Targets and Mechanisms

Structure of MutY adenine DNA glycosylase reveals how it recognises mismatches between adenine and 8-oxoguanine

Reactive oxygen species that are generated during aerobic respiration can lead to the oxidation of guanine bases in DNA to form 8-oxoguanine (oxoG). DNA polymerases that replicate opposite this lesion insert adenine, so both bases must be removed to prevent mutagenesis. The adenine is removed from these mismatches by MutY adenine DNA glycosylase (hMYH in humans). However, it is not known how this enzyme discriminates the adenines within A-oxoG mismatches from the normal A-T base pairs, which are present at a much higher concentration.

Fromme *et al.* [4] have solved the crystal structure of a MutY–DNA complex, showing how this enzyme distinguishes the mismatched adenines from those that are correctly base paired. The structure of full-length MutY from *Bacillus stearothermophilus* was solved bound to DNA containing an A-oxoG mismatch by using disulphide crosslinking to bond the DNA and protein together. To prevent the enzyme turning over within the crystals, the authors used MutY with a single point mutation, making it catalytically inactive.

MutY forms a two-domain structure; the catalytic domain is homologous to other proteins of the same family and the C-terminal domain is unique. The DNA backbone of the strand containing the adenine binds along a cleft on the catalytic domain, whereas the C-terminal domain contacts the other strand. The DNA helix is bent ~55° at the site of the lesion and the adenine base to be excised is flipped out of the DNA helix into a pocket within the enzyme. Interestingly, the glycosidic bond of the oxoG is in the anti orientation (it is in the syn position to pair with adenine), indicating that it has rotated 180° about the bond. This rotation could drive the flipping out of the adenine, because with oxoG in the anti orientation the two bases would sterically clash.

The DNA distortions are caused by several residues penetrating into the helix. These include tyrosine 88 intercalated 5′ to the oxoG, and glutamine 48 inserted into the space for the adenine. The oxoG base itself is contacted by residues from the C-terminal and catalytic domains, which form hydrogen bonds, such that every available face of the base is specifically recognised. It is these contacts that ensure the selection of MutY for adenine bases within the context of an A-oxoG mismatch, as they are unsuitable to bind a thymine. Thymine is presumably also not selected because the A-T base pair is more stable, preventing the adenine from flipping out of the DNA helix in the first place.

4 Fromme, J.C. *et al.* (2004) Structural basis for removal of adenine mispaired with 8-oxoguanine by MutY adenine DNA glycosylase. *Nature* 427, 652–656

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Business

Collaborations

Collaboration between Y's Therapeutics and Abmaxis

Y's Therapeutics (http://ysthera.com) and Abmaxis (http://www.abmaxis.com) have announced an agreement to collaborate on the development of a monoclonal antibody anticancer therapeutic targeting antigens that are overexpressed in tumours. It is also expected that this approach might be efficacious in autoimmune disease.

As a result of the details of the agreement, Abmaxis will be responsible for the discovery of high affinity, human antibodies directed against and specific for the antigen. Y's will be involved in the downstream development of the potential product. The agreement gives Abmaxis manufacturing, sales and marketing rights in China while Y's Therapeutics retains rights in the USA, Europe, Japan and ROW.

Masanori Murayama, scientific co-founder, President and CEO of Y's Therapeutics commented: 'We are very favourably impressed by the Abmaxis AISIM™ technology platform, which has already generated a number of humanized antibody candidates.' He continued: 'We look forward to working with Abmaxis in our quest to deliver therapeutic antibodies to patients as quickly as possible.'

Shirley Liu Clayton, CEO of Abmaxis, was equally optimistic about the collaboration, adding; 'We have a high degree of confidence in the potential drug development capability of Y's Therapeutics. We are pleased that Y's Therapeutics has selected Abmaxis to develop therapeutic antibodies to their antigen and we are eager to work with Y's Therapeutics and Dr. Morimoto, a world-renowned expert in molecularly targeted drugs.' She added that they had the ability to custom design an antibody for the specific therapeutic requirements of the project, using their proprietary library of sequence/structure information. She believes that the Abmaxis approach will rapidly identify appropriate optimal therapeutic antibodies.

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