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Chip Indicates Mutation

DNA chips for the rapid and reliable identification of point mutations

Sometimes the tiniest of differences convert a normal gene to a sick one. For example, a single nucleotide is switched in a gene segment known as oncogen p53–a mutation found in over 50 % of human cancer types. While it is possible to identify such single-point mutations, a rapid, simple, routine method that works quickly and reliably enough has yet to be found. Japanese researchers led by Kenzo Fujimoto and Shinzi Ogasawara have now developed a DNA chip for the accurate identification of point mutations. The success of this new method, which could be the basis for automated high-throughput diagnosis, is the photochemical linking of two DNA fragments.

The detection process works like this: short single strands of DNA are fixed onto a chip. These “capture strands” are complementary to the single-stranded DNA (which contains the point mutation of interest) being analyzed. The special trick used here is that the capture strand has a nucleotide at the end that has been chemically altered to become reactive when irradiated with UV light. When a sample is placed on the chip, the analyte DNA binds to the capture strand. If the counterparts fit perfectly, this happens very fast. A single “incorrect” nucleotide is enough to make the pairing go about a thousand times more slowly, so that when the reaction is stopped only a few capture strands are occupied.

In the next step, another short single strand of DNA is added, the sensor strand. This strand is complementary to the next segment of the analyte DNA and can only dock onto it when the analyte DNA is bound to the capture strand. Now the UV-activated nucleotide comes into play: when the chip is irradiated the nucleotide reacts with the adjacent end of the sensor strand, firmly binding the captive strand to the sensor. Even when the sample DNA is washed off of the chip, the sensor strand remains firm-

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ly coupled to the analyte. The sensor strand contains biotin, a kind of chemical “hook”. Next, a fluorescence dye, which carries the corresponding “eye” (streptavidin), is added. Strong fluorescence on the chip indicates that many sample DNA molecules are bound, meaning that their sequence exactly matches the capture strand. Minimal fluorescence indicates very slow strand pairing–the probe DNA must be different.

"While many methods for enzymatic ligation of DNA fragments have been demonstrated, there are only a few methods for photoinduced non-enzymatic ligation,” say Fujimoto. “The merit of photochemical ligation that avoids the need for additional reagents is obvious. Furthermore, their actions are controllable in space and time by the choice of proper irradiation methods. The photoligation methods can be used as a tool for DNA engineering and nanotechnology."

(2836 characters)

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http://www.jaist.ac.jp/~kkgi/thisyear/soe/00331soe.html

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