for future reproduction), but such factors are impractical for accurate measurement. Instead, much of the support for signal-of-need came from substituting hunger for need. The problem here is that an offspring can be crammed with food even as it dies of malnutrition, and a robust nestling can be made hungry through brief deprivation[3]. It has been shown for dozens of species[4] that depriving youngsters of food induces escalated begging, but that may not reveal future reproductive potential. Desire is not a synonym for need.

Ironically, the opposite view — 'signal-of-quality', wherein parents generally favour stronger offspring over weaklings — had been proposed a year earlier[5], albeit buried in a long paper. Echoing the advertisement roots of sexual signals, that hypothesis requires no inversion of message and no voluntary abstention. Instead, it proposes that strong offspring are essentially bragging. The signal-of-quality concept also aligns with classic life-history theory[6], in which parents engineer offspring disparities that often facilitate brood reduction, for example by hatching some eggs 1–2 days later than the others. If food availability is unpredictable, competitive mismatches expedite the deferred correction of family size.

Caro *et al.* show that both types of offspring-signalling system may exist in nature, because ecological realities constrain what parents can hope to accomplish. In their meta-analysis, the authors assessed key environmental features and the quality and predictability of food supply for each of 143 species. Variation in environmental quality was scored on the basis of high versus low offspring survival and/or experimental manipulations (additions or subtractions of brood or food), and food predictability was inferred from parental strategies (mainly, whether broods hatched synchronously).

The researchers found that these ecological factors were strongly associated with offspring signalling and within-brood patterns of feeding bias that support two very different parental strategies. If food is relatively predictable, natural selection will favour parents that match family size to the indicated family food budget (creating fewer eggs when food is scarce). In this scenario, survival of the whole brood is the best outcome for everyone, such that a lagging chick should beg more and be fed preferentially, without sibling interference. Conversely, in volatile conditions, parents probably do best by overproducing initially and then pruning later, if necessary, on the basis of offspring size or other physical markers (which devalue the role of behavioural signals). Some species, such as American coots (*Fulica americana*; Fig. 1), actually switch their game mid-cycle, initially letting larger young enjoy their parentally conferred size advantage until brood reduction occurs, and then actively catering to the smallest that remain[7].

By validating pluralism in the explanation for offspring signals, Caro *et al.* encourage further expansion of hypotheses. One to consider is simpler than either signal-of-quality or signal-of-need because it does not require the nestling to possess any 'insider information' about its own long-term prospects, either high (indicating quality) or low (indicating need). Instead, a system could work on the basis of the only 'cryptic' information already known to exist — hunger pangs. In tandem with 'public-domain' cues such as body size, offspring signals might simply answer the mundane but useful question, "Who's ready for another worm?", and thus help parents to make fast allocation decisions. Parents already have knowledge of current food conditions, and for the darker question about who is most expendable, they could rely on visible cues such as size and vigour. This signal-of-hunger hypothesis has strong empirical support[4], and may prove a fine example of Occam's razor — the philosophy that the hypothesis that requires the fewest assumptions is often the most plausible. ■

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CANCER GENOMICS

Hard-to-reach repairs

Two studies find that the molecular machinery that initiates gene transcription prevents repair proteins from accessing DNA, resulting in increased mutation rates at sites of transcription-factor binding. SEE LETTERS P.259 & P.264

EKTA KHURANA

The genetic mutations that lead to cancer are caused by diverse, often poorly understood processes, some of which involve exposure to external agents. Excessive ultraviolet light is linked to melanoma, for example, and tobacco smoke to lung cancer. A molecular mechanism called nucleotide excision repair deals with UV- and smoke-induced genetic damage by removing damaged pieces of DNA, preventing mutations from arising. However, this process is complicated by the fact that repair occurs alongside other crucial genetic activities, such as DNA transcription. Two papers[1,2] in this issue of *Nature* demonstrate how interplay between the DNA-repair and transcription-initiation machinery leads to an increased mutation rate in regulatory regions of the genome.

Although most cancer studies have focused on mutations in protein-coding DNA, there is a growing understanding of the importance of the non-coding DNA regions that regulate gene expression[3–6] — promoter sequences, which are located close to genes, and distant elements called enhancers. Binding of these regions by transcription factors modulates the expression levels of associated genes. On page 264, Sabarinathan *et al.*[1] describe the use of whole-genome sequences from human melanoma samples to analyse mutations in regulatory regions. They found that the cores of the regulatory regions, where transcription factors are predicted to bind, have a mutation rate five times higher than the flanking sequences.

Because of the major role of nucleotide excision repair (NER) in fixing UV-induced DNA damage, Sabarinathan and colleagues next analysed the locations of NER activity[7]. This revealed that the increased mutation rates at transcription-factor binding sites were caused by reduced levels of NER. The authors reasoned that mutations in other cancers that rely on NER should also exhibit this pattern. And indeed, they found increased mutation rates at transcription-factor binding sites in lung-cancer samples, particularly for mutations linked to smoking.

On page 259, Perera *et al.*[2] report the analysis of mutations in regulatory elements in multiple cancer types. They found increased mutation density in the centres of active promoters associated with reduced levels of NER. Moreover, the authors' data suggest that mutation density in regulatory regions is linked not only to transcription-factor binding, but also to the level of transcription initiation.

Thus, two independent studies show that NER at regulatory DNA regions is inhibited by the bound transcription-initiation machinery. This discovery is especially interesting in light of a previous study[8] that showed that

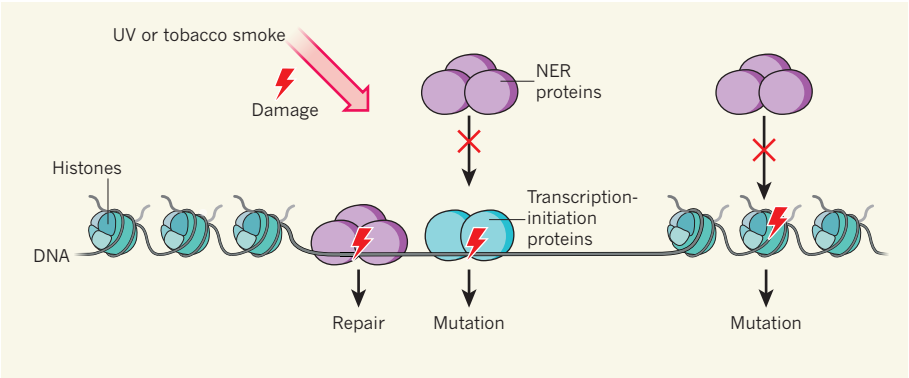

Figure 1 | Easy access prevents mutations. Most DNA is wrapped around histone proteins. By contrast, active regulatory regions are histone-free, to enable binding by transcription-initiation proteins. Exposure to ultraviolet radiation (UV) or tobacco smoke damages DNA, but this damage can be fixed by a process called nucleotide excision repair (NER), which requires DNA binding by NER proteins. Two studies[1,2] now show that NER is disrupted when NER proteins cannot bind DNA because of histones or because of bound transcription-initiation proteins. Mutations accumulate in the inaccessible sites.

mutation density is decreased over active regulatory regions as a whole, relative to their flanking sequences. The authors of that paper proposed that this decrease occurred because active regulatory regions are more accessible than most DNA regions to repair proteins — DNA is typically packaged around proteins called histones, but regulatory regions are unwound for binding by the transcription-initiation machinery. This apparent discrepancy with the current studies reflects the fact that, although regulatory regions as a whole are accessible for NER, the repair machinery is unable to access the core sites within those regions at which transcription factors bind (Fig. 1).

Certain mutations are considered to be drivers of cancer, because they provide a growth advantage to tumour cells. Such mutations are generally identified by the high frequency at which they occur across patients. However, the current studies highlight that protein binding can also lead to high mutation frequency — and so can other factors, such as late replication of a region during cell division[9]. Understanding how these features co-vary with mutation rate is vital for designing accurate computer algorithms to identify driver mutations[10].

It is notable that the variables affecting mutation rate differ for cancer types and subtypes. For instance, unlike in skin and lung cancer, NER does not have a major role in colon cancer. Accordingly, the current studies found no increase in mutation density at the centres of active promoters in colon-cancer samples.

Errors introduced by DNA replication in colon cells are normally resolved by a process called mismatch repair, which is most effective in genomic regions that replicate early during cell division. Thus, mutation rates in colon-cancer cells are generally lower in early-replicating than in late-replicating regions[11]. Mismatch-repair proteins are, however, inactivated in some colon tumours, resulting in the loss of strong correlation between mutation density and replication timing. In fact, the regional 'landscape' of mutation rates can be used to infer the time of mismatch-repair inactivation in the history of a colon tumour.

In the past few years, the complex interplay between DNA-repair mechanisms and genomic properties not originally associated with repair (such as replication timing and DNA accessibility) has become evident, largely thanks to the increasing availability of whole-genome sequences from tumour samples. The need for such sequences from cancer cells has been debated, because they are costly and have limited immediate clinical value[3]. But the current studies demonstrate the immense potential of whole-genome sequences as a lens through which to examine the cellular processes that shape the cancer genome. Genomic studies such as these lay the groundwork for future diagnostic tools and treatments tailored to individuals.

It remains unclear how many more genomic features that correlate with mutation rate are yet to be found. All mutations are ultimately the result of faulty DNA repair — do we need to know all the details of the many ways in which repair can break down to harness the full power of genomics for cancer care? The increasing number of tumour-genome sequences, coupled with our ever-improving knowledge of the machinery involved in genome function, will hold the answer to this question. ■

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REGENERATION

Not everything is scary about a glial scar

After spinal-cord injury, cells called astrocytes form a scar that is thought to block neuronal regeneration. The finding that the scar promotes regrowth of long nerve projections called axons challenges this long-held dogma. SEE ARTICLE P.195

SHANE A. LIDDELOW & BEN A. BARRES

It has long been a mystery why neurons in the peripheral nervous system can regenerate long projections called axons following injury, whereas neurons in the central nervous system (CNS) cannot[1]. One difference is that injured CNS axons lose their intrinsic ability to regrow, but studies have also implicated differences in non-neuronal cells called glia[1,2], which surround neurons to support them and provide insulation. Damaged glia in the CNS release inhibitors of axon regeneration[1], and reactive CNS astrocytes — a type of activated glial cell found at the damaged site — also seem to be powerfully inhibitory[3]. Research[1–3] into spinal-cord injury has centred mostly on the consequences of removing or inhibiting development of the reactive-astrocyte scar. It thus comes as a surprise that Anderson *et al.*[4], on page 195 of this issue, find that this scar in fact strongly supports axon regeneration after spinal-cord injury.

Several studies[5–8] in which reactive