



A REVIEW ON NOTCH SIGNALING PATHWAY FOR CARDIOVASCULAR DISEASE

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ABSTRACT

Notch is a receptor that intervenes intercellular motioning through a pathway moderated over the metazoan. It is associated with cell destiny improvement and example arrangement amid advancement. The surface portrayal of Notch1 receptor sees multipotent Cardiac undeveloped cells, which are adjusted for family history obligation, while the region of receptor reflect cells with a particular slant to relocate out of the claim to fame go. The Insulin like Growth Factor - 1 receptor is imparted in a compartment of Cardiac immature microorganisms' that can be wheedled to recoup tremendous bits of hurt myocardium, while the Insulin like Growth Factor - 2 receptor is acquainted in Cardiac undifferentiated organisms with encounter apoptosis.¹ At exhibit, bio simulated claims to fame are being created by displaying nanomaterial, stages and heart settles in an undertaking to upgrade the myocardial recovery after limited necrosis. According to this exploration the cardiovascular specialty are the most essential central foundational microorganisms and the indent flagging pathway assumes a critical part in cardiovascular ailments. On the off chance that this pathway is hindered it prompts heart failure and if these pathways are actuated it prompts the widening of cardiovascular cells and aides in the heart recuperation. It helps in the recuperation after myocardial dead tissue. Along these lines the actuation of score flagging pathway demonstrates an extensive variety of utilization in the accompanying sicknesses: 1) Myocardial localized necrosis 2) Arrhythmia 3) Angina pectoris 4) Atherosclerosis.

KEYWORDS: Notch cells, Hey receptors, Cardiac stem cells, Cardiac niches, Notch receptor system.

INTRODUCTION

The establishments of the idea that the heart is a static organ unequipped for recovery was set up in the mid-1930s. A noteworthy distribution in 1930 asserted that the mitotic figures are not perceivable in human cardio myocytes which were considered as cells irreversibly pulled back from any cell cycle. This work is tested with broad investigations recorded from 1865 to 1920 in which the general thought was that cardiovascular hypotrophy was the gigantic manifestations of hypoplasia and hypotrophy of effectively introduce heart cells.^[1] The level of DNA generation in stem cores was exceptionally unimportant and this perception, together with all the powerlessness to recognize mitotic pictures in cardio myocytes, repeated the hypothesis that this grown-up heart is made out of same populace of parenchymal cells are in a perpetual condition of development arrest.^[2] However, now different quantitative estimations of myocyte mass and number and quality, performed in human heart cells gathered from number of patients who kicked the bucket as a result of decompensate heart hypertrophy and unending heart disappointment, which started to challenge this idea of myocardial science. In the late 1930s and mid 1960s, Linz Bach recorded a decent perception that, without a

heart mass comparable to or superior to 400 g, cell multiplication spoke to the overwhelming society of the expansion in cardiovascular muscle mass.^[3] These outcomes were tremendously affirmed quite a while later. In every one of these cases, hearts weighing 400 g or superior to anything that were included by a point increment in cell number and it indicated more importance than most myocyte more cell passing; this adjustment is related with the left and right ventricular myocardium. An inborn irregularity turned out to be extremely obvious. On the off chance that we accept that cardio myocytes does not have the capacity to re enter the cell cycle and repeat, contrasts in myocyte size and it is relied upon to reflect perfect recognizes in the idea of the organ. Notwithstanding, these adjustments in heart weight and cardio myocyte volume would once in a while agree testing the idea that the quantity of myocytes is an outrageous element which stays steady all through the organ lifespan.^[4] This disparity has been accounted for generally with postnatal development, myocardial maturing and cardiovascular maladies. Changes in these myocyte number and are the outcome of two interrelated systems, myocyte passing and myocyte development. This somewhat straightforward organic guideline is regularly for the most part overlooked; and this

versatility of the myocardium can't be likened to myocyte hypertrophy. This basic association of cell passing and cell reestablishment isn't extremely one of a kind to the heart.^[5] An Organ mass which is in pre-birth and postnatal life is exceptionally directed by the amicability between cell death and cell division, and deals with the amount of parenchymal cells. Inside the system with various diseases, cell hardship might be compensated by a move in size of all the surviving cells, regardless of the way this very response may get the chance to be rapidly maladaptive stuck in an unfortunate situation of hypertrophied cells to perform gainfully their beginning and end specific limit. Postnatal heart change, tirelessness action getting ready, and pregnancy are a couple of ordinary instances of physiological cardiovascular hypertrophy. The quick advancement in this myocardial mass after origination in warm blooded animals incorporates both an augmentation in size and number of cardio myocytes, yet the improvement of the coronary vasculature outstandingly outperforms the improvement of the myocyte compartment. It is outstandingly difficult to take a gander at the astounding addition in heart weight that happens postnatal with the most by and large unassuming level of cardiovascular hypertrophy progressed by component work out. Besides, there are couple of information concerning the cell start of action and all pregnancy-affected myocardial hypertrophy. Moreover, the segments which are used as a piece of the backslide of cardiovascular hypertrophy with the loss of physical embellishment, or taking after movement, isn't been bound and determined. Regardless of whether new myocytes are formed with an extensive measure of action and pregnancy and whether myocyte

disaster, myocyte rot, or both, add to the recovery of myocardial mass with stoppage of action and pregnancy are obscure.^[6] Thusly, the fundamental conclusion that can be shut is that preservation of myocardial structure depicts postnatal change, direct duration getting ready, pregnancy, and the beginning times of extended weight and volume stacking on the adult heart.^[7] This balanced "physiological" response, of course, is uncommonly concise, and developing, diligent work out, and kept up workload prompt the assistant and pragmatic appearances of "over the top" hypertrophy, designating "time" as the basic determinant of the move from physiological to masochist heart hypertrophy.^[8] A satisfactory regenerative result relies upon its essence of exogenous as well as endogenous foundational microorganisms, or on the nearness of a pool of continually cycling parenchymal cells. Quick duplicating myocytes are little in measure and mononucleotide, demonstrating that they could be gotten from: an) actuation and separation of stem/begetter cells; as well as b) multiplication of prior juvenile myocytes. At present, there is a contradiction in established researchers identified with the beginning and greatness of cell recovery happening in the mammalian heart. Naming investigations with thymidine analogs and its scientific displaying of progressively organized cell populaces have both archived and recorded a steady arrangement of new myocytes. On the other hand, a negligible commitment of cardio myogenesis has been accounted for amid its physiological maturing in different creatures and people. The verbal confrontation proceeds, and at the reality of the situation will become obvious eventually whether the capacity of the heart to restore.^[9]

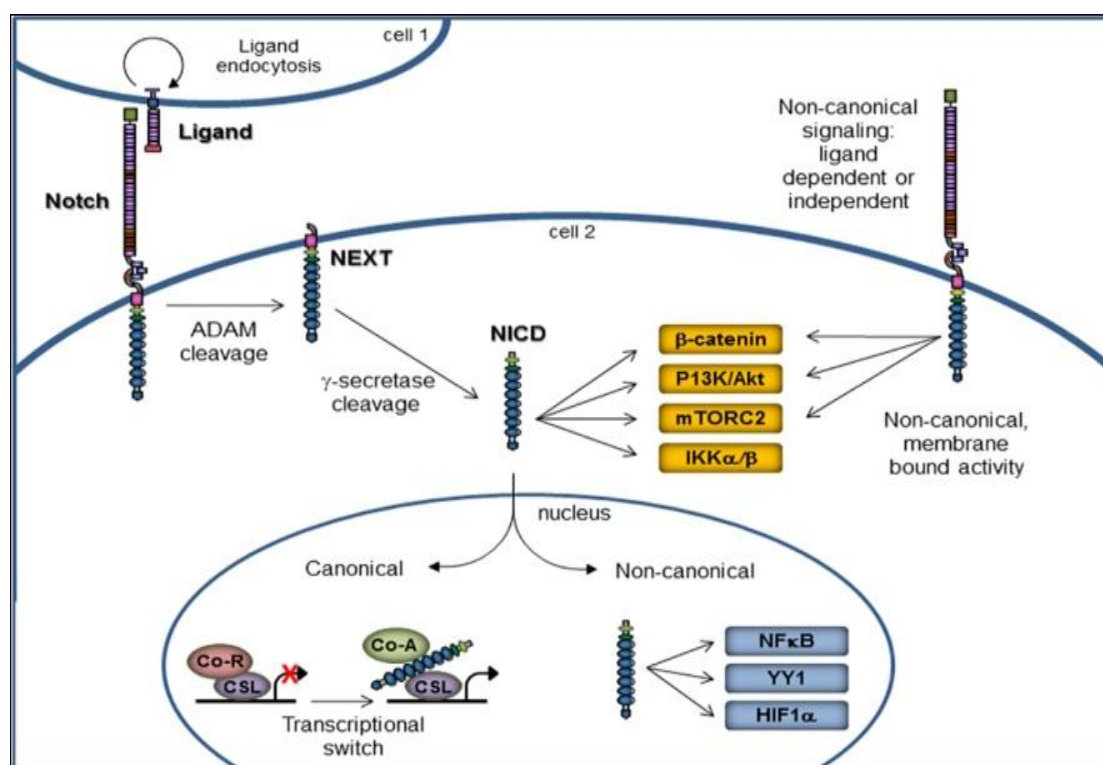


Figure 1: notch receptor, upon contact with its ligand^[24]

TISSUE SPECIFIC ADULT STEM CELLS

Hematopoietic foundational microorganisms (HSCs) were the primary tissue-particular grown-up undifferentiated organisms and has been portrayed, with the goal that these undeveloped cells in different organs are really considered additionally in view of the considerable number of attributes of these blood-framing cells. For all intents and purposes, HSCs were recognized as same cells that develop multiline age hematopoietic settlements in the spleen. Notwithstanding the essential qualities of self-restoring, clonogenicity and multi possibility, HSCs is likewise been depicted as units of a progressively confused framework, in which these undifferentiated organisms offer ascent to oligolineage ancestors which lose its self-recharging application and deliver an offspring of transient opening up cells with bound separation potential.^[10] It may likewise be troublesome now days to conceptualize that the exploration of HSCs was gotten with colossal incredulity, in respect to the one that are encompassed with the documentation of heart immature microorganisms (CSCs). In antiquated circumstances of 1970s, the likelihood that HSCs existed and kept up platelet arrangement was never acknowledged. Bone marrow undifferentiated organisms were depicted selective or cryptic and the conventions utilized for their assurance were criticized.^[11]

In vivo bioassays were made of intravenous infusion of huge bone marrow cells took after by the keeping record of provinces being delivered in the spleen. By transplanting progressively littler quantities of marrow cells, the arrangement of settlements found in the spleen was specifically relative to the span of the inoculums, while the measurements of the states is viewed as straightforwardly corresponding to the time post-immunization. Thus these outcomes were legitimate with the idea that the spleen settlements were constantly gotten from unit cells. Besides, the investigation of the single cell substance of these provinces demonstrated that all these platelet sorts were for the most part spoken to, advancing the multi possibility of the basic cell. The spleen settlement delivering cell, or CFU-S, were viewed as the characterized HSC. Arranging information, it was, uncovered that CFU-S lost one of the fundamental undifferentiated organism properties: CFU-S ought not be prepared for long haul duplication and irregular cell division. These strategies center relative irregularity. On its one side, the long haul increasing limit of bone marrow cells did not decay extraordinarily with age and, on the opposite side, the bone marrow-interceded spleen provinces were demonstrative of an "age-structure," which was found in the progressive transplantation measure and in every one of the mice that were getting perpetual irradiation.^[12] Thus how, Schofield concluded that the CFU-S is never the main HSC. The best possible HSC was resolved as a cell that, on extraction and transplantation, produces spleen settlements, yet stays in the bone marrow in conjunction with single or more cells, accomplishing a "settled tissue cell". The cell

structure accomplished by foundational microorganisms was portrayed as "specialty". In these specialties, foundational microorganisms dwell undifferentiated and is isolated uncommonly creating a little girl undeveloped cell, which stays inside the specialty immature microorganism, and its girl cell, that is similar to its original of settlement delivering cells. The last cell keeps a specific level of produced pliancy and, when required, can involve any vacant specialty, achieving a settled immature microorganism. The left CFC is handled with a limited number of divisions. At each and every division, the increasing limit is lost and its continuous development is required. After a given number of divisions, CFCs produces separated, demonstrating a cell populace that has an "age structure". At the point when these quantities of immature microorganisms is lost because of debasing jolts, physiological maturing or following sequential transplantation in following beneficiaries, a fragmented and uncalled for filling.^[28] Of the left specialties shapes. By advancing more-divisions at the season of the improvement of the CFU-S, a compensatory result for the upkeep of adjust of the body is enacted. With time, the likely number of CFU-S with long haul duplicating limit diminishes and a progressive more modest number of specialties are filled.^[13] The last exchange isn't tantamount with survival since the cells created in the last division having a less increasing limit. This trial prove demonstrated the field of the science of adjust of the body.^[14]

THE NICHE, STEM CELLS AND SUPPORTING CELLS

Undifferentiated organisms are protected in specialties, and these are kept somewhere down in the tissue for conservation from corrupting jolts. These specialties comprise of a dynamic moiety in which the direction of essential cell movement relies upon the entangled response of interior and outside controllers. Immature microorganisms are depicted by their temperament instead of by its specific qualities that they have. The complex of qualities that recognizes immature microorganisms from the old containing cell descendants has never been portrayed so far, and is given the versatility and separation of grown-up undeveloped cells, a "sternness distinguisher" can't exist. Synthetic and physical jolts control the idea of foundational microorganisms. In addition summation to cytokines and cell surface staying mixes, shear weight, oxygen strain, innervations, and components are for the most part utilized describers of undifferentiated organism activity. Cell-to-cell association and enhanced effectors animate the destiny of these cells display in the specialties, delivering self-restoration or advancing their development and recognized identification.^[15] The two directional connections between these undifferentiated organisms and required cells necessities are the highlights of the specialty, demonstrating either a tranquil or receptive state. Around couple of cases of these responses utilized as a part of the control of undeveloped cell development are appeared here. From

the earliest starting point, the limit of the specialty to ensure stemness were displayed in the *Drosophila* oriole that comprises of two germ line immature microorganisms (GSCs) involved by a progression of recognized physical cells, ensnaring Hedgehog and Wntless. The JAK-STAT pathway stresses the development of GSCs by acting in conjunction with the bone transform genic protein (BMP). The BMP2/4 homologous decapentaplegic comprise of a genuine factor that manages female GSCs by consolidating cell division. Thus, Hedgehog directs the Hippo pathway in the ovarian follicle base cells where in it ensures their undeveloped cells and separation. The specialty cells in the bone marrow research different excipients. The underwrite state is essential for hematopoietic while the developing osteolineage cell has no immediate part in controlling HSCs. The bone-shaping osteolineage cells lives in upgraded neighborhood convergences of Ca^{2+} , and the Ca^{2+} -accepting receptor improves the engraftment of HSCs.^[16]

CARDIAC NICHES AND NOTCH RECEPTOR SYSTEM

The Notch component is a formative observed intercellular additionally, intracellular framework that manages undeveloped cell predetermination. The Notch quality framework guarantees layer receptors that are sanctioned by ligand tying and proteolytic cleavage, achieving the landing of the Notch intra cytoplasm space (NICD). Together, five Notch isoforms have been depicted. Upon migration deeply, NICD develops a compound with the DNA recombinant tying protein RBP-Jk, which at that point loses its repressor limit and begins translation.^[17]

An Organ mass which is in pre-birth and postnatal life is profoundly directed by the amicability between cell destruction and cell division, and deals with the amount of parenchyma cells. Inside the strategy with various contaminations, cell setback might be compensated by a move in size of all the surviving cells, despite the way this very response may get the opportunity to be rapidly maladaptive stuck in an unfortunate situation of hypertrophied cells to perform beneficially their beginning and end specific limit. Postnatal heart change, tirelessness movement planning, and pregnancy are a couple of ordinary instances of physiological cardiovascular hypertrophy. The quick improvement in this myocardial mass after origination in warm blooded animals incorporates both an augmentation in size and number of cardio myocytes, yet the advancement of the coronary vasculature quite outperforms the improvement of the myocyte compartment. It is uncommonly difficult to take a gander at the thrilling addition in heart weight that happens postnatal with the most by and large unassuming level of cardiovascular hypertrophy progressed by component work out. Besides, there are couple of information concerning the cell start of action and all pregnancy-induced myocardial hypertrophy.

Furthermore, the segments which are used as a piece of the backslide of cardiovascular hypertrophy with the loss of physical embellishment, or taking after movement, isn't been never going to budge. Regardless of whether new myocytes are molded with an impressive measure of movement and pregnancy and whether myocyte incident, myocyte rot, or both, add to the recovery of myocardial mass with stoppage of action and pregnancy are dark. In this manner, the primary conclusion that can be shut is that protection of myocardial structure depicts postnatal change, direct continuation getting ready, pregnancy, and the beginning times of extended weight and volume stacking on the adult heart. This balanced "physiological" response, on the other hand, is extraordinarily concise, and developing, diligent work out, and kept up workload prompt the helper and useful appearances of "fanatical" hypertrophy, designating "time" as the basic determinant of the move from physiological to psychotic heart hypertrophy and Hey gathering of proteins that are transcriptional repressors of Score subordinate qualities. Score ligands are film bound proteins and Notch sanctioning associates the fate decision of one cell to that of its neighboring cell through sidelong obstruction or inductive coordinated effort. The effects of Notch on the upkeep of stemness or begin of partition are association subordinate additionally, time-subordinate. The Notch1 receptor and its ligand Jagged1 are segregating parts of the heart claim to fame. In the neonatal and adult mouse heart, most cardiovascular corners contain Notch1-positive CSCs, which are settled in the myocardial. The Notch ligand Jagged1 is imparted in heart cells and is passed on at the interface amidst CSCs and myocytes.^[18]

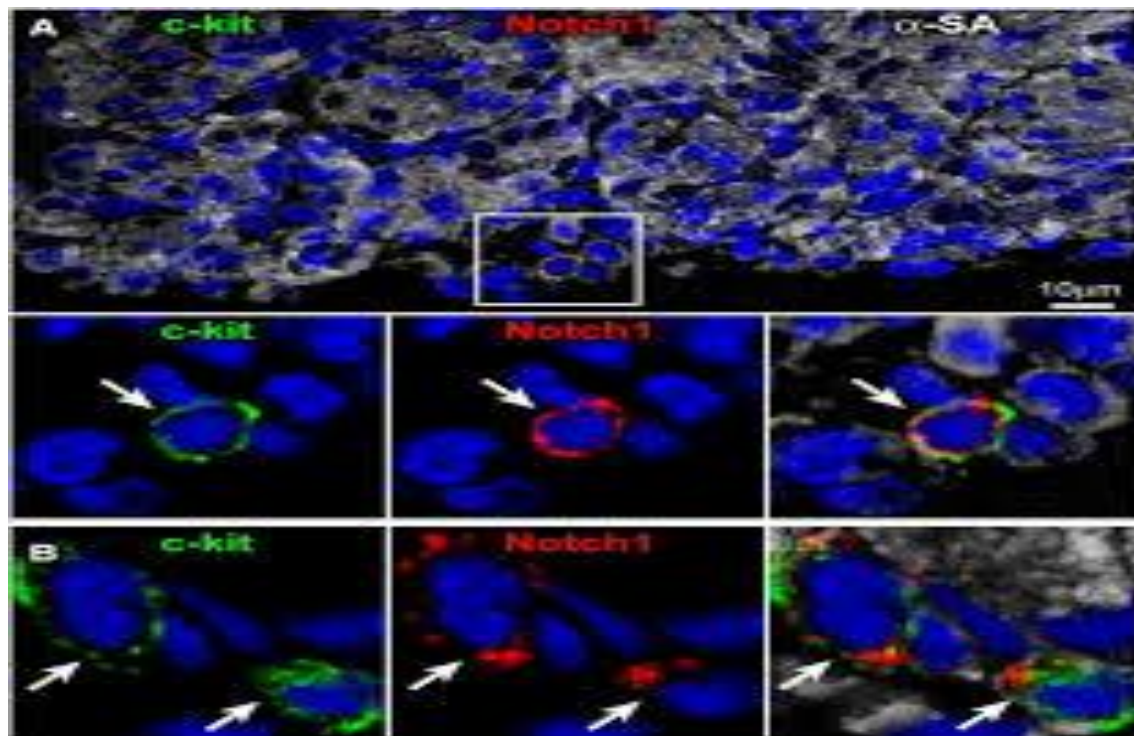


Figure 2: Notch targets in CSCs^[19]

The extracellular territory of Notch1 is kept to heredity negative CSCs, which don't express interpretation segments and markers of cell obligation. Imperatively, the Notch receptor isoforms Notch2– 4 are demonstrate just in ~10% of CSC, showing to Notch1 as the genuine constituent of the Notch pathway in CSCs inside the corners. The announcement of the Notch1 receptor on the plasma film without the nuclear translocation of its intracellular zone might be associated with a tolerant state in which the multi possibility of CSCs is secured. Strikingly, activation of the Notch1 receptor in CSCs realizes upregulation of Nkx2.5, in vitro and in vivo. Sanctioning of the heredity duty marker Nkx2.5 fail to block cell extension. Nuclear co-limitation of Nkx2.5 and Notch1 intra-cell space (N1ICD) is combined with entrance in the cell cycle and updated myocyte development.¹⁹ These recognitions reinforce the possibility that Notch1 controls the move of CSCs from the primitive energetic phenotype to the compartment of expanding myocytes. This cell grouping has the ability to detachment and at the same time independent. In undifferentiated living being controlled organs, the pool size of transient expanding cells describes the improvement store of the organ and its ability to oversee tissue homeostasis and propel the basic recover taking after harm. Actuation of the Notch1 pathway underpins the commitment of CSCs to the myocyte parentage and controls the degree of the compartment of rehashing myocytes in vitro and in vivo. This lead may identify with a model of division delay in which upheld upregulation of Notch1 hailing drags out the increasing state of CSC-deduced myocytes and foresees terminal partition and improvement catch. This limit of Notch1 incorporates the announcement of the translation part.^[20]

EPICARDIAL FOREBEAR CELL NICHES

A piece of EPDCs in the advancement of the coronary epithelium additionally, cardio myocytes is ill defined. At in the first place, the civil argument incorporating the predetermination of EPDCs was coordinated by unique revelations in chick and mouse examines. All the more starting late, the inconsistency has incorporated the comprehension of heredity following in mind lox-based reporter mouse lines. Fate mapping examines using Wt1 and Tbx18 Ce lines have suggested that endocardial progenitors contribute on a very basic level to the making myocardium in the rabbit. In any case, these disclosures were tried in perspective of the recognition that Tfx18 is conveyed in the between heart sulcus and left ventricular epicardium, even in epicardium-lacking creating lives. Likewise, the defective and inefficient recombination perceived in the Wt1 reporter lines and the endogenous endocardial Wt1 understanding has investigated the help of EPDCs in cardio cytogenesis. This data emphasizes the need to ensure the specificity of Crelox based predetermination mapping and the careful depiction of the neighborhood explanation case of the quality driving the center recombinase. Clonal looks at should be familiar with affirm the disclosures. In the adult mouse heart, the embryonic pericardial quality task is up managed. Taking after harm, the epicardium goes about as a multipotent cell source and releases trophic components that change tissue recovering, a response depicted by the reactivation of the embryonic quality project.^[22] Then once more, Wt1 positive sub-pericardial cells structure basically fibroblasts moreover, an unassuming number of myocytes that is missing for effective myocardial recuperation. Starting late, a people of epicardially-decided CPCs with mesenchymal-like

properties has been portrayed in the making and adult mouse heart. The documentation of these cells was gained by showing the in vitro state encircling unit (CFU) test, which is frequently used for the unpredictable quality of parenchymal undifferentiated living beings (MSCs) in the bone marrow. At the same time isolated cardiovascular mononuclear cells organized states in the public arena made out of fibroid cells named cardiovascular CFUfibroblasts (CFU-Fs). These cells were described as MSCs in perspective of their capacity for congenic expansion, whole deal in vitro advancement, and multiline age division. The CFU-Fs separated from embryonic and grown-up hearts express the MSC markers CD44, CD70, CD09 and CD705 and the embryonic foundational microorganism markers Oct4 and Myc. Also, CFU-Fs are sure for Sc α 1 and PDGFR α , yet are negative for hematopoietic and endothelial antigens. By using fate mapping systems, the beginning of CFU-Fs was painstakingly looked into. Mesp1 (transdermal) and Wnt1 (neural pinnacle) Ce-recombinase family following looks at revealed that CFU-Fs begin from the mesoderm however not from the neural pinnacle. Additional family line following investigations using Wt1-Cre and Gata5-Cre endocardial heritage marks found that CFU-Fs rise up out of the myocardium and epicardium.^[23]

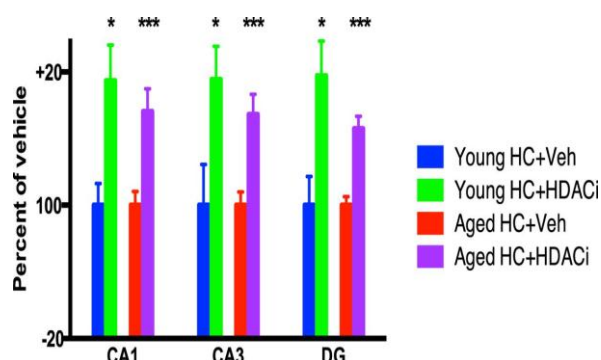


Figure 3: (Graphical representation of various receptors)^[22]

CFU-Fs rise up out of the myocardium and epicardium. Curiously, the limit of this people to convey CFU-Fs appeared to diminish in the adult heart. Predetermination mapping with My2-Ce and Nkx2.5-Cre did not check liberal amounts of CFU-Fs, which suggests that they don't rise up out of Nkx4.5 cardiovascular begetters. This putative foundational microorganism masses includes a perivascular, adventitial forte coterminous to coronary arterioles. The significance of these cells for tissue homeostasis and repair in vivo remains to be recorded.^[24, 25]

CONCLUSION

The Notch pathway has imperative capacities in embryonic advancement and undeveloped cell age. It helps in upkeep of the cardiovascular framework. Likewise its control gives potential new remedial roads to be resolved for the treatment of numerous cardiovascular infections. Though the focusing of Notch

pathway in tumor is as of now in clinical trials, the examination in the cardiovascular field to create if the focusing of receptors of the Notch pathways for cardiovascular malady will be effective in the facility is still in its outset. The joined endeavors of cardiovascular and malignancy researcher and clinical examiners will be important to effectively and securely total this undertaking.

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