolved mechanisms that slow down or block cell proliferation (so-called cell-cycle checkpoints), promote DNA repair, or eliminate damaged, hazardous cells by engaging a cellular suicide program. How cells make the choice between life and death in response to DNA damage is critical not only for the fate of each cell, but also for avoiding life-threatening diseases such as cancer (1). Despite efforts to better understand this funda-

mental cellular decision-making process, its molecular basis has until recently been obscure. Exciting work reported by Wu and colleagues on page 1141 of this issue (2) now provides mechanistic insights into the life-or-death choice in human cells exposed to the most deadly type of genetic damage, the DNA double-strand breaks.

It has been known for years that in response to double-strand breaks in DNA, cells activate the protein kinase ATM (ataxia telangiectasia mutated), a master regulator that phosphorylates (adds phosphate groups to) numerous other proteins and thereby modulates their functions in cell-cycle control, DNA repair, or cell death (1, 3). Wu *et al.* have now identified a new substrate for ATM—NEMO (NF- κ B essential modulator), a key modulator of the prosurvival transcription factor NF- κ B (nuclear factor- κ B) (4). In doing so, they have elucidated dynamic interplay between ATM and NEMO within the cell fate–decision machinery in response to DNA damage.

NF- κ B and its activator IKK (I κ B kinase) operate as an evolutionary conserved signaling

A cell's response to damaged DNA is triggered when two proteins leave the nucleus and converge upon a signaling complex in the cytoplasm. This activates a key transcription factor that then moves into the nucleus to promote cell survival.

module that orchestrates inducible gene expression in diverse cell types and biological processes, allowing cells and organisms to adapt to environmental changes. Both the IKK activator complex and NF- κ B are usually in a dormant, inactive state in the cytoplasm, poised to respond to signals from outside the cell (4). But the unorthodox ATM-NEMO-dependent mechanism (2) works “in the opposite direction,” as a nuclear-to-cytoplasmic signaling cascade to activate the IKK–NF- κ B system. Notably, although NEMO also participates in other modes of IKK activation (4), the ATM-NEMO interplay is signal specific, responding to DNA damage (2, 5) but not to other types of stress or environmental stimuli that activate the IKK–NF- κ B module through other mechanisms (cytoplasm-to-nuclear signaling cascades) (4).

Another fascinating feature of this mechanism is its very dynamic spatiotemporal regulation. Under normal, nonstressful conditions, both NEMO and NF- κ B rapidly move back and forth between the cytoplasm and the nucleus. The apparent cytoplasmic localiza-

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