IN BRIEF

KINASES

Screening for cell migration inhibitors via automated microscopy reveals a Rho-kinase inhibitor

Yarrow, J. C. *et al. Chem. Biol.* **12**, 385–395 (2005)

Cell migration is often studied using small molecules to perturb the complex underlying pathways, but a shortage of tool compounds led Yarrow *et al.* to develop a high-throughput image-based screen to identify inhibitors of this process. The screen is based on scratch-wound healing and measures decreased cell migration and aberrant morphology. A screen of 16,000 drug-like compounds identified subsets of different chemical classes that modulate cell migration. Secondary screening isolated 3-(4-pyridyl)indole (Rockout), a Rho-kinase (ROCK) inhibitor with comparable potency to the known ROCK inhibitor Y-27632.

MALARIA

Crystal structure of the malaria vaccine candidate apical membrane antigen 1

Pizarro, J. C. *et al. Science* **308**, 408–411 (2005)

Despite entering clinical trials as a malaria vaccine candidate, little is known about the structure or antigenicity of *Plasmodium* apical membrane antigen 1 (AMA1). Pizarro *et al.* provide the first crystal structure of the endoplasmic region of AMA1 from *Plasmodium vivax* and map an epitope within domain II that is recognized by an invasion-inhibitory monoclonal antibody specific for *Plasmodium falciparum*. Homology studies revealed a potential ligand-binding site within domain II that could be useful for drug design.

IMMUNOTHERAPY

A chimeric human–cat fusion protein blocks cat-induced allergy

Zhu, D. *et al. Nature Med.* **352**, 777–785 (2005)

IgE-induced mediator release, which contributes to allergic rhinitis and asthma, can be blocked by aggregating the type II receptor for IgG (FcγRIIb) to the high-affinity IgE receptor FcεRI. Zhu *et al.* created a chimera (GFD) comprising human Fcγ and cat allergen Fel d1 that co-aggregates FcγRIIb with FcεRI-bound IgE, thereby blocking mediator release. GFD was shown to inhibit allergen-induced IgE-mediated mediator release *in vitro* from human basophils and mast cells, and *in vivo* in cat-allergen-sensitized mice.

IMAGING

Noninvasive visualization of the activated αvβ3 integrin in cancer patients by positron emission tomography and [^{18}F]galacto-RGD

Haubner, R. *et al. PLoS Med.* **2**, 244–252 (2005)

The integrin αvβ3 is a target for anti-angiogenic therapies and several clinical trials of αvβ3 antagonists are under way. Existing imaging technologies are limited in their capacity to monitor the effect of treatment. Haubner *et al.* have developed a radiolabelled αvβ3 antagonist, [^{18}F]galacto-RGD, that was successfully used as a tracer for positron emission tomography (PET) to detect expression of αvβ3 *in vitro* and *in vivo*. Tracer uptake correlated with αvβ3 expression and was able to detect expression exclusively from tumour blood vessels. The study represents the first non-invasive assessment of αvβ3 expression in patients with malignant tumours.

CARDIOVASCULAR DISEASE

New use for cannabinoids

Cannabinoids might be valuable for treating cardiovascular disease, according to recent research published in *Nature*. Steffens and colleagues show that oral treatment with a low dose of Δ-9-tetrahydrocannabinol (THC) — the major constituent of marijuana — inhibits disease progression in a mouse model of atherosclerosis.

Atherosclerosis, the main cause of cardiovascular disease and stroke in Western countries, is generally recognized as a chronic inflammatory disorder. Given the growing evidence that cannabinoids such as THC have anti-inflammatory and immunomodulatory effects, Steffens *et al.* set out to investigate whether cannabinoid treatment would alter inflammatory processes pivotal for the development of atherosclerosis in the well-established apolipoprotein-E -knockout (ApoE$^{-/-}$) mouse model.

A daily oral dose of THC that was sufficient to produce anti-inflammatory effects, but lower than that associated with psychotropic effects, was given to ApoE$^{-/-}$ mice that had established atherosclerotic lesions as a result of being fed a high-cholesterol diet for 5 weeks. After 6 further weeks on the same high-cholesterol diet, mice that received daily THC during this period showed significantly reduced progression of atherosclerotic lesions compared with control mice.

So, what underlies this effect? It has been suggested that the immunomodulatory effects of cannabinoids are mediated by the CB2 receptor, which is primarily expressed on immune cells (the CB1 receptor that is thought to mediate their psychotropic effects is expressed primarily in the brain). Indeed, the authors found that CB2 receptors were present in atherosclerotic plaques of human and mouse diseased arteries, but not in non-diseased arteries. Moreover, the inhibitory effect of THC on atherosclerotic lesion progression was completely abolished in the presence of a specific CB2 receptor antagonist.

Further experiments provided evidence that THC suppresses the T_H1 response, which is thought to be important during early atherosclerosis development, and that it inhibits the migration of inflammatory cells into atherosclerotic lesions; this inhibitory effect was also blocked by the CB2 receptor antagonist. Overall, the findings indicate that developing compounds with activity at the CB2 receptor could be a promising novel therapeutic strategy for atherosclerosis.

Peter Kirkpatrick

References and links

ORIGINAL RESEARCH PAPER Steffens, S. *et al.* Low dose oral cannabinoid therapy reduces progression of atherosclerosis in mice. *Nature* **434**, 782–786 (2005)

FURTHER READING Di Marzo, V. *et al.* The endocannabinoid system and its therapeutic exploitation. *Nature Rev. Drug Discov.* **3**, 771–784 (2004)