IDENTIFICATION OF ENDOGENOUS OVEREXPRESSION OF CATALASE, AS A INHIBITOR OF EMT SIGNALLING THE PROGRESSION OF BREAST CANCER.

[1]Kaviya.S, [2]Lavanya Prathap, [3]Dr. Selvaraj Jayaraman, [4]Preetha. S

Running Title: Docking analysis of interaction catalase in EMT signalling.

Type of article: Original Research

[1]Kaviya.S
Department of Anatomy
Saveetha Dental College and Hospitals
Saveetha Institute of medical and technical sciences
Saveetha university,
Chennai - 600077
kaviyaselvaraj2003@gmail.com

[2]Lavanya Prathap
Associate Professor
Department of Anatomy
Saveetha Dental college and hospitals,
Saveetha institute of medical and technical sciences
Saveetha university,
Chennai - 600077

[3]Selvaraj Jayaraman
Associate Professor
Department of Biochemistry
Saveetha Dental college and Hospitals,
Saveetha Institute of Medical and Technical Sciences,
Saveetha university,
Chennai - 600077

[3]Preetha. S
Assistant Professor
Department of Physiology
Saveetha Dental college and hospitals,
Saveetha institute of medical and technical sciences
Saveetha university,
Chennai - 600077

.

Corresponding Author:
Lavanya Prathap
Associate Professor
Department of Anatomy
Saveetha Dental college and hospitals,
Saveetha institute of medical and technical sciences
Saveetha university,
Chennai - 600077

Email ID: lavanyap.sdc@saveetha.com

ABSTRACT:

KEYWORDS: Breast tumor; Exercise; Catalase; Vimentine; Beta-catenin; Ecadherin; innovative method.

BACKGROUND: Tumor is an abnormal cell growth that spreads to other organs. Breast tumor develops in the tissues of the breastRegular exercise can help to lower the chance of developing breast tumor. For the year 2020, the expected incidence of tumor patients in India was 679,421 (94.1 per 100,000) for males and 712,758 (103.6 per 100,000) for females.. **AIM:** To analyse the endogenous over the expression of catalase as an inhibitor of EMT signaling in breast tumor through molecular docking.

MATERIALS AND METHODS:

The molecular docking analysis is a bio informatic study conducted in a private dental college. The endogenous substance catalase which is secreted after post exercise is used as our target protein. The interaction of catalase with the proteins relevant to breast tumor namely Vimentin, Beta-catenin, Ecadherin are included for docking analysis. The protein structure is retrieved using protein data bank, Protein protein docking done using patch Dock server followed by visualisation of protein-protein interaction using pymol.

RESULT:

The surface representation of catalase with Vimentin, Beta-catenin and Ecadherin showed good shape complementarity.The results showed that Catalase forms strong interaction with Vimetine, Beta catenin, Ecatherine proteins in terms of hydrogen bond interaction, hydrophobic and non bonded interaction. Through this interaction these proteins might control the overexpression of catalase activity in breast tumor.

CONCLUSION:

From the obtained result it can be concluded that catalase may have a protective role against breast tumor through its interaction with Vimentin, E-Cadherin, Beta-Catenin. The present study has suggested a possible mechanism of catalase in the inhibitor of EMT signaling in breast tumor.
KEYWORDS: Breast tumor; Exercise; Catalase; Vimentine; Beta-catenin; Ecadherin;innovative method.

INTRODUCTION:

The catalase CC genotype is associated with 17% reduction in breast tumor and has a therapeutic role and antioxidant enzyme that decomposes hydrogen peroxide, damages the DNA and protein and builds up toxic levels. Using mitochondrial tumour cells and tumour stromal cells to target catalase inhibits ROS-driven tumour development and metastasis. As a result, enhancing the mitochondrial compartment's antioxidant capacity could be a sensible therapeutic strategy for invasive breast tumor.[1]

Using mitochondrial tumour cells and tumour stromal cells to target catalase inhibits ROS-driven tumour development and metastasis. As a result, enhancing the mitochondrial compartment's antioxidant capacity could be a sensible therapeutic strategy for invasive breast tumor.[3]. The trials from previous studies[4] [5,67,85,65910111210,121314] [15] have led us to concentrate on the study.

Important characteristics of basal breast tumor, such as its proclivity for poor overall survival, imply that it could be a promising pharmaceutical target for this aggressive breast tumor subtype16. Ecadherin is a calcium-dependent cell adhesion protein that is one of the most investigated tumour suppressors in breast tumor. In various cases, signalling molecules and transcription factors that regulate Ecadherin expression have been identified to promote EMT [17]. Evidence suggests that EMT may play a role in the course of human breast tumor, as well as the prognostic value of vimentin expression.[18]. Studies at molecular levels were performed by our team of researches which insisted us to proceed this study [19–26],[27],[28],[29],[30,31],[32],[33],[34–38]Thus the present study attempts to analyse the role of endogenous over the expression of catalase as an inhibitor of EMT signalling the progression of breast tumor.

MATERIALS AND METHODS:

The molecular docking analysis is a bio informatic work conducted in a private dental college. The endogenous substance catalase which is secreted post exercise is used as our target protein. The interaction of catalase with the proteins relevant to breast tumor namely Vimentin, Beta-catenin, Ecadherin are included for docking analysis.

Procedure:

Retrieval of Target proteins structures from Protein data bank

In order to study the mechanism of interaction between Catalase with Vimetine, Beta catenin, Ecatherine proteins, the three dimensional structures were downloaded from Protein Data Bank using the respective ids(Pdb ids: Catalase- 1DGF; Vimetine –1GK4; Beta catenin -4DJS; Ecatherine - 2O72)[39]

Protein-Protein Docking.

Patch Dock (http://bioinfo3d.cs.tau.ac.il/PatchDock) is a geometry-based molecular docking technique[40] used to study the interaction between Catalase with Vimetine, Beta catenin, Ecatherine proteins. The Patch Dock service calculates docked transformations that result in strong molecular shape complementarity. The Connolly dot surface representation of the molecules is divided into concave, convex, and flat patches using the algorithm.. In order to produce various transformations, the patches were paired according to their complementarity. For clustering, a default value of 4 Å was used and redundant solutions were discarded by RMSD clustering. The geometric score, desolvation energy, interface area scale, and the actual rigid transformation of the solutions are created by the Patch Dock output. For each complex, twenty solutions were created, from which one complex was selected for further analysis based on the scoring geometric shape for both complexes.

Visualization of Protein – Protein interactions.

Using the academic version of the Pymol, the residual interactions between docked complexes were viewed. The colour intensity for interactions was clearly visible here, and the findings were exported. [41] Pdbsum was used to determine the types of interactions that Catalase has with the proteins Vimetine, Beta catenin, and Ecatherine..

RESULTS:

The results suggests that Catalase forms strong interaction with Vimetine, Beta catenin, Ecatherine proteins (Figure 1,2,3) in terms of hydrogen bond interaction, hydrophobic and non bonded interaction. Once the docking process is completed, it will send the web link to the mail which we gave during the docking process. The output of results contains 20 top ranked complexes. Based on the, the interface area size the best complex was selected for each protein and further analyzed using a pymol visualization tool. Some the amino acids from catalase like ALA-8, SER-9, LYS-77,THR-115, ALA-117, GLY-118,jjj GLY-121, SER-122, ALA-123, VAL-126, ARG-127,ASP-128, GLN-168, LYS-19, THR-174, LEU-176, ASP-178 and VAL-182 alternatively involved in the formation of complex with the Vimetine, Beta catenin, Ecatherine. Through this interaction these proteins might control the overexpression of catalase activity in breast tumor. The present study has suggested a possible mechanism of catalase in the inhibition of EMT signaling in breast tumor.(table 1)

S.No	Protein Name	Score	ACE (Atomic contact energy)
1	Vimetine	15794	- 389.49
2	Beta catenine	22658	-490.24
3	Ecatherine	19246	-273.28

Table 1: Molecular docking results of Catalase with Vimetine, Beta catenine, Ecatherine proteins

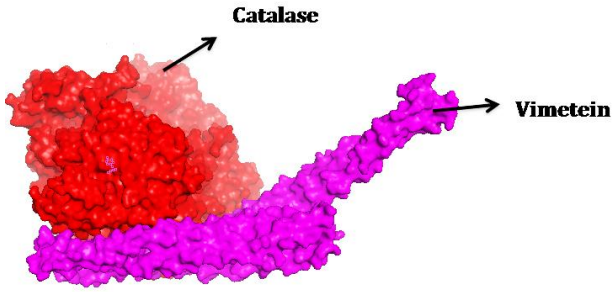

Figure 1-Protein-Protein interaction between Catalase-Vimetein

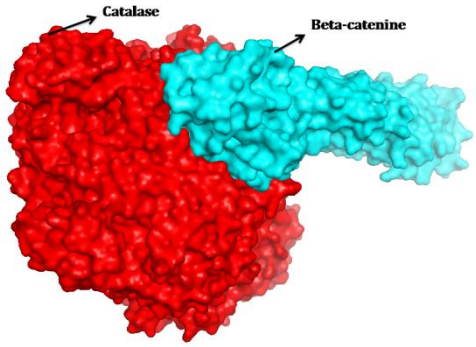

Figure 2- Protein-Protein interaction between Catalase-Beta catenin

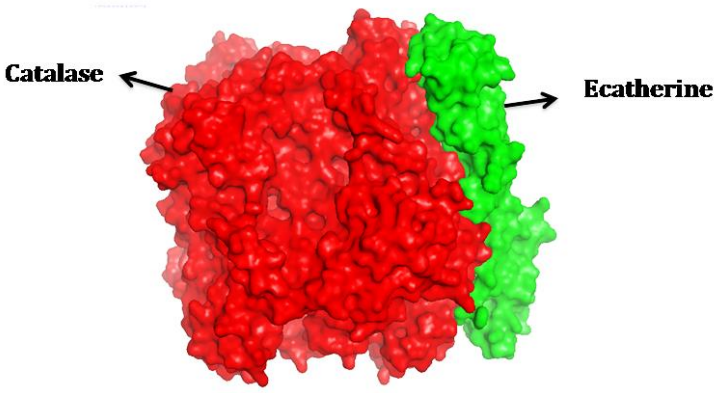

Figure 3-Protein-Protein interaction between Catalase-Ecadherin

DISCUSSION:

The docking study's findings could add to the growing body of data indicating exercise-induced endogenous catalase is a protective molecule against breast tumor cell growth. It was possible to design a more selective and efficient inhibitor by understanding these types of interactions. We found that catalase, which is created after exercise, functions as a regulator for EMT signalling in breast tumor in our study..

Protein-protein interactions (PPI) are important in cellular biological processes, immunological response, and cellular organisation. As a result, PPI analysis is extremely important and can aid in the identification of pharmacological targets as well as treatment design. High-throughput technologies like yeast two-hybrid screenings (Y2H) and mass spectrometric protein complex identification (MS-PCI) have yielded a lot of data, but they're also expensive and time-consuming. Furthermore, these approaches may not be relevant to proteins from all species, resulting in false-positive results. Its goal is to find docking changes that result in substantial molecular shape complementarity. When applied, such enhancements result in extensive interface areas as well as minor amounts of steric conflicts. Patch dock takes two molecules in PDB format as input, which we can upload or have the server obtain from the pdb using their respective pdb ids. Regular exercise has an influence on acute and chronic symptoms of breast carcinoma. [42].

EMT allows epithelial tumour cells to acquire mesenchymal characteristics that aid in metastasis. [43]. During the epithelial to mesenchymal transition during early metastasis, the impact of Vimentin on tissue factor expression is limited by negative regulation of TF in mRNA. [44].. Beta-catenin is also known as Catenin-1. It has a dual function that is regulation and coordination. Cell-Cell adhesion, gene transcription takes place. It is located in the membrane at the side of the cytoplasm. [45].[46],[47]

Ecadherin determines whether the tumour is ductal or lobular. It regulates the formation and stability of ECadherin. It plays an important role in morphogenesis and homeostasis. The EGF receptor was shown to be overexpressed in tumors. Ecadherin expressions in menopausal status, hormone receptor status, and age were found to have no significant association.[48]. Ecadherin expression is controlled by a number of signalling molecules and transcription factors. Ecadherin loss has been linked to EMT in a number of situations. Because of the frequent changes in their expression, it's possible that the Ecadherin pathway's loss of function is important in the development of breast tumor.[49]. Understanding the basic development of tumours and increasing early diagnosis to expediting the process of turning prospective therapeutic targets into clinical features are all things that we're working on. [50]. For further understanding the study can be carried out in vitro and in a large population.

CONCLUSION:

The study concludes that exercise induced endogenous over the expression of catalase may act as an inhibitor of EMT signaling in preventing breast tumor initiation and progression. From this we analyse the role of endogenous over the expression of catalase as an inhibitor of EMT signalling in the progression

ACKNOWLEDGEMENT:

We would like to thank Saveetha dental college and hospitals for the successful completion of the study.

CONFLICT OF INTEREST

All the authors declare that there was no conflict of interest in the present study.

SOURCE OF FUNDING:

The present study was supported by the following agencies

- Saveetha Dental College,
- Saveetha Institute of Medical and Technical Sciences,
- Saveetha University
- Prompt paper products private limited ,SK Traders.

REFERENCES:

1. Goh J, Enns L, Fatemie S, Hopkins H, Morton J, Pettan-Brewer C, et al. Mitochondrial targeted catalase suppresses invasive breast tumor in mice. BMC Tumor. 2011 May 23;11:191.

2. Glorieux C, Calderon PB. Catalase, a remarkable enzyme: targeting the oldest antioxidant enzyme to find a new tumor treatment approach. Biol Chem. 2017 Sep 26;398(10):1095–108.

3. Gilles C, Polette M, Mestdagt M, Nawrocki-Raby B, Ruggeri P, Birembaut P, et al. Transactivation of vimentin by beta-catenin in human breast tumor cells. Tumor Res [Internet]. 2003 May 15 [cited 2021 Mar 12];63(10). Available from: https://pubmed.ncbi.nlm.nih.gov/12750294/

4. Shruthi M, Preetha S. Effect of Simple Tongue Exercises in Habitual Snorers [Internet]. Vol. 11, Research Journal of Pharmacy and Technology. 2018. p. 3614. Available from: http://dx.doi.org/10.5958/0974-360x.2018.00665.0

5. Preetha S, Packyanathan J. Comparison of the effect of Yoga, Zumba and Aerobics in controlling blood pressure in the Indian population [Internet]. Vol. 9, Journal of Family Medicine and Primary Care. 2020. p. 547. Available from: http://dx.doi.org/10.4103/jfmpc.jfmpc_607_19

6. J SK, Saveetha Dental College and Hospitals, Road PH, Chennai, Tamilnadu, Preetha S, et al. Effect of aerobics exercise and yoga on blood pressure in hypertensives [Internet]. Vol. 6, International Journal of Current Advanced Research. 2017. p. 3124–6. Available from: http://dx.doi.org/10.24327/ijcar.2017.3126.0200

7. Preetha S, Packyanathan J. Comparison of the effect of Yoga, Zumba and Aerobics in controlling blood pressure in the Indian population [Internet]. Vol. 9, Journal of Family Medicine and Primary Care. 2020. p. 547. Available from: http://dx.doi.org/10.4103/jfmpc.jfmpc_607_19

8. J SK, Saveetha Dental College and Hospitals, Road PH, Chennai, Tamilnadu, Preetha S, et al. Effect of aerobics exercise and yoga on blood pressure in hypertensives [Internet]. Vol. 6, International Journal of Current Advanced Research. 2017. p. 3124–6. Available from: http://dx.doi.org/10.24327/ijcar.2017.3126.0200

9. Prathap L, Suganthirababu P, Ganesan D. Fluctuating Asymmetry of Dermatoglyphics and DNA Polymorphism in Breast Tumor Population [Internet]. Vol. 10, Indian Journal of Public Health Research & Development. 2019. p. 3574. Available from: http://dx.doi.org/10.5958/0976-5506.2019.04141.x

10. Lavanya J, Prathap S, Alagesan J. Digital and palmar dermal ridge patterns in population with breast carcinoma. Biomedicine. 2014 Jul 1;34(3):315–21.

11. Prathap L, Jagadeesan V. Association of quantitative and qualitative dermatoglyphic variable and DNA polymorphism in female breast tumor population. Online J Health [Internet]. 2017; Available from: https://www.researchgate.net/profile/Prathap_Suganthirababu/publication/321606278_Association_of_Quantitative_and_Qualitative_Dermatoglyphic_Variable_and_DNA_Polymorphism_in_Female_Breast_Tumor_Population/links/5a28c8f1a6fdcc8e8671c0cd/Association-of-Quantitative-and-Qualitative-Dermatoglyphic-Variable-and-DNA-Polymorphism-in-Female-Breast-Tumor-Population.pdf

12. Lavanya J, Kumar VJ, Sudhakar N, Prathap S. Analysis of DNA repair genetic polymorphism in breast tumor population. Int J Pharma Bio Sci [Internet]. 2015; Available from: https://scholar.google.ca/scholar?cluster=8949053652564257518&hl=en&as_sdt=0,5&sciodt=0,5

13. Prathap L, Suganthirababu P. Estrogen Exposure and its Influence in DNA Repair Genetic Variants in Breast Tumor Population [Internet]. Vol. 13, Biomedical and Pharmacology Journal. 2020. p. 1321–7. Available from: http://dx.doi.org/10.13005/bpj/2001

14. Ravikumar H, Prathap L, Preetha S. ANALYSIS OF PALMAR ATD ANGLE IN POPULATION WITH MALOCCLUSION. 2020 Jan 1;1174–82.

15. Prathap L. INTERPLAY OF OXIDATIVE STRESS AND LIPOPROTEINS IN BREAST CARCINOMA INITIATION, PROMOTION AND PROGRESSION -A SYSTEMATIC REVIEW. PalArch's Journal of Archaeology of Egypt/ Egyptology [Internet]. 2021 Jan 7 [cited 2021 Mar 9];17(7). Available from: http://dx.doi.org/

16. Khramtsov AI, Khramtsova GF, Tretiakova M, Huo D, Olopade OI, Goss KH. Wnt/β-Catenin Pathway Activation Is Enriched in Basal-Like Breast Tumors and Predicts Poor Outcome [Internet]. Vol. 176, The American Journal of Pathology. 2010. p. 2911–20. Available from: http://dx.doi.org/10.2353/ajpath.2010.091125

17. Baranwal S, Alahari SK. Molecular mechanisms controlling E-cadherin expression in breast tumor. Biochem Biophys Res Commun. 2009 Jun 19;384(1):6–11.

18. Kokkinos MI, Wafai R, Wong MK, Newgreen DF, Thompson EW, Waltham M. Vimentin and Epithelial-Mesenchymal Transition in Human Breast Tumor – Observations in vitro and in vivo [Internet]. Vol. 185, Cells Tissues Organs. 2007. p. 191–203. Available from: http://dx.doi.org/10.1159/000101320

19. Sekar D, Lakshmanan G, Mani P, Biruntha M. Methylation-dependent circulating microRNA 510 in preeclampsia patients. Hypertens Res. 2019 Oct;42(10):1647–8.

20. Princeton B, Santhakumar P, Prathap L. Awareness on Preventive Measures taken by Health Care Professionals Attending COVID-19 Patients among Dental Students. Eur J Dent. 2020 Dec;14(S 01):S105–9.

21. Logeshwari R, Rama Parvathy L. Generating logistic chaotic sequence using geometric pattern to decompose and recombine the pixel values. Multimed Tools Appl. 2020 Aug;79(31-32):22375–88.

22. Johnson J, Lakshmanan G, M B, R M V, Kalimuthu K, Sekar D. Computational identification of MiRNA-7110 from pulmonary arterial hypertension (PAH) ESTs: a new microRNA that links diabetes and PAH. Hypertens Res. 2020 Apr;43(4):360–2.

23. Paramasivam A, Priyadharsini JV, Raghunandhakumar S, Elumalai P. A novel COVID-19 and its effects on cardiovascular disease. Hypertens Res. 2020 Jul;43(7):729–30.

24. Pujari GRS, Subramanian V, Rao SR. Effects of Celastrus paniculatus Willd. and Sida cordifolia Linn. in Kainic Acid Induced Hippocampus Damage in Rats. Ind J Pharm Educ. 2019 Jul 3;53(3):537–44.

25. Rajkumar KV, Lakshmanan G, Sekar D. Identification of miR-802-5p and its involvement in type 2 diabetes mellitus. World J Diabetes. 2020 Dec 15;11(12):567–71.

26. Ravisankar R, Jayaprakash P, Eswaran P, Mohanraj K, Vinitha G, Pichumani M. Synthesis, growth, optical and third-order nonlinear optical properties of glycine sodium nitrate single crystal for photonic device applications. J Mater Sci: Mater Electron. 2020 Oct;31(20):17320–31.

27. Wu S, Rajeshkumar S, Madasamy M, Mahendran V. Green synthesis of copper nanoparticles using Cissus vitiginea and its antioxidant and antibacterial activity against urinary tract infection pathogens. Artif Cells Nanomed Biotechnol. 2020 Dec;48(1):1153–8.

28. Vikneshan M, Saravanakumar R, Mangaiyarkarasi R, Rajeshkumar S, Samuel SR, Suganya M, et al. Algal biomass as a source for novel oral nano-antimicrobial agent. Saudi J Biol Sci. 2020 Dec;27(12):3753–8.

29. Alharbi KS, Fuloria NK, Fuloria S, Rahman SB, Al-Malki WH, Javed Shaikh MA, et al. Nuclear factor-kappa B and its role in inflammatory lung disease. Chem Biol Interact. 2021 Aug 25;345:109568.

30. Rao SK, Kalai Priya A, Manjunath Kamath S, Karthick P, Renganathan B, Anuraj S, et al. Unequivocal evidence of enhanced room temperature sensing properties of clad modified Nd doped mullite Bi2Fe4O9 in fiber optic gas sensor [Internet]. Vol. 838, Journal of Alloys and Compounds. 2020. p. 155603. Available from: http://dx.doi.org/10.1016/j.jallcom.2020.155603

31. Bhavikatti SK, Karobari MI, Zainuddin SLA, Marya A, Nadaf SJ, Sawant VJ, et al. Investigating the Antioxidant and Cytocompatibility of Mimusops elengi Linn Extract over Human Gingival Fibroblast Cells. Int J Environ Res Public Health [Internet]. 2021 Jul 4;18(13). Available from: http://dx.doi.org/10.3390/ijerph18137162

32. Marya A, Karobari MI, Selvaraj S, Adil AH, Assiry AA, Rabaan AA, et al. Risk Perception of SARS-CoV-2 Infection and Implementation of Various Protective Measures by Dentists Across Various Countries. Int J Environ Res Public Health [Internet]. 2021 May 29;18(11). Available from: http://dx.doi.org/10.3390/ijerph18115848

33. Barma MD, Muthupandiyan I, Samuel SR, Amaechi BT. Inhibition of Streptococcus mutans, antioxidant property and cytotoxicity of novel nano-zinc oxide varnish. Arch Oral Biol. 2021 Jun;126:105132.

34. Vijayashree Priyadharsini J. In silico validation of the non-antibiotic drugs acetaminophen and ibuprofen as antibacterial agents against red complex pathogens. J Periodontol. 2019 Dec;90(12):1441–8.

35. Priyadharsini JV, Vijayashree Priyadharsini J, Smiline Girija AS, Paramasivam A. In silico analysis of virulence genes in an emerging dental pathogen A. baumannii and related species [Internet]. Vol. 94, Archives of Oral Biology. 2018. p. 93–8. Available from: http://dx.doi.org/10.1016/j.archoralbio.2018.07.001

36. Uma Maheswari TN, Nivedhitha MS, Ramani P. Expression profile of salivary micro RNA-21 and 31 in oral potentially malignant disorders. Braz Oral Res. 2020 Feb 10;34:e002.

37. Gudipaneni RK, Alam MK, Patil SR, Karobari MI. Measurement of the Maximum Occlusal Bite Force and its Relation to the Caries Spectrum of First Permanent Molars in Early Permanent Dentition. J Clin Pediatr Dent. 2020 Dec 1;44(6):423–8.

38. Chaturvedula BB, Muthukrishnan A, Bhuvaraghan A, Sandler J, Thiruvenkatachari B. Dens invaginatus: a review and orthodontic implications. Br Dent J. 2021 Mar;230(6):345–50.

39. Berman HM, Westbrook J, Feng Z, Gilliland G, Bhat TN, Weissig H, et al. The Protein Data Bank, 1999– [Internet]. International Tables for Crystallography. 2006. p. 675–84. Available from: http://dx.doi.org/10.1107/97809553602060000722

40. Schneidman-Duhovny D, Inbar Y, Polak V, Shatsky M, Halperin I, Benyamini H, et al. Taking geometry to its edge: Fast unbound rigid (and hinge-bent) docking [Internet]. Vol. 52, Proteins: Structure, Function, and Genetics. 2003. p. 107–12. Available from: http://dx.doi.org/10.1002/prot.10397

41. Schiffrin B, Radford SE, Brockwell DJ, Calabrese AN. PyXlinkViewer: a flexible tool for visualisation of protein chemical crosslinking data within the PyMOL molecular graphics system [Internet]. Available from: http://dx.doi.org/10.1101/2020.06.16.154773

42. P. Rajarajeswaran RV. Exercise in tumor. Indian J Med Paediatr Oncol. 2009;30(2):61.

43. Karihtala P, Auvinen P, Kauppila S, Haapasaari K-M, Jukkola-Vuorinen A, Soini Y. Vimentin, zeb1 and Sip1 are up-regulated in triple-negative and basal-like breast tumors: association with an aggressive tumour phenotype. Breast Tumor Res Treat. 2013 Feb;138(1):81–90.

44. Francart M-E, Vanwynsberghe AM, Lambert J, Bourcy M, Genna A, Ancel J, et al. Vimentin prevents a miR-dependent negative regulation of tissue factor mRNA during epithelial–mesenchymal transitions and facilitates early metastasis [Internet]. Vol. 39, Oncogene. 2020. p. 3680–92. Available from: http://dx.doi.org/10.1038/s41388-020-1244-1

45. Lento W, Ito T, Zhao C, Harris JR, Huang W, Jiang C, et al. Loss of β-catenin triggers oxidative stress and impairs hematopoietic regeneration. Genes Dev [Internet]. 2014 May 1 [cited 2021 Mar 12];28(9). Available from: https://pubmed.ncbi.nlm.nih.gov/24788518/

46. Essers MAG, de Vries-Smits LMM, Barker N, Polderman PE, Burgering BMT, Korswagen HC. Functional Interaction Between ß-Catenin and FOXO in Oxidative Stress Signaling. Science. 2005 May 20;308(5725):1181–4.

47. Wang Z, Zhang H, Hou J, Niu J, Ma Z, Zhao H, et al. Clinical implications of β-catenin protein expression in breast tumor. Int J Clin Exp Pathol. 2015;8(11):14989.

48. Oka H, Shiozaki H, Kobayashi K, Inoue M, Tahara H, Kobayashi T, et al. Expression of E-cadherin cell adhesion molecules in human breast tumor tissues and its relationship to metastasis. Tumor Res. 1993 Apr 1;53(7):1696–701.

49. Pierceall WE, Woodard AS, Morrow JS, Rimm D, Fearon ER. Frequent alterations in E-cadherin and alpha- and beta-catenin expression in human breast tumor cell lines. Oncogene [Internet]. 1995 Oct 5 [cited 2021 Mar 12];11(7). Available from: https://pubmed.ncbi.nlm.nih.gov/7478552/

50. Cagan R, Meyer P. Rethinking tumor: current challenges and opportunities in tumor research. Dis Model Mech [Internet]. 2017 Apr 1 [cited 2021 Mar 12];10(4). Available from: https://pubmed.ncbi.nlm.nih.gov/28381596/