

hybrid domain and knee regions that occurs when integrins are in a high-affinity state^{6,9}. Movement of the hybrid domain is also linked to changes in the shape of the neighbouring β I-domain. These changes allow the head region to undergo a metaphorical facelift so that ligands can bind with higher affinity. The major recognition site for ligands, including the classical arginine–glycine–aspartate amino-acid sequence found in many extracellular proteins, is in a groove between the α - and β -subunits (as shown¹⁰ for integrin $\alpha_v\beta_3$); however, the new structure reveals a larger subregion of the α -subunit that provides a secondary ligand-binding site (Fig. 2).

Although many of the long-standing mysteries of integrin structure have now been solved, several gaps remain. For instance, there is still a need to obtain a co-crystal between an integrin and a larger (macromolecular) ligand fragment, so that the ligand-binding pocket can be completely defined. Furthermore, nine integrins contain an additional ligand-binding region, called the α A- or I-domain, inserted into the head. Solving the structure of one of these integrins would explain the atomic basis of communication between this domain and the β I-domain.

In addition, the paper by Xiao *et al.*³ raises several specific questions. First, given that different $\alpha_{\text{IIB}}\beta_3$ -binding therapeutic peptides stabilized similar integrin conformations, how is the binding of different ligands to integrins converted into a graded signal inside the cell? One possibility is that variable ‘outside-in’ signalling is determined by differences in the kinetics of leg separation in different ligand–integrin complexes. Alternatively, there might be situations in which different ligands stabilize conformations with subtle differences in the angles of the joints (Fig. 1c). Determining the atomic basis of knee flexing will help in this regard. Second, to what extent are the same conformational changes involved in inside-out and outside-in signal transduction? In particular, to what extent does inside-out signalling cause unbending or the hybrid domain to swing out?

Finally, inappropriate integrin–ligand interactions contribute to aberrant cell adhesion in many diseases, including inflammation, the blockage of blood vessels by blood clots, and tumour progression. Can the availability of structures of integrin $\alpha_{\text{IIB}}\beta_3$ in complex with therapeutic peptides aid the rational design of drugs to target other integrins? Perhaps: it is certainly likely that the strategy of crystallizing a truncated form of $\alpha_{\text{IIB}}\beta_3$ could also be used for other integrins (including $\alpha_4\beta_1$ and $\alpha_v\beta_3$) that are major therapeutic targets in rheumatoid arthritis, multiple sclerosis and cancer. ■

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Land management

Forests, fires and climate

Cathy Whitlock

A new analysis of the effect of climatic variation on forest fires goes back several thousand years. One take-home message is that a one-size-fits-all forest management strategy is, literally, short-sighted.

Seemingly unprecedented events in human lifetimes can be business-as-usual when viewed on longer timeframes. But that’s not always recognized. For example, management strategies in the United States that seek to restore landscapes to the conditions that prevailed at the time of first European contact often fail to consider the events that created those conditions. This short-sightedness is particularly evident in the area of wildfire management.

On page 87 of this issue, however, Pierce *et al.*¹ provide a long-term perspective on the effects of fire in ‘low-elevation’ pine forests in the western United States. These dry, open forests lie above the steppe and grasslands that occupy most intermontane basins in the Rocky Mountains; in more moist settings at higher elevations, they are replaced by closed montane and subalpine forests. The low-elevation forests have been extensively modified by human activities, and there is intense debate about the appropriate action needed to restore them to their prehistoric state².

In the past 15 years, the western United States has experienced some extreme fires, notable for their size and severity. The annual costs of fire suppression now exceed \$1.6 billion, and the ceiling seems nowhere in sight³. In the absence of large fires during most of the twentieth century, many forests have become filled with a dense understory of shrubs and small trees that provide ‘ladder fuels’ that set the crowns of trees alight: these crown fires are the most destructive types of wildfire. The Healthy Forest Restoration Act⁴, signed into law by President George W. Bush in 2003, purportedly seeks to redress the ecological effects of fire suppression by establishing programmes of aggressive thinning, deliberate burning, and replanting to create open conditions. For local communities with economies based on timber extraction, this law is good news; for environmentalists, it is a travesty that limits scientific analysis and public participation in decision-making and policy.

But are the fires of the past 15 years



Figure 1 Slide show. This slope failure occurred following rainfall on melting snow in 1997, in an area of the South Fork Payette River, Idaho, that was severely burned in 1989. Herbs and low shrubs had regrown after the fire. But the decay of tree roots probably caused the fatal weakening of the slope.

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unprecedented in their severity? Another consideration in this debate is the unusual climate over that time that has dried fuels and created conditions conducive to the ignition and spread of fire⁵. Current fires, driven by strong winds, have burned both open and closed forests, ignoring conventional wisdom about fire behaviour. This conventional view is that closed, fuel-laden forests should experience severe stand-replacing fires, whereas open forests should be relatively fire resistant.

Understanding how present-day fires are influenced by climate requires information both on past fire conditions and on climate variability. If fire activity is a predictable consequence of the interconnectedness of climate, fire and vegetation, then in the Rocky Mountains we can expect fire regimes typical of a warmer, drier climate in the future⁶.

Our knowledge of fire history in low-elevation pine forests is based largely on analyses of fire scars on living and dead trees⁷. Most tree-based studies offer information about the past 500 years or so, but are biased towards surface fires that scar, but do not kill, trees. Charcoal records from lake sediments extend the fire chronology back several millennia; however, these studies generally focus on montane and subalpine forests⁸.

Pierce *et al.*¹ offer an alternative data set for studying past fire regimes at low elevations — the record of fire-related sedimentation, preserved as accumulations of rock, soil and wood known as debris-flow deposits. Severe fires can remove ground litter and reduce infiltration of water; following that, storms and melting snow in spring can initiate landslides that deposit fire-related sediment in valley bottoms⁹ (Fig. 1). In contrast, the geomorphological effects of low-severity surface fires are less dramatic, because of a more discontinuous burn pattern and lesser impact on the soil.

Pierce *et al.* determined the age of charcoal particles in different types of debris-flow deposits, and established a chronology of fire-related erosion for the past 8,000 years. Their data suggest that fire-related debris flows were associated with warm, dry periods, such as the Medieval Climate Anomaly (roughly AD 950–1350), when grass cover was sparse and fires were severe. In contrast, during cooler, wetter periods, such as the Little Ice Age (AD 1350–1900), dense grass cover supported frequent surface fires and there were only comparatively minor episodes of sedimentation.

Two points that emerge from this study¹ are worth mentioning. First, fire is influenced by climate variations that occur on several timescales, and shifts in fire regimes affect the various factors — vegetation, and hydrological and geomorphological processes — that stabilize or destabilize landscapes. In a given year, fire occurrence and severity are governed by particular

weather patterns and their influence on fuel moisture, ignition conditions and fire behaviour¹⁰. Fire-related geomorphological events are determined by the fire intensity, as well as the subsequent weather and the characteristics of the mountain slopes involved. On inter-annual timescales, fuel availability and slope stability are affected by variations in climate arising from atmosphere–ocean interactions, such as the El Niño–Southern Oscillation. On longer timescales, alternation of wet and dry periods during past centuries and millennia has shifted pine-forest ecosystems between surface-fire and crown-fire regimes and, in turn, has shifted the character of post-fire sedimentation.

Second, recent fires in low-elevation forests near sizeable human populations have led to calls for draconian tree and understorey thinning. Yet the investigations of Pierce *et al.*¹, and tree-ring studies^{11–13}, suggest that fire activity in these forests has varied in the past and includes episodes of severe crown fires and large debris flows. We should consider this long-term perspective before embracing one-size-fits-all management strategies. And in the future, we need to be guided by a firm understanding of both the relationship

between fires, climate and landscape processes on different timescales, and the interactions between climate and land-management activities in shaping fire regimes. ■

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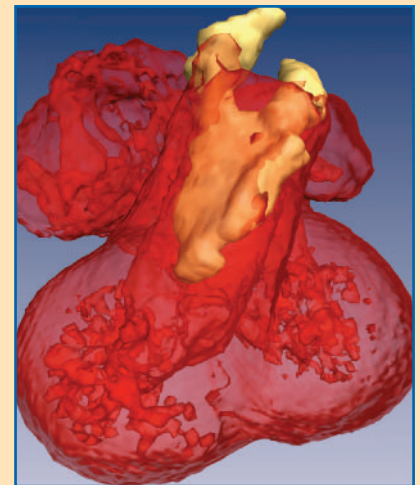
Cardiovascular biology

How genes know their place

Embryonic development is largely a matter of switching on the right genes, in the right place, and at the right time — it's no use activating heart-manufacturing genes in the limbs, for instance. Elsewhere in this issue (*Nature* **432**, 107–112; 2004), Benoit G. Bruneau and colleagues describe a protein that keeps heart-specific genes in their place.

Using mice, the authors first discovered that the protein in question, named Baf60c, is initially expressed only in the developing heart. Investigating further, they found that completely eliminating Baf60c from mouse embryos led to major cardiac defects (and early death). Knocking out about 50% of the protein led to somewhat milder, although still ultimately fatal, problems, such as an abnormally straight and split outflow tract (the yellow area in this picture).

Why do these problems occur? Baf60c is part of a complex that controls the accessibility of genes by interacting with transcription factors — proteins that regulate gene expression. So perhaps, without Baf60c, heart-specific genes cannot gain access to the transcriptional machinery and therefore remain inactive. Indeed, Bruneau and colleagues found that many genes that are characteristic of different aspects of heart development are not expressed when Baf60c is eliminated, including various genes involved in the formation of the outflow tract. Moreover, in *in vitro* studies, the authors showed that Baf60c enhances the interaction between Brg1, a key component of the complex in which Baf60c is found,



and certain heart-specific transcription factors.

So, at early stages of development, Baf60c seems to ensure that a complex that alters the structure of DNA — and hence its accessibility to proteins that activate genes — is targeted specifically to genes that are needed for heart development. This mechanism might also work in other tissues, with proteins other than Baf60c providing the necessary specificity. And the findings might bear on human disease: the defects caused by a partial lack of Baf60c are somewhat similar to those seen in some people with congenital heart defects. It remains to be seen, however, how the heart-specific expression of Baf60c is achieved in the first place.

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