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Molecular Docking Analysis on The Identification The Activation of Endogenous Beta Endorphin on The Regulation of Neuro Inflammatory Signalling Relevant To Inflammatory Mediated Cancer

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ABSTRACT

BACKGROUND: Beta-endorphin is an opioid neuropeptide which has an important role in paracrine communication of brain messages. Beta-endorphin is the missing link between the neuron and the wall of the arteriole, it is a fundamental neurotransmitter.When you exercise, a chemical is released by the body called beta-endorphins which interact with the receptors in your brain to reduce the perception of pain.

AIM: To analyse the beta endorphin interaction with inflammatory markers and also to identify the activation of endogenous beta-endorphin on the regulation of neuro inflammatory signalling.

MATERIALS AND METHODS: The molecular docking analysis is a bioinformatic study conducted in a private dental college. The endogenous substance Beta-endorphin which is secreted after exercise is used as a target protein.The interaction of beta-endorphin with the proteins relevant to inflammatory mediated cancer namely IL-6,TNF-alpha, MMP are included for docking analysis. The protein structure is retrieved using protein data bank, protein protein docking done using patch dock server followed by visualization of protein-protein interaction using pymol.

RESULTS: The representation of beta endorphin with IL-6, TNF-alpha, MMP complex showed good shape complementarity. From that we identified that the amino acids THR-16, LEU-17, PHE-18, LYS-19, ASN-20, ALA-21, ILE-22, LYS-24, ALA-26, TYR-27, GLY-30 AND GLU-31 residues of Beta endorphin mostly involved in the interaction wilt IL-6, TNF-alpha and MMP. These residues are also present in the active site region of beta-endorphin.

CONCLUSION: From the results of the analysis and within the limitations of the study it can be concludeb the role of exercise induced beta endorphin may act as a regulator of IL-6, TNF- alpha signalling in inflammatory mediated cancer.

Keywords: *Cancer; beta-endorphin;TNF-alpha; IL-6; MMP; inflammatory mediated cancer;innovative method.*

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1. INTRODUCTION

There are two types of inflammation related to cancer 1) precancerous inflammation lesions 2) inflammation present in all cancer tissues including no precancerous inflammation lesions. There are two pathways: extrinsic mechanism, intrinsic mechanism. Inflammation is always associated with cancer. Intrinsic means cancer elicited inflammation through cancer initiating mutations. Extrinsic means bacterial and viral infections, tobacco smoking(1). Exercise induced modulation of the immune system which tumour initiation and progression. Exercise modulates the number of cell innate and adaptive immunity(2).

Chronic inflammation is malignant cellulase transformation. Exercise and inflammation in cancer favorably alter numerous components of the immune system, modulating tumorigenesis(3).Precancerous inflammation increases genetic and epigenetic damage, aberrant oncogenic signalling induces inflammation and studying inflammation is RET(4). Inflammation and development progression of cancer increase body's response and tissue damage mechanism and mutagenic potential of inflammation cancer cachexia causes muscle wasting and mitochondrial dysfunction and mechanism associated with cancer(5).

The experience from our previous studies (6) (7,8) (7)(9)(10)(11)(12)(10,12)(13)(14) (15) have led us to focus on the current topic.

Beta-endorphins are abundant and stored in the anterior pituitary gland. Neurohormones induce inflammatory mediators such as IL-6,TNF-alpha activate key transcription factors which promote angiogenesis, immunosuppressant and metastasis leads to cancer(16). Endorphins are endogenous morphine which are responsible for the relaxed psychological state creation known as "runners high". Beta endorphin cell treated animals showed decrease in inflammatory cytokines in inflammatory tumour milieu, thus inhibiting tumour growth. Exercise can be one of the most important cancer treatments(17). Our team has extensive knowledge and research experience that has translate into high quality publications (18–25),(26),(27),(28),(29,30),(31),(32),(33–37) Aim of the study is to analyse the beta endorphin interaction with inflammatory markers and also to identify the activation of endogenous beta-endorphin on the regulation of neuro inflammatory signalling.

2. MATERIALS AND METHODS

Retrieval of Target proteins structures from Protein data bank
In order to study the mechanism of interaction between Beta endorphin with IL-6, TNF-alpha, MMP proteins, the three dimensional structures were downloaded from Protein Data Bank using the respective ids (Pdb ids: Beta endorphin- 6TUP, IL-6- 1ALU;TNF-alpha -2AZ5; MMP-4AU0) (38)

Protein-Protein Docking
A geometry-based molecular docking algorithm called Patch Dock (http://bioinfo3d.cs.tau.ac.il/PatchDock) [2,3] was used to study the interaction between Beta endorphin with IL-6, TNF-alpha, MMP proteins. The server of the Patch Dock calculates docked transformations that produce strong complementarity of molecular shape. The algorithm splits the molecules' Connolly dot surface representation into concave, convex, and flat patches. 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. Here the color intensity for interactions was visualized clearly and exported for results **[4**]. Pdbsum was used to identify the types of interaction occurring between Beta endorphins with IL-6, TNF-alpha, MMP proteins**.**

3. RESULTS

The three dimensional structure of these proteins were separately uploaded in the patch server. The top 20 docked complexes were listed once the docking was completed. Among them based on the scoring parameters best one docked complexes of each protein were selected for further analysis. This docked complex was visualized by using pymol software. From that we identified that the amino acids THR-16, LEU-17, PHE-18, LYS-19, ASN-20, ALA-21, ILE-22, LYS-24, ALA-26, TYR-27, GLY-30 AND GLU-31 residues of Beta endorphin mostly involved in the interaction wilt IL-6, TNF-alpha and MMP. These residues are also present in the active site region of beta-endorphin. So it was confirmed that these proteins IL-6, TNF-alpha and MMP might activate the Beta-endorphin and play a main role in the regulation of neuroinflammatory signaling.(Table 1)

TABLE 1: Molecular docking results of beta endorphin with IL-6, TNF-alpha and MMP proteins.

PROTEIN NAME	SCORE	ACE (atomic contact energy)
IL-6	12682	-397.34
TNF-alpha	16966	-424.00
MMP	16108	-332.40

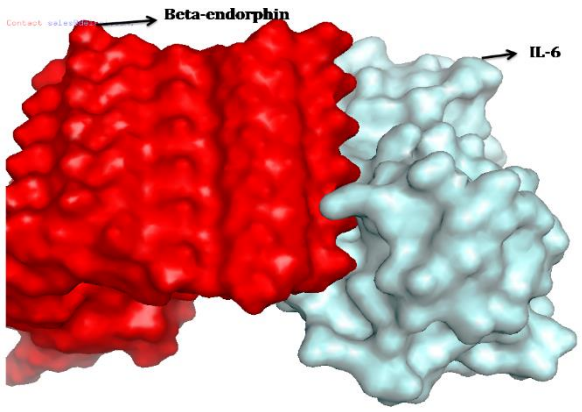

Figure 1: The figure represents the protein -protein interaction between the IL-6 and Beta endorphin.

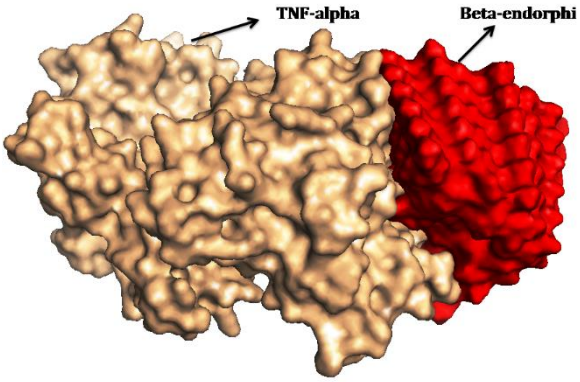

Figure 2: The figure represents the protein protein interaction between TNF-alpha and Betaendorphin.

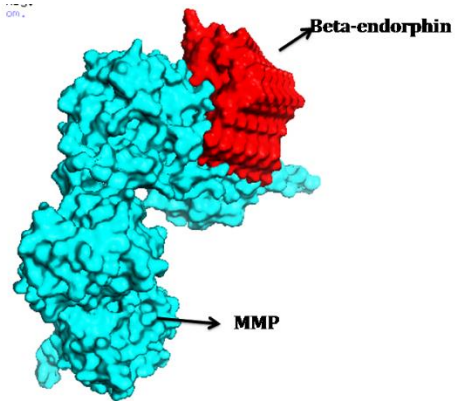

Figure 3: The figure represents the protein protein interaction between MMP and beta-endorphin.

4. DISCUSSION

The present study is evidence that exercise-induced endogenous beta endorphin may act as a protective compound against inflammatory mediated cancer.There is a positive interaction between the beta endorphin and IL-6, TNF-alpha and MMP. Immune cells secrete various interleukins which regulate the cell growth and motility. The important role is stimulating immune responses, such as inflammation(39). Tumour necrosis factor is an extraordinary pleiotropic cytokine with a role in immune homeostasis and inflammation. TNF-alpha causes inflammation by triggering the production of immune system molecules like IL-1 and IL-6.Tumours utilize MMPs to cleave chemokines by preventing inflammatory cell chemotaxis. The basic building blocks of life formed by amino acids are proteins. The amino acids are gene-coded and form peptides, P peptides are further formed proteins, and living tissues are formed by proteins. In addition, proteins also play a key role in biological processes, such as catalytic reactions, molecular transmission, immune reactions to different pathogens, and cell-to-cell signal transduction. The biological activities described above are regulated by protein complexes, which are usually mediated by protein-protein interactions (PPIs). "In cells, PPIs form a dynamic network with a concept called "interactome". In physiological and pathological processes, the interactome has an important function, including signal transduction, cell proliferation, development, differentiation, and apoptosis, etc. Therefore, many human illnesses, such as cancer, infectious disorders and neurodegenerative diseases, are linked with aberrant PPIs. Since enzymes, ion channels, or receptors are typically the classic drug targets, PPIs suggest new possible therapeutic targets. PPIs have gained growing recognition in recent years and have become appealing targets. Recent studies suggest that PPIs have tremendous potential as an intervention target for new refractory disease therapy, and their control is generally regarded as a promising drug development technique. Identification of Protein –protein complex in experimental methods is time consuming and cost effective. Nowadays so many computational methods are available to identify the interaction between the two protein targets. Patch dock is one of the docking servers commonly used for protein-protein docking. It is a geometry-based molecular docking algorithm. It is aimed at finding docking transformations that yield good molecular shape complementarity. Such transformations, when applied, induce both wide interface areas and small amounts of steric clashes. In this study, we studied the interaction between Beta endorphin with IL-6, TNF-alpha, and MMP proteins patch dock

Beta endorphin is the most abundant endorphin, it is more potent than morphine. It acts as a precursor of POMC which is synthesized and secreted in the anterior pituitary gland. Mechanisms like analgesic activity, anti inflammatory activity. Chronic psychological stress is the predisposing factor for cancer with depression, fear, hatred release of CRH from hypothalamus. Through the SNS activity of ANS release neurohormones like cortisol, ACTH, and noradrenaline(40,41). Neurohormones which induce inflammatory mediators IL-6 which activate the key transcription factors like survival, invasion, metastasis it leads to cancer. Beta endorphin inhibits the chronic psychological stress mediated inhibition of HPA-axis through ANS. These neurohormones activate mediators such as IL-6 activate STAT-3 transcription factors tumour progression(40).

Biochemical and immunological characteristics measured by immuno enzymes. Study revealed inverse correlation between beta endorphin levels and those of leptin, TNF-alpha. Endorphins are endogenous morphine that act as holistic preventive therapeutic, promotive and palliative treatment of diseases like cancer and infectious diseases. TNF alpha inhibits the tyrosine phosphatase protein activity which leads to reduced production of MHC class 1 antigen of cell surface tumour immune invasion. TNF-alpha protumorigenic cytokines. Beta endorphin cell treated animals showed an increase in anti-inflammatory cytokines such as (IL-8, IL-12) and decreased inflammatory cytokines (TNF -alpha)(42). Thus inhibiting tumour growth and transformation stress is one of the important predisposing factors for cancer by releasing cortisol and catecholamines induced inflammatory mediators such as IL-1, IL-6, TNF-alpha(43).

The normal regulatory T cells are involved in self tolerance and immune homeostasis. Proteolytic enzymes such as MMP's-2,9 are involved in tissue damage and all these changes lead to tumour progression, Invasion and metastasis(44) . Later results in tissue damage and cellulase changes by activating matrix metalloproteinases leads to autoimmune diseases while their upregulation facilitates aging and cancer; they are essential to epidermal differentiation and the prevention of wound scars(45). MMP are produced by many cells including lymphocytes and granulocytes.As it is a computer based study, feature researches should be done in invitro and in vivo

5. CONCLUSION

From the results of the analysis and within the limitations of the study it can be concluded that the role of exercise induced endogenous beta endorphin may act as a regulator of IL-6, TNF- alpha signalling in inflammatory mediated cancer.

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CONFLICT OF INTEREST:
All the authors declare that there was no conflict of interest in the present study.

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