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Entrez Database Searching

Scenario – You notice a gene of interest in the literature and you want more…

Imagine that you're a [grad student/postdoc/researcher/insert yourself here] working in a yeast genetics lab. Your lab studies mechanisms of DNA mutation and DNA repair. It's your first week on the job and you're excited to be working on a project connecting DNA repair and cancer. Your new to this research area so you've madly been reading papers on PubMed to learn all about DNA repair. Your boss puts a review article on your desk. The review mentions that mutations in DNA mismatch repair genes result in a hereditary form of colon cancer.

You'd like to learn as much as possible about these genes – We'll start by exploring MutL – or MLH1 (MutL homolog 1) the first gene mentioned in the abstract.

Here's the paper: PMID: 18031259

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Humanizing mismatch repair in yeast: towards effective identification of hereditary non-polyposis colorectal cancer alleles

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Abstract

The correction of replication errors is an essential component of genetic stability. This is clearly demonstrated in humans by the observation that mutations in mismatch repair genes lead to HNPCC (hereditary non-polyposis colorectal cancer). This disease accounts for as many as 2–3% of colon cancers. Of these, most of them are in the two central components of mismatch repair, *MLH1* (mutL homologue 1) and *MSH2* (mutS homologue 2). *MLH1* and *MSH2* function as a complex with two other genes *PMS2* and *MSH6*. Mismatch repair genes, and the mechanism that ensures that incorrectly paired bases are removed, are conserved from prokaryotes to human. Thus yeast can serve as a model organism for analysing mutations/polymorphisms found in human mismatch repair genes for their effect on post-replicative repair. To date, this has predominantly been accomplished by making the analogous mutations in yeast genes. However, this approach is only useful for the most highly conserved regions. Here, we discuss some of the benefits and technical difficulties involved in expressing human genes in yeast. Modelling human mismatch repair in yeast will allow the assessment of any functional effect of novel polymorphisms found in patients diagnosed with colon cancers.

Mismatch repair

The mismatch repair system serves to correct errors that occur during DNA replication. These errors can take the form of misincorporated nucleotides that result in mispaired bases or insertion/deletion loops that can result from replication slippage at polynucleotide tracts [1,2]. The mismatch repair proteins are conserved from prokaryotes to humans. *Escherichia coli* uses homodimers of MutS and MutL proteins, while yeast and humans utilize multiple orthologues to each of MutS and MutL. The mismatch repair proteins function together as complexes in different combinations, each complex having activity against specific types of mismatches (Figure 1). In yeast, the paralogous proteins yMlh1p and yPms1p form a heterodimer called MutLα based on one of the founding members of the family. MutLα binds with a repair process and therefore an increase in mutation rate or 'mutator' phenotype. As yMlh1p and yMsh2p are involved in the correction of multiple types of mismatch, deletion or mutation of these genes has a greater effect on mutation rate than the equivalent disruption of yMsh6p, which is involved in only one form of mismatch repair (Figure 2).

HNPCC (hereditary non-polyposis colorectal cancer)

HNPCC is an autosomal dominant disease that accounts for as many as 2–3% of colon cancers [6,7]. The disease is diagnosed according to the Amsterdam criteria [8,9], which require a presenting patient to have: (i) three or more family members with colorectal cancer, one of whom must be a first degree relative of another. (ii) The disease must have