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Molecular Docking Study of Canine Olfactory Receptor and Cancer Compounds: Implication in designing of novel biochemical test for detection of cancer

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ABSTRACT

Dogs' smell sense has been used by humans in a variety of search operations. It has just lately began to be used to diagnose diseases, including cancer. Dogs can detect volatile organic compounds (VOCs) produced by cancer patients in their breath, urine, saliva, and other bodily fluids and tissues. The researchers looked at the interactions between various VOCs from the VOCC database and mouse receptors from the ODORactor database. iGEMDOCK was also used to investigate the docking of different VOCs and receptors in mice and dogs.

Because there was no database of olfactory receptors for dogs, we used the mouse receptor and compared it to the dog olfactory receptor. According to the docking study, one or more VOCs can bind to a specific receptor. A VOC can bind to many receptors at the same time. According to our findings, the amino acid residues LEU-61, 62, 113, 65, and MET-117 are important in a mouse receptor's binding to butyl acetate and 2-methylpropanal. VOCs were discovered to interact with a variety of typical amino acid receptors in dogs and mice. As a result of the in-silico study, an unique technique for cancer diagnosis based on the sense of olfaction of diverse animals has been studied, which will be further validated by laboratory experiments.

Conclusions: We also discovered that, in addition to dogs, a variety of other animals can be employed for illness diagnosis, giving a non-invasive method for disease detection and prevention.

Keywords: Cancer, canine, docking, Non-Invasive technique, Odorant, Olfactory Receptor (OR), Volatile organic compounds (VOCs).

INTRODUCTION

Cancer is a condition in which abnormal cells in the body divide rapidly and can infect other

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tissues.[1] Cancer cells have a substantially faster metabolic rate than normal cells. Physical testing, laboratory tests, imaging tests, and biopsy are some of the current cancer screening approaches. Although cancer biopsy is the only certain way to screen for most cancers, the findings can take up to 2-3 days, and more complex cases might take up to 7-10 days, necessitating the creation of a quick, non-invasive cancer screening test.

Dogs have an incredibly acute sense of smell. Dogs have a 10,000-100,000 times stronger scent sensing capacity than humans.[2] At the same time, cancer cells are discovered to emit various Volatile Organic Compounds (VOCs) during tumour growth as a result of metabolic pathway changes.[3] These VOCs attach to the olfactory receptors (OR) in dogs and act as ligands. According to a study conducted on five trained dogs, the dogs can detect cancer from breath samples.[4,5] The dogs were 88 percent accurate in detecting breast cancer and 99 percent accurate in detecting lung cancer. Vomeronasal Receptors, Trace Amine-Associated Receptors, and formyl Peptide Receptor-Like Proteins are the receptors involved in olfaction and chemo sensation in dogs.[6] Receptors of the Olfactory System Cilia are cilia that have external regions that bind odorants and intracellular portions that are linked to G-protein. The G-protein A-subunit splits when an odorant binds to the extracellular region of the receptor, activating adenyl cyclase, which converts ATP to Camp.[6] cAMP increases the signal strength of odorant molecules by activating multiple sodium gated channels, causing depolarization, which is then transmitted to brain regions and activates olfactory receptors.

In this paper, we looked at how canine olfactory receptors interact with VOCs, a ligand generated by cancer cells, to learn more about a highly effective cancer screening mechanism. Several common amino acids have been discovered to play a function in the interaction between VOCs and receptors. As a result, a one-of-a-kind biochemical disease detection test will be developed. VOCs that interact with olfactory receptors that haven't been studied yet are also investigated. This research could be useful as a new disease detection approach.

Materials and Methods

1. The VOCC database was used to access congregate knowledge on the varied Volatile organic compounds found in several sorts of cancer.[7]
2. The canonical SMILES of several VOCs were facsimiled from the PubChem server and analyzed for the property as an odorant on ODORactor server.[8,9]
3. BLAST incorporated in Uniprot consortium server cum database was performed to spot Homology between sequences.[10]
4. The conserved interacting residues and binding pocket were identified using iGEMDOCK.[11]

Results

The VOCC database was used to analyse twenty-seven (27) volatile organic chemicals emitted from various physiological fluids as a characteristic pattern for cancer.[7] On entry into the ODORactor server, nine of the VOCs were found to be odourless. [9] As a result, they were excluded from further investigation. The main goal of our research is to figure out how dogs can detect cancer. We employed the mouse OR and explored its similarity with dog OR because there was no database of OR for dogs. We discovered that whereas mice have multiple olfactory receptors, odorants only bind to specific receptors after investigating the interaction of odorants

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with mouse receptors. The G-protein coupled receptor 1 family includes the ORs of dogs and mice.

OR with ID Olfr641 attaches to the odorant 2-chloroethanol and is placed on chromosome 7, whereas OR with ID Olfr1351 binds to 2-Methylpyrazine and is located on chromosome 10. Similarly, OR with ID Olfr168 binds to 2-phenyl-2-propanol, cyclohexanone, butyl acetate, and 2-methylpropanal, which are all found on chromosome 16, and OR with ID Olfr1352 binds to Isophorone, which is found on chromosome 10. The OR with the ID Olfr167 attaches to tetrahydrofuran on chromosome 16 while the OR with the ID Olfr599 binds to 2,2-dimethyldecane on chromosome 7. On chromosome 7, the OR with the ID Olfr690 binds to GHB 4-Hydroxybutanoic acid and caproic acid. The OR with the ID Olfr1105 binds to sulfuric acid and is found on chromosome 2. OR with the ID Olfr992 binds to 3-Octanone, which can be found on chromosome 2. OR with the ID Olfr2 binds to pentanal, which is present on chromosome 7. OR with the ID Olfr154 binds to 2-Nonanone, which can be found on chromosome 2. OR with the ID Olfr160 binds to Benzaldehyde, which is present on chromosome 9. Ethyl phenol binds to OR with ID Olfr556. OR with ID Olfr57 is a protein that binds to phenol and is present on chromosome 10.

In dogs, a gene for OR binding with 2-chloroethanol can be found on chromosome 21. OR7A65 is a protein located on chromosome 20 that binds to 2-Methylpyrazine. OR2L13 was shown to bind to 2-phenyl-2-propanol, cyclohexanone, butyl acetate, and 2-methylpropanal on chromosome 14. OR7A54 binds to the gene Isophorone, which is situated on chromosome 20. The OR2L3B gene interacts to tetrahydrofuran and is found on chromosome 14. OR52AB4 is a protein on chromosome 21 that interacts with 2,2-dimethyldecane. GHB 4-Hydroxybutanoic acid and caproic acid, both located on chromosome 21, bind to OR52B2. OR5J1 is a sulfuric acid-binding protein that is found on chromosome 18. OR5AK6 is a protein on chromosome 18 that interacts with 3-Octanone. OR6A2 is a pentanal-binding protein that is present on chromosome 21. The OR5G5 gene interacts to 2-Nonanone and is situated on chromosome 18. OR8A1 is a protein that interacts to Benzaldehyde and is found on chromosome 5. OR52I1 is a chromosome 21 OR that binds to ethyl phenol and has the ID OR52I1. OR7A65 is an OR that binds to phenol and is found on chromosome 20.

This suggests that OR, which is found on numerous chromosomes, may have a role in odour perception. The preserved section of those OR was revealed by comparing their structures, as illustrated in figure 1, which appears to be critical for their activity. The odorant receptors of dogs and mice were docked with the odorant in this investigation. We also built the 3D structure of mouse and dog OR proteins, verified them using the Ramachandran plot, and docked them with the odorant. Table 1 shows the interaction energy between the OR of *Canis lupus familiaris* and VOCs. In table 2, the interacting residues that contribute to binding free energy are listed from iGEMDOCK. Table 3 shows the interaction energy between OR of Mus musculus and VOCs. Figure 3 shows the docking of 2chloroethanol and OR F1PX16 of *Canis lupus familiaris*.

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VOCs that bind to the same receptor have been discovered:

1. 2methylpropanal, 2phenyl2propanol, butylacetate and cyclohexanone bind with OR Q8VF05 of *Mus musculus*.
2. 2 methylpyrazine and Phenol bind to the OR A0A5F4CCH8 of *Canis lupus familiaris.*
3. Butylacetate, 2methylpropanal, 2-phenyl-2-propanol and Cyclohexanone bind to F1PQ65 OR of *Canis lupus familiaris.*
4. 4hydroxybutyric acid and hexanoic acid bind toQ8VH18 of *Mus musculus* and E2R1F3 OR of dog as shown in figure1.

We discovered that a VOC can connect to one or more receptors in our research.
As with 3-octanone, it interacts to two distinct dog receptors, A0A5F4C105 and A0A5F4C4F7, as illustrated in Figure 2. Isophorone interacts to three distinct mouse receptors: Q8VGX6, Q8VGU6, and Q8VGX5.

Common amino acid residues are shown in the following receptor-odorant interaction:

1. For mouse receptorQ8VF05 binding to butyl acetate and 2methylpropanal, amino acids LEU-61, LEU-62, LEU-113, LEU-65, MET-117 are common as given in table 4.
2. Similarly for mouse receptor Q8VH18 binding to 4hydroxybutyricacid and GHB4Hydroxybutanoic acid, HIS-90, ALA-91, TYR-180, ILE-86, TYR-180, GLY-92, CYS-181 are found to be common.
3. For dogs receptor A0A5F4CCH8 binding to 2METHYLPYRAZINE and phenol VAL-69 has been found to be common.
4. For F1PQ65 binding with butyl acetate and methyl propanal GLN-88, PHE-177, CYS-178, ASP-83, LYS-89, are common whereas for F1PQ65-2phenyl2propanol only CYS-178 is common.
5. E2R1F3-4hydroxybutyric acid, E2R1F3-GHB4Hydroxybutanoic acid, ALA-91, HIS-92, ASN-93, ILE-86, are common.

Other organisms' olfactory receptors were revealed to be homologous to the mouse's olfactory receptor. Mesocricetus auratus (Syrian hamster), Tupaia chinensis (treeshrew), Marmota monax (groundhog), Ictidomys tridecemlineatus (thirteen-lined Ground Squirrel), Erinaceus europaeus (hedgehog), Vulpes vulpes (red fox), Otolemur garnettii (northern greater galago), As a result, these organisms can be used to detect volatile chemical substances. Although dogs have been reported to be useful in the detection of carcinoma, prostate cancer, colorectal cancer, and malignant melanoma, other organisms can also be useful with correct training. [5,12-14]

Discussion

Because dogs are the best at being trained and comprehending human intuition, they are used to detect cancer. Other organisms, such as the rat, Syrian hamster, treeshrew, groundhog, thirteen-lined Ground Squirrel, kangaroo rat, hedgehog, red fox, northern greater galago, and vesper bat, can aid in the development of different cancer detection systems.

Recently, there have been instances of dogs being used to detect the corona virus. [15] 15 Ethyl butanoate is found in higher concentrations in COVID-19 patients, whereas isopropanol and butyraldehyde are found in higher concentrations in patients with respiratory diseases other than

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COVID-19. [16] Our research into the interaction of dogs' OR and volatile organic compounds has revealed that, in addition to cancer, a variety of other diseases such as corona, plague, and other bacterial infections can be detected effectively if we develop a technique to understand the basis of their interaction.

CONCLUSION

Bisht et al. previously employed computational docking and simulation to decipher the interaction between Tetherin Protein and SARS-COV-2ORF7A Proteins and Mutants.[17] The use of similar docking interactions in this work showed a number of significant common amino acids that are involved in the interaction of odorants with olfactory receptors. As a result, focusing on these amino acids could lead to the creation of a new non-invasive biochemical test for cancer detection.

Although dogs have been reported to be used in cancer detection, our research found that a variety of different animals, in addition to dogs, may be used and trained to detect a variety of diseases.

Because the same odorants may be emitted in various diseases, combining signatures for the detection of two or more disease-related odorants can be advantageous. Alternative illness detection approaches, such as the one described in this study, can benefit the scientific community and be established as state-of-the-art technology with proper training and testing.

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Conflict of Interest

There are no conflicts of interest between us and anyone else.

Author's Contribution

Dr. Kumud Pant planned the work and examined the data for our research project. Dr. Devvret Verma provided input while Kaveri, Shikha, Khushi, and Dr. Kumud Pant carried out the implementation and prepared the manuscript. Dr. Kumud Pant was the one who came up with the idea for the study and was in charge of the general planning and direction.

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