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Enticing Smell of Cancer

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Commentary

Cancer is one of the leading causes of morbidity and mortality. In 2012, around 14 million new cancer cases and 8.2 million deaths were reported in the world and the success to beat cancer lies in early detection [1]. What if one day you come back after work with a bag of fruits, leave them for few days to ripen, and 'voilà'- you created your home-made quick and cheap screening tool to detect cancer. Now just leave a drop of urine, sweat, or phlegm and wait till the flying buddies from fruits show your health state. Although this might sound as science fiction, entomologists and biologists are fascinated by fruits flies *Drosophila melanogaster* not in vain. As recent studies show, odours might serve as early markers for tumours that are still too small to be detected by imaging techniques, and thanks to the very sensitive olfactory systems could be sniffed out by *Drosophila*.

Cancer cells as well as healthy cells produce volatile organic compounds (VOCs) which are released as part of metabolism. Interestingly, rapidly dividing tumours release abnormal amounts of VOCs and thus they can potentially serve as diagnostic markers. Various volatile substances (for example, 2-xylene and cyclohexanol) are significantly increased in breast cancer cell cultures [2]. In thyroid cancer cases a decrease in VOCs such as sulfurous acid and ethylhexanol was detected in breath samples [3]. Volatile cancer markers can also be detected in blood as was shown in case of liver cancer [4] and ovarian carcinoma [5]. Prostate cancer may be detected by dogs by sniffing characteristic odour present in urine [6]. Moreover, melanoma, a malignant type of skin cancer was shown to be also detectable by dogs [7]. All these studies clearly show a common feature of various cancer types to release volatile metabolites that could be detected in breath, urine, blood, or other body fluids.

The first trials in screening for cancer using odours involved specially trained dogs. Because of their sensitive noses, they help the police to detect drugs and explosives in addition to sniffing, peeing a little and leaving a short message "Toby was here" to other dogs. This incredible ability to distinguish a variety of odour signals is attributable to several factors. First of all, because of evolutionary pressure in nature dogs and other animals, including fruit flies, have evolved very sensitive olfactory systems in which only a few molecules can elicit a response in the nervous system creating perception of odour. Secondly, coding of olfactory signals is combinatorial which means that smell receptors have overlapping receptive ranges of molecules in response to which they are activated or sometimes inhibited. This in turn indicates that a single odorant molecule can activate more than one olfactory neuron. The information must then be interpreted in the brain to produce smell perception characteristic of that scent. Although dogs are useful sniffing detectives, however, the pattern of behaviour they exhibit after exposure to various odorant is subject to bias by a human interpreter. To circumvent this problem, organisms such as fruit flies with external olfactory systems that are accessible to scientific investigation might prove more useful in creating a novel cancer screening system.

The mature fruit fly possesses the antennae and maxillary palps which contain olfactory hair-like extensions called sensilla [8]. In *Drosophila*'s genome there are around 80 odorant receptor genes which produce 50 neuronal classes and 1300 olfactory neurons which in turn possess different receptive ranges for odorant molecules. Because of combinatorial coding, there are around 250 patterns of odours that could be detected. Moreover, once a receptor is activated, so is the neuron and this physiological response can be easily detected using a microscope. The molecular trick lies in calcium-sensitive fluorescent protein named GCaMP [9]. When an odorant molecule binds to and activates the receptors on sensilla, calcium ions rush into and activate neurons. Thus, the more calcium comes into the cells, the more neurons are activated by odours, and the stronger fluorescence of GCaMP is visible under the microscope. By presenting scents from culture media of breast cancer cells and healthy cells, scientists have showed that fruit fly odour sensors can discriminate medically important volatile molecules at low concentrations [10]. In their research, scientists inserted calcium-sensing fluorescent proteins in senislla cells, which shone when neural activity followed by raising calcium levels increased due to odorant molecule binding to sensilla receptors. Thus, different scent samples from healthy and diseased tissues can create distinct patterns of fluorescent neurons that could be easily observed under the microscope. Important to note is the fact that in most cases not the presence of absence of specific odour is related to cancer, but the modified relative concentrations of volatile molecules, indicating that a priori knowledge of odorant is not required.

Owing to prevalence and immense impact on the society, cancer research will remain intensely investigated. Currently used artificial chemosensing systems have limited receptive range of odour molecules and to achieve sufficient sensitivity new systems with improved scent detecting capability are needed for clinical applications. Surprising as it may sound but the "fly detectors" because of their superior sensing systems may one day become indispensable in early cancer detection.

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