directly to CXCR2 because it fails to block CXCL8 binding to the receptor and does not activate the intracellular signaling cascade that CXCL8 elicits (*12*). One possibility is that PGP causes neutrophil chemotaxis indirectly, by provoking the release of CXC chemokines by the lung epithelium.

Snelgrove *et al*. report that PGP is normally inactivated in the lungs by the enzyme LTA_4H, which is released from neutrophils and epithelial cells (see the figure). This is entirely appropriate in the context of acute microbial infection of the lungs because neutrophilic inflammation resolves once the pathogen disappears. The authors show that acute infection of mouse lung with either influenza virus or *Streptococcus pneumoniae* is associated with self-limiting neutrophilic inflammation and undetectable PGP in the lungs. By contrast, in mice lacking the gene encoding LTA_4H, substantial PGP was detected in bronchoalveolar lavage fluid. Thus, by secreting MMP-8 and MMP-9, neutrophils trigger the production of PGP to attract more neutrophils. These very neutrophils also release LTA_4H to terminate the action of PGP and resolve inflammation. In addition to peptidase activity, LTA_4H has hydrolase activity that generates the chemoattractant LTB_4. Thus, LTA_4H has two opposing actions that control the inflammatory response during acute infection of the lung.

Snelgrove *et al*. further show that cigarette smoke extract increases acetylation of PGP (possibly by components such as acrolein) and inhibits the peptidase activity of LTA_4H (without affecting its hydrolase activity), making PGP resistant to degradation by LTA_4H. Because degradation of the chemoattractant is blocked, neutrophil chemotaxis is increased and prolonged by cigarette smoke. This mechanism may underlie chronic neutrophilic inflammation in the lungs of smokers. PGP and *N*-α-PGP are increased in the sputum of COPD patients (*10*) and can be generated from collagen by sputum extracts from COPD patients, which contain MMP-8 and MMP-9 (*13*). This could account for the greater and persistent neutrophilic inflammation in airways of COPD patients compared to normal smokers. These tripeptides are also increased in the sputum of cystic fibrosis patients. In this disorder, the concentration of extracellular chloride ions is low (due to a defective chloride ion channel in lung epithelial cells), which may reduce the peptidase activity of LTA_4H.

What are the therapeutic implications for these new findings? Blocking the activity of PGP and *N*-α-PGP may be useful in treating neutrophilic inflammation. This could be achieved by its complementary peptide arginine-threonine-arginine (RTR), which blocks the chemotactic activity of PGP and inhibits PGP-induced emphysema in mice (*14*). Because the effect of PGP is mediated by CXCR2, small-molecule antagonists of this receptor (which are now in clinical development for treating COPD, cystic fibrosis, and other neutrophilic diseases) should be effective (*6*). However, drugs that block the production of LTA_4H, such as inhibitors of 5′-lipoxygenase or phospholipase A_2, would be less effective because they could increase the concentrations of PGP and *N*-α-PGP in the lungs and therefore overcome any potential benefit of blocking LTB_4 generation.

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ARCHAEOLOGY

When Humans Arrived in the New Guinea Highlands

In a high valley, humans were using plants and felling trees nearly 50,000 years ago.

Chris Gosden

People now inhabit every continent on Earth, with the partial exception of Antarctica. How and when this occupation unfolded is the subject of considerable debate, in part because the process raises questions about the development of human intelligence, adaptability, and technology. On page 78 of this issue, Summerhayes *et al*. (*1*) add to the discussion with a thought-provoking report on what may be the earliest documented human occupation of Sahul, the land mass that once joined Australia and Papua New Guinea (PNG). Stone tools and plant remains indicate that, at least 43,000 years ago, people were living in PNG's high Ivane Valley and exploiting plants for food, and also altering their environment.

By at least 50,000 years ago, modern humans had occupied lowland rainforest and savannah habitats across southeast Asia. Then they crossed the open ocean to Sahul, which existed when sea level was much lower than it is today. Previous research has identified early human settlement sites along PNG's coast and documented evidence of highland occupation in the Ivane Valley dating to as early as 41,000 years ago (*2*). In 2007 and 2008, Summerhayes *et al*. identified seven more sites of early occupation in the valley. Within four layers of sediment, they found stone tools of various types and evidence of hearths, plant remains, and smashed animal bone that could not be assigned to a species. Calibrated carbon-14 dating indicated that the oldest site was occupied between 49,000 and 43,000 years ago.

Today, a favorite slogan of PNG's tourist board is "expect the unexpected," and much would have been unexpected for humans arriving in the Ivane Valley during the late Pleistocene. Although it lies just 8 south of the equator, palynological evidence suggests that the valley has been a cold, difficult, and unpromising place to live at any time over the past 50,000 years. It sits at an altitude of 2000 m, above the limits of today's agriculture and has long been home to unusual species of plants (and probably animals). The environment would have posed a wide range of challenges to the tiny migrating groups of human

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Early arrivals. New evidence, including stone tools apparently used for clearing trees (**inset**), shows humans were in the Ivane Valley from 43,000 to 49,000 years ago and later migrated to offshore islands.

hunter-foragers, who had somewhat restricted technologies. But they certainly had survival skills: The capability to map, remember, and experiment would have been key to their ability to navigate through this new physical and social landscape and to identify potentially useful, and possibly lethal, plants (*3*).

Although the evidence of plant use presented by Summerhayes *et al*. is scant, it suggests that the settlers were exploiting pandanus, which produces useful leaves and starchy fruit. They also used yams, which were probably growing in their natural range at lower altitudes. Given the altitude and cold of the Ivane Valley, however, it is unlikely that people lived there permanently. Instead, it appears that they were moving and bringing with them plants to eat, but not to grow. Still, these people did not just take the ecosystem as they found it; they altered it. Summerhayes *et al*. found heavy "waisted" stone tools, which were probably used to clear forests. The Bobongara site on PNG's Huon Peninsula has also produced slightly younger evidence of waisted tools, suggesting that limited tree clearing may have been relatively common across mainland PNG at this time.

The world of Sahul's early hunter-foragers was very different from anything found in the region today. One can imagine small and highly mobile populations moving up and down the interior mountain chains of what is now PNG, engaged in small-scale clearance and some movement of plants. This set the stage for what came next: Within a few thousand years, archaeological evidence shows that people were crossing the sea to the offshore islands of the Bismarck Archipelago, as well as migrating into Sahul's wet and semi-arid areas, now in Australia. By 20,000 years ago, sites such as Matenkupkum in New Ireland, PNG, suggest that people were introducing wild animals—such as wallabies and rats—into ecosystems naturally poor in animal protein. Some 9000 years ago, what we label as farming appeared in PNG's highlands (above 1000 m), occurring in cleared landscapes and exploiting introduced plants and animals. Today, PNG's highlands, particularly the western highlands, have some of the country's densest populations and most intensive agricultural areas, and are surrounded by higher and lower regions with less dense populations. The extraordinary evidence presented by Summerhayes *et al*. provides insight into how this colonization began and testifies to the capabilities of these early human settlers.

High in the highlands. The Ivane Valley sits some 2000 m above sea level and has long been a challenging place to live.

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