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A Review: Role of Dipeptidyl Peptidase 4 (DPP4) Enzyme Levels in Severity of Diseases

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Abstract

This literature review article discusses the latest developments in the mechanism and role of dipeptidyl peptidase 4 (DPP4) actions in the severity of diseases, particularly in women with polycystic ovary syndrome PCOS, coronavirus disease 2019, autoimmune thyroid diseases, diabetic patients, cardiovascular disease, cancer, and clarified the functions of DPP4 inhibitors in variety of diseases.

Recent scientists have revealed experimental, preclinical, and clinical data for DPP4 inhibitors, which demonstrate the enzyme's functional role in illness treatment or severity reduction. Interestingly, DPP4 actions are a complicated mechanism, with numbers of metabolic pathways engaged depending on the kind and severity of the disease. DPP4 is one of the serine proteolytic enzymes that function via multiple biochemical processes mediators in a variety of endocrinological tissues, including the effect on the regulation of the incretin hormones, play a major role in regulate insulin secretion based on blood glucose. Interestingly, current experimental and preclinical findings suggest that DPP4 inhibitors may also maintain glycemic control in PCOS disease development, have beneficial effects in cancer, and prevent cardiovascular disease in T2DM. In this present review, we summarized the impacts of DPP4 inhibitors therapies based on the latest studies, as well as the possible mechanism of action and the effects of DPP4 enzyme levels and activity with its relation to disease progression.

مراجعة: دور مستويات إنزيم (DPP4) في زيادة حدة الأمراض

فرقد عبد الجواد البيضاني، زينة عبد الأمير مهدي، نور عبد الأمير عودة

الخلاصة

تناقش هذه المقالة البحثية أحدث التطورات في آلية العمل والدور الفعال لأنزيم ديبتيديل ببتيداز النوع الرابع في ازدياد حدة الأمراض، وتطرقنا في هذه المقالة لعديد من الامراض ذات الصلة بعمل هذا الأنزيم ومنها النساء المصابات بمتلازمة تكيس المبايض، ومرض فيروس كورونا 2019، وأمراض الغدة الدرقية المناعية الذاتية، ومرضى السكري، وأمراض القلب والأوعية الدموية، والسرطان، وقد تطرقنا ايضا الى توضيح وظائف مثبطات الانزيم ديبتيديل ببتيداز في أمراض مختلفة ودورها الفعال. حيث كشف العلماء مؤخرًا عن بيانات تجريبية وسريرية وما قبل السريرية لمثبطات ديبتيديل ببتيداز، والتي توضح الدور الوظيفي للإنزيم في علاج المرض أو تقليل شدته. ومن المثير للاهتمام أن اليه العمل لهذا الانزيم تعتبر آلية معقدة، حيث يشارك في عدد من المسارات الأيضية اعتمادًا على نوع وحدة المرض. يعتبر ديبتيديل ببتيداز هو أحد الإنزيمات البروتينية السيرينية التي تعمل عبر عمليات كيميائية حيوية متعددة في مجموعة متنوعة من الأنسجة الغدد الصماء، بما في ذلك التأثير على تنظيم هرمونات إنكريتين، وتلعب دورًا رئيسيًا في تنظيم إفراز الأنسولين بناءً على نسبة الجلوكوز في الدم. ومن المثير للاهتمام أن النتائج التجريبية والسريرية الحالية تشير إلى أن مثبطات ديبتيديل ببتيداز قد تحافظ أيضًا على التحكم في نسبة السكر في الدم في تطور مرض متلازمة تكيس المبايض، ولها تأثيرات مفيدة في السرطان، وتمنع أمراض القلب والأوعية الدموية في مرض السكري من النوع 2. في هذه المقالة الحالية، قمنا بتلخيص اليه عمل الانزيم في المرض وتأثير العلاجات بالمثبطات لهذا الانزيم ديبتيديل ببتيداز بناءً على أحدث الدراسات، بالإضافة إلى آلية العمل المحتملة وتأثيرات مستويات إنزيم ديبتيديل ببتيداز ونشاطه وعلاقته بتطور المرض.

الكلمات المفتاحية : انزيم ديبتيديل ببتيداز , حدة الامراض , وظيفة الانزيمات, متلازمة تكيس المبايض

1. Introduction

Dipeptidyl peptidase 4 DPP4 is a type II integral membrane protein. Containing a cytoplasmic tail of compressing six amino acids. It acts as a dimer with a molecular weight of monomer soluble Dipeptidyl peptidase 4 sDPP4, a soluble enzyme structure, identified through the fluids of human body. sDPP4 is limited to the intracellular region, and serum sDPP4 begins at residues 39 Serine amino acid (Durinx et al., 2000), with the enzyme commission number EC3.4.14. and 766 amino acids. In additional, there are nine sorts of DPPs: DPP1, 2, 3, 4, and DPP6 to10(Gao et al., 2015) .

DPP1, actually also referred to as Cathepsin C. Is a cellular lysosomes enzyme and exocysteine peptidase; acts in two forms, namely aminopeptidase and carboxypeptidase. related to the peptidase C1 class that works as a major activator to various serine proteases in immune and inflammatory cells(Zhong et al., 2013). This enzyme is presents in many body tissues comprise adipocytes, skeletal myocytes, vascular smooth muscle cells, and cell derived of bone marrow(Durinx et al., 2000).

DPP2 is thought to play an essential role in the differentiation of cells and the destruction of interstitial matrix of proteins, which includes collagen. Membrane bound aminopeptidase enzyme DPP4 travels in bloodstream and performs a variety of roles, including cells nutrition, the metabolism, and the immunological and hormonal systems(Casrouge et al., 2018). DPP3 is a cytoplasmic zinc-dependent aminopeptidase whose activity is linked to protein metabolism, blood pressure management, pain relief, and promising biomarker of bone fragility in postmenopausal women(Meng et al., 2024). DPP4 is found on the surfaces of many different types of human body cells. Indeed, DPP4 exopeptidase preferentially acts as cleaves the N-terminal of dipeptides in a wide range of substrates, including the cytokines, growth regulators, the neuropeptides, and hormones, specifically gastric inhibitory peptide, and regulates inflammation via enzymatic cleavage of immunoregulatory polypeptide and its soluble form sDPP4, which interacts directly with immune cells(Maes et al., 2007). Whereas the DPP6 different voltage-gated potassium channels are controlled by this membrane protein, which also controls the biophysical properties of the cell(Higashijima et al., 2015; Prajapati and Chauhan, 2011). DPP7, an exopeptidase, its role inhibits coagulation and thus may stimulate hemorrhages and immune cell evasion(Wada et al., 1992) DPP8 main function in immune system(Hack et al., 2017; Qi et al., 2003), whereas DPP9 inhibits the inflammation and protects against auto-inflammatory disorders(Donzelli et al., 2023). Membrane protein DPP10 has infrequent protease activity in studies. On the other hand, it has been noted that it binds to human body nervous system voltage-gated potassium channels, regulating their electrical characteristics and expression(Abbott et al., 2000). Current research found DPP4 an enzyme broadly found in the circulatory system, comprising cells of endothelial, macrophages, heart muscle cells, mural cells, the cells of valve interstitial, and various types of cells(Huang et al., 2022), indicating that it might have a role in the development and severity of numerous conditions. Our review attempted to elucidate some of the roles of this human body enzyme.

2. Methodology

A comprehensive review articles was executed by electronic searches of MEDLINE, PubMed, Google Scholar, Web of Science and Scopus databases by using several keywords for searching related to “DPP4”, “Diabetic”, “severity of diseases”, “PCOS”, “Cancer”, “thyroid diseases” and “COVID-19” in the titles of articles and keywords of researches. the experimental, preclinical, and clinical data for DPP4 enzyme as the main source to the studies that included in this

literature review article, and the researches that inform various results and studies of disease severity that correlation with this enzyme levels, activity, and used inhibition therapy for DPP4 enzyme.

3. Structure and Function of DPP4

DPP4 is a serine peptidase glycoprotein is sometimes referred to as T-cell activation antigen CD26 or deaminase adenosine binding peptide [ADBP), was described for the first time in 1966 a 110 kDa(Bezerra et al., 2015; Zhong et al., 2018). DPP4 gene encodes a protein that found on the surfaces and inside verity body cell, soluble structure of this enzyme found broadly in the body fluids. DPP4 involved in immunological control, signals transformation and apoptotic process of the cells. DPP4 enzyme in both forms considered the transmembrane glycoprotein type II, although a soluble structure of this enzyme presents in the circulating blood plasma and other physiological fluids but missing inside of cells and transmembrane components, thus DPP4 exists in both bound to the membrane and the soluble counterparts. In additionally, DPP4 enzyme secreted through specialized protein breakdown via a non-classical secretion mechanism from the cell membrane, producing a soluble structure with comparable levels of activity of enzymes(Chen et al., 2022). A serine exopeptidase i.e., DPP4 enzyme will breaks down the N-terminus of polypeptides to release the X-proline or X-alanine dipeptides, it may be able to split a dipeptide following a proline residue in the location before the last N-terminal position. Indeed, majority of proteases cannot cleave peptide bonds with proline, a cyclic amino acid, therefore an N-terminal of X-proline "shields" numerous bio peptides(Valverde-Pozo et al., 2023). Furthermore, to its membrane form, DPP4 can be found in plasma with a soluble form sDpp4, which refers as enzymes of extracellular region that is thought to have been broken from the cell surface(Nargis and Chakrabarti, 2018). DPP4's actions are dependent additionally on its ability to catalyze as a peptidase, but also on its internal structure, due to the fact that it has the ability to bind to a wide range of proteins, including fibronectin, collagen, chemokine receptor CXCR4, tyrosine phosphatase CD45, and some viral proteins like the gp120 envelope protein of the human immunodeficiency virus (HIV). As such, it impacts numerous biological processes, such as attaching to the cell matrix, proliferating, and T-cell maturation and function(Nargis and Chakrabarti, 2018). Factors including aging and food with a large amount of fat were responsible for an increase in plasma DPP4 activity, which was also associated with an increase in total body weight or fat mass(Matteucci and Giampietro, 2009), DPP4 enzyme is widely produced by numerous cell types, such as immune cells including T cells, B cells, and monocytes, in additional on endothelium and epithelia. On the human polarizing epithelium's terminal surfaces, DPP4 is highly expressed in organs including the lung, hepatocyte, pancreatic cells, stomach, and kidney tubules. DPP4 enzyme is also present on the interior surfaces of capillary endothelial cells as shows in Fig.1(Mon et al., 2022).

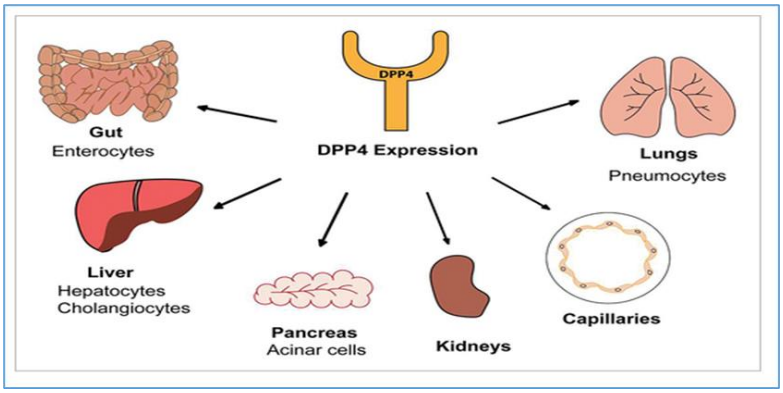

Figure 1: The Cite of DPP4 Expression in Human Body(Mon et al., 2022).

Nevertheless, it is unclear where sDPP4 comes from or how it is released. Adipocytes, lymphocytes, Bone marrow-derived mesenchymal stem cells, cells which found in the walls of arteries and veins, and musculoskeletal cells are among the few recognized sources(Zhong et al., 2018). Implying that changes in DPP-4 expression and activity might participate in the pathogenesis of autoimmune diseases. In this review article comprising focusing on function and roles of DPP4 enzyme in diseases:

4. DPP4 Levels in Women with Poly Cystic Ovary PCOS

Poly cystic ovary PCOS is defined as hyperandrogenism, menstrual abnormalities, and different size cysts in the ovaries, albeit there are significant variances between people. Adolescents with this syndrome are more likely to have comorbid conditions such mental, cardiovascular, endometrial dysplasia, diabetes type 2, obesity, and infertility(Varin et al., 2019), as a compensatory response to the absence of ovulation, PCOS is characterized by an increased level of luteinizing hormone, or LH, to follicle stimulating hormone, also known as FSH. This leads to increased androgen production and release from the ovaries and adrenal glands, which disrupts the menstrual cycle, however, in contrary, fat tissues start to release more estrogen as a compensate mechanism to the absence of ovulation(Bassendine et al., 2020). PCOS patients generally have glucose homeostasis disorders, insulin resistance, obesity, and more susceptible to diabetes type 2(El Hayek et al., 2016).

Insulin resistance is a result of hyperinsulinemia acts an important role in the etiology of PCOS, while higher cells sensitivity to the insulin hormone and decreased insulin hormone levels improves ovulatory function(Baskind and Balen, 2016; Glintborg et al., 2022).

As yet, the prevalent of reproduction disturbance condition i.e. PCOS has been associated to an overexpression of DPP 4 enzyme. Numerous studies have different results from blood levels, genetic and activity for this enzyme, for instance comparing the activity of the enzyme DPP 4 in women with PCOS who have insulin resistance with those who do not, and in non-PCOS controls, they found the activity in PCOS women regardless of whether it exists in high level with women in PCOS with IR, there is convincingly demonstrate that the level and activity is higher in PCOS women(Karakas, 2022; Zhao et al., 2023). PCOS treatment is primarily symptomatic and includes lifestyle modifications and special medications that depend on patient's level of PCOS(Abolghasemi et al., 2022).

During the last few decades, the study's focusing on inhibitions DPP4, elevated DPP4 enzyme levels in PCOS women patients indicate that treating by using DPP4 inhibitors could be useful(Sharma et al., n.d.). Other authors have reported that higher risk of diabetes type 2, dyslipidemia, as well as, cardiovascular illnesses correspond to polycystic ovarian syndrome PCOS. DPP4 enzyme was found in PCOS patients and showed favorable correlations with dehydroepiandrosterone sulfate, total testosterone, free testosterone, sex hormone binding globulin, and LH(Rashid et al., 2022). The results of these investigations suggested that one more feature of the metabolic abnormalities linked to PCOS may be a dysregulation of DPP4 serum levels(Öztürk et al., 2019).

5. DPP4 Relation to Coronavirus Disease 2019 - COVID-19

Coronavirus known as severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2) is the source of the coronavirus disease 2019 COVID-19 pandemic. It is very similar to SARS-CoV and Middle East respiratory syndrome MERS-CoV and leads to severe acute respiratory distress syndrome in addition to case mortality(Sharma et al., n.d.). The severity of COVID-19 illness is higher in older, obese individuals with concurrently with conditions like diabetes, hypertension, cardiovascular disease, and chronic lung disease. Coronaviruses that infect humans bind to and infect mammalian cells through host surface cellular receptors. In this sense, cellular entrance is dependent on the spikes of viral which is glycoprotein structure will be attached to a particular protease for cell membranes that functions as a receptor; The metalloprotease angiotensin-converting enzyme 2, or ACE2, is bound by SARS-CoV, while MERS-CoV employs DPP4 during invasion cells and study suggests it might involve with cellular DPP4 interaction in addition to angiotensin-converting enzyme 2. An essential protein bound to the membrane DPP4 facilitates the infiltration of viruses into target lymphocytes. DPP4 inhibitor therapy has been demonstrated in recent studies to reduce coronavirus entrance into host cells by competitive inhibition in vitro, and reduced blood DPP4 levels have been found in MERS-CoV-infected human participants as compared to healthy controls in vivo(Xu et al., 2024). The activity of DPP4 is increase when is highly severity of disease COVID-19, as well as, using the DPP4 inhibitors, also known as Gliptin in treatment of COVID-19 is a topic of research since DPP4 overexpression may be a risk factor in the severity of the condition. Interestingly, by understanding the chemistry structure and biological behavior of DPP4 enzyme, new treatments to prevent the entering of various betacoronaviruses, possibly including SARS-CoV-2, could be created(Tasnim, 2023). The authors conclude that DPP 4 upregulation may be a predictor of the severity of COVID-19 disease, which has sparked interest in gliptin therapy for COVID-19(Iacobellis, 2020; Xi et al., 2020).

6. DPP4 With Autoimmune Thyroid Diseases

Several studies report an association between blood levels and altered DPP4 activity in people with autoimmune diseases such multiple sclerosis and diabetes(Debora et al., 2022; Mora-Rodríguez et al., 2024). The most prevalent organ-specific autoimmune disorders are those that affect the thyroid (Huang et al., 2022). Graves' disease and Hashimoto's thyroiditis are the most common to the clinical manifestations of autoimmune thyroid disorders, which are distinguished by lymphocytic invasion of the thyroid parenchyma(Douros et al., 2019).

During the last several years, investigations have found that Graves' disease patients have higher serum concentrations and expression of DPP4 enzyme, as well as, hyperthyroidism and patients with Graves' disease(Bartalena et al., 2023). T lymphocytes are among the specific cell types on which DPP4 expression is restricted. Inhibiting DPP4 may help patients with Hashimoto thyroiditis by reducing inflammatory responses. When compared to the normal population

group, the thyroids of the Hashimoto thyroiditis patients had higher levels of DPP4 expression, which was primarily seen in the lymphocytes. In co-cultured thyroid cells, inhibition of lymphocyte DPP4 activity decreased the generation of inflammatory factors(Antonelli et al., 2020). Soluble DPP4 enzyme concentrations were inappropriate in patients with autoimmune thyroid disease, and lower soluble DPP4 expression could be involved in the development of thyroid illness(Chang et al., 2023). According to reports from other authors, soluble DPP4 is a diagnostic biomarker for thyroid papillary cancer and Hashimoto's thyroiditis. Thyroid nodules in patients with Hashimoto's thyroiditis and papillary thyroid carcinoma exhibit high levels of DPP4, along with elevated concentrations of soluble DPP4 in the serum. These findings demonstrate an independent risk factor predictive value of soluble DPP4 for papillary thyroid carcinoma diagnosis(Wen et al., 2024), Consequently, there was a significant connection between soluble DPP-4 levels and autoimmune thyroid disorders, Inhibiting DPP4 may help patients with Hashimoto's thyroiditis by reducing inflammatory responses(Antonelli et al., 2020). Recent research has indicated that there may be an association between reduced DPP4 expression and the advancement severity of Graves' illness and Graves' ophthalmopathy(Zhang et al., 2022). This, aberrant on other studies that mention previously. Significantly, there is association between soluble sDPP4 enzyme levels and autoimmune thyroid diseases. Acceding to the authors' reports, there is no doubt that DPP4 enzyme inhibition helps patients with thyroiditis through lowering responses to inflammatory factors.

7. DPP4 with Diabetic Patients

The problem with diabetes does not underlying only in the symptoms it causes in the short term, but its danger usually in the effects it causes in the long term, which may extend to all the body's systems and organs. DPP4 glycoprotein is effects of wide range substrates, this exopeptidase preferentially cleaves N-terminal dipeptides from these molecules including Incretin hormones, whose functions include regulates glucose metabolism by increasing insulin hormone release from pancreatic β cells while suppressing glucagon hormone release from pancreatic α cells(Zhang et al., 2023). DPP4 enzyme expression is significantly disturbance in a variety of disease states, particularly inflammation conditions such as diabetes, Glucagon-Like Peptide-1 (GLP)-1 and Glucose-dependent Insulinotropic Polypeptide (GIP), which are secreted by the gastrointestinal track's epithelial cells, are the major regulators of post-prandial insulin production because they enhance impaired insulin secretion and lower postprandial glucagon concentrations(Aso et al., 2019). GIP was the main incretin that needed to be described. When nourishment is consumed that contains carbohydrates or fat, K-cells of both the duodenum and jejunum produce this polypeptide hormone in a single physiologically active form. Its primary functions include stimulating insulin release in a manner depending on glucose and contributing in metabolism of in fat cells. It affects the proliferation properties of β cells. GLP-1, the second primary incretin hormone, is released by L-cells in gastrointestinal tract; specifically, colon and distal ileum(Sadidi et al., 2022). GLP-1 corresponds to GIP, but as opposed to GIP, its activities are better retained in diabetic type 2 patients, making it a particularly promising target for diabetic type 2 patients medication focusing(Radbakhsh et al., 2021). Actually, incretin hormone including GLP-1 and GIP are eliminated very rapidly just in a few minutes by DPP4 enzyme(Kuhre et al., 2021). This process is explained in Fig.2.

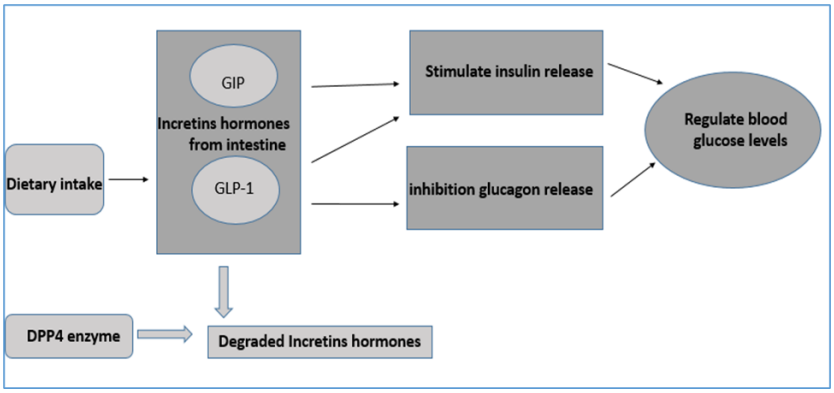

Figure 2: Diagram Illustrating the Relationship Between the Hormones of DPP4 Inhibitors and Incretins in Regulating Glucose Homeostasis(Kuhre et al., 2021).

The DPP4 inhibition; gliptin medication family's suppression first introduced for treatment T2DM in 2006 (Badran et al., 2020). In patients receiving treatment for type 2 diabetes, DPP4 inhibition has been demonstrated to be beneficial in lowering glycosylated hemoglobin (HbA1c) and fasting blood glucose (FBG). Moreover, it is known that different metalloproteases can cleave the type II transmembrane protein DPP4 off the cell membrane in a manner that is particular to certain cell types. Importantly, circulating DPP4 is elevated in obese individuals and diabetic type 2 patients, suggesting a biological connection between obesity and vascular dysfunction(Deacon, 2020).

8. DPP4 With Cardiovascular Disease

Evidence suggests that DPP4's adipokine-related activities may act as crucial role in development of cardiovascular disease. Generally, a number of risk factors, including high cholesterol levels, elevated blood pressure, and excessive triglycerides, combine over time to cause cardiovascular disease, obesity and people with diabetes type 2 is one of the Primary warning signs for heart disease and stroke(Sharma et al., 2021). It increases the pressure of blood on the walls of the arteries and can damage them by hardening them. For instance, if glucose levels are not controlled for a long time, it can damage the blood vessels and nerves that control the heart, thus, will increase risk for serious complications including cardiovascular problems, evidence suggests that DPP4's adipokine related activities may act crucial role in the progression of cardiovascular disease, the risk of subclinical atherosclerosis increased significantly with higher levels of DPP4 activity(Omran et al., 2024; Sell et al., 2013). recent research demonstrated that DPP4 has a broadly expression in the circulatory system, comprising endothelial cells, the macrophages heart muscle cells, cells of smooth muscle, cells of valves interstitial and other types of cells, indicating that it may assist in the development and progress of cardiovascular illnesses(Zheng et al., 2020). drugs treatment with pharmacological DPP4 inhibitors are very safe for using in cardiovascular cases(Zhao et al., 2021). Clinical studies demonstrated that DPP4 inhibitors have potentially beneficial in a number of such conditions of cardiovascular, heart failure, coronary atherosclerosis, calcification of aortic valves, and hypertension. DPP4 inhibitors, on the one hand, help control cardiovascular risk factors in addition to improving blood sugar regulation. In contrary, DPP4 inhibitors directly regulate the incidence and developments of cardiovascular illnesses via some different pathways(Liu et al., 2020; Sinha and Ghosal, 2019a).

9. DPP4 with Cancer

Dipeptidyl peptidase 4 DPP4 plays a critical role in immune system modulation and tumor development. In addition to interacting with extracellular matrix proteins, DPP4 enzyme carries out non enzymatic functions that regulate the physiological and pathological mechanisms underpinning adhesion of cells, migration, as well as cancer metastasis(Sinha and Ghosal, 2019a). DPP4 enzyme is over expressed in patients with malignancy. DPP4 can be found on surfaces of cancer cells and immune cells that infiltrate tumors, in additional, some normal cells also express enzyme of DPP4(Liu et al., 2019; Zheng et al., 2021). It is detected in the blood stream as a soluble form, sDPP4, as well as on immune cell surfaces as shows in the Fig.3(Al-Madany and Oudah, 2024; Chitadze et al., 2021).

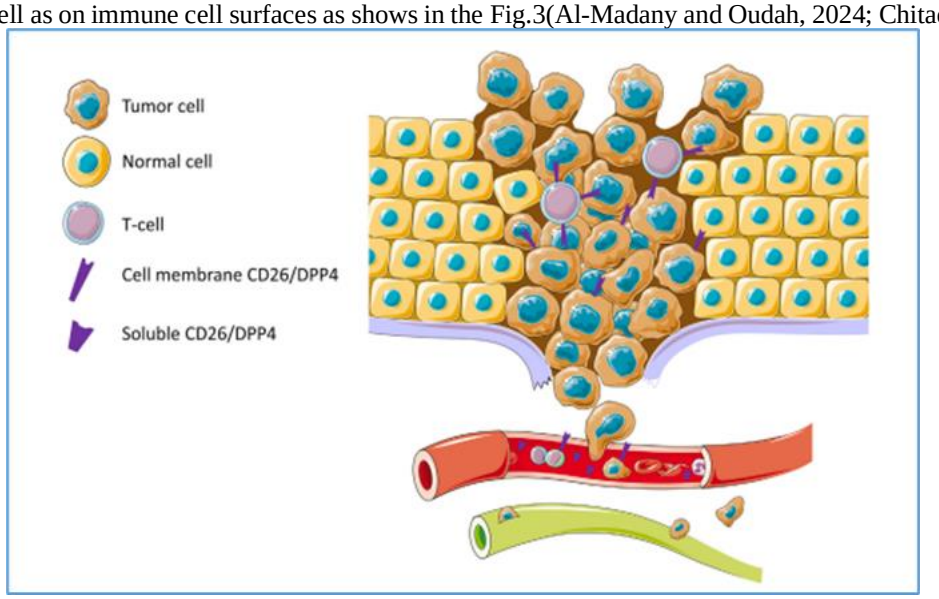

Figure 3: DPP4 is Expressed in Tumor Cell(Chitadze et al., 2021).

Used of DPP4 inhibitors increase survival results in patients with cancer of prostate but not in breast cancer or patients with pancreatic cancer(Busek et al., 2022)

As DPP4 regulates numerous pathways linked to tumors, it is believed to be a pro-tumor factor in a broad range of malignancies(Mahdi et al., 2024). DPP4 is a possible melanoma biomarker since it can also be released in a soluble form that is enzymatically active (Shah et al., 2020), variety malignancies associated with DPP4 enzyme over expression, including; the lung cancer(Matić et al., 2012), the prostate cancer(Enz et al., 2019), gastric intestinal cancer(Piatkowska-Chmiel et al., 2021), and colon cancer(Blanco-Prieto et al., 2015). Nonetheless, little is known about DPP4's role in tumor cell-microenvironment interactions and related molecular processes.

Noteworthy, the findings of the studies show there is still uncertainty regarding the safety of drugs that inhibit DPP4 in diabetic cancer patients, and additional clinical research is needed in this area(Marano et al., 2018).

10. DPP 4 Inhibitors

Dipeptidyl peptidase 4 DPP4 inhibitors, also referred to as Gliptins; a medications group act as lowering blood glucose(Beckenkamp et al., 2016), thus, lead to treat type 2 diabetes(Kawakita et al., 2021; Soare et al., 2020). Actually, can eventuate help to reducing the risk of heart attack, heart failure, and coronary heart disease and many diseases related to the cardiovascular illness(kareem et al., 2022). Their mechanism of action is regulation of the

hormones of incretin including; GLP-1 and GIP(Beckenkamp et al., 2016). These hormones; play a major role because during a meal, the small intestine secretes GLP-1and GIP into bloodstream to regulated insulin hormone secretion based on blood glucose levels(González-Rocha et al., 2023) ·GLP-1 has many roles in the human body, including stimulating insulin biosynthesis, lowering appetite, delaying stomach emptying, preventing glucagon secretion, and promoting pancreatic beta cell renewal. Interestingly, GLP-1 and GIP have extremely brief plasma half-lives because the DPP4 enzyme quickly inactivates them(Sinha and Ghosal, 2019b). Consequently, Scientists have long sought to discover DPP4 inhibitors because they illustrate the functional importance of this enzyme. Inhibition of DPP4 slows down their inactivation and thus increases their effect, which lowers plasma glucose levels, thus being useful in treatment of diabetic type 2 patients. DPP4 inhibitors may be beneficial in treatment, other disease such as PCOS women patients(Holst et al., 2021)· COVID-19(Kaur et al., 2023), cardiovascular disease(Ferjan et al., 2018), cancer (Zhang et al., 2023), and lowering risk of Parkinson's disease in T2DM(Alrouji et al., 2023).

11. Conclusion

In this review we focus on DPP4 enzyme levels and activity in diseases, Increased DPP4 activity and expression have been repeatedly linked to PCOS, autoimmune thyroid diseases, T2DM and diabetes complications, cancer, severity of COVID-19 and cardiovascular diseases. Gliptins, or DPP4 inhibitors, are a well-recognized grouping of oral antidiabetic medications used to treat type 2 diabetes. Finally, Using DPP4 inhibitors effect to treat type 2 diabetes is a relatively new therapy approach. DPP4 inhibitors are attract attention since they not only supplement but also expand existing therapy routes for treating T2DM. DPP4 inhibitors improve diabetic type 2 by delaying stomach emptying, lowering postprandial glucose levels, and inhibiting releasing of glucagon. As previously mention, they can be effectively act along with therapy.

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13. Conflicts of Interest

No conflicts of interest exist.

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