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Compact Introduction of Stem Cell Association with Skin Cancer

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Stem cells are defined as specific undifferentiated cells with self-replicating ability which are common to multicellular organisms. They possess the characteristics to replace, generate and endure terminally differentiated cells. Normal adult stem cells reside in most somatic tissues, where they form the cellular basis for tissue homeostasis, maintenance, and repair, as has been shown, for example, in the skin. It has been recently suggested that oncogenic mutations and other genetic and epigenetic defects could be inherited from transformed normal stem cells, giving rise to some of the cell populations observed in many tumors. A number of hypotheses, mostly based on new experimental evidences, have been proposed to explain the presence of cancer stem cells in cancer and the implications for future therapies.

Key words: Cancer, Drug delivery, Immune system, MSC, Regenerative medicine.

Introduction

Stem cells are defined as specific undifferentiated cells having self-replicating ability which are common to multicellular organisms. They possess the characteristics to replace, generate and endure terminally differentiated cells. Stem cells depict two important features; firstly, self-renewal; a characteristic with maintenance of division of cells with undifferentiated state and secondly, their potential of in vitro and in vivo restoration of a tissue or cell into specialized type of cells.[1] Stem cells could be found in the body throughout having ability to grow up with specialized functions. These types of cells replicate to give arise cells that are either specialized cells with differentiation ability or stem cells having the ability of self-renewal, which play an essential role to made skin, blood, bone and brain cells. Thereby, stem cells have a great potential to function as repair system for damaged cells replacement. Plasticity could be defined as stem cells ability of differentiation completely into other type of area whereas, embryonic stem cells are said to be more plastic one in nature.[2] Stem cells holds the ownership of two very distinguishable properties which are of self-renewal ability into an undifferentiated state and another property to be able to differentiate into a variety of cell specialized lineages which also known as 'Potency'.[3] Potency is defined to have various levels including Pluripotency that is having characteristics to evolve into three germ layers such as endoderm, mesoderm and ectoderm, Unipotency that is the ability to transform into a single type cell and the Totipotency which enables cell into formation of all types of cells.[4]

Stem Cells Classification

Stem cells are undifferentiated cells that pose the ability of self-renew and differentiation. Hierarchy of stem cells could be displayed on the basis of their potential of evolvement into other types of cells. Embryonic stem cells are believed to have the topmost potential of differentiation characteristic. Whereas, tissue specific stem cells have limited differential potential and lastly there are types at base which are said to have very restricted capacity of differentiated cells. There are another special kind of stem cells known as Cancer stem cells which holds the ability of a tissue specific stem cell but mostly give rise to tumors involved in deterioration and metastasis. Depending on potency, stem cells are classified into multipotent totipotent, pluripotent, unipotent and oligopotent. Firstly, Totipotent stem cells could be described as the cells that are involved in the formation of an organism with entirely functional system by transforming into embryonic and extra-embryonic tissue. These are said to have restricted number of differentiated cells and only could be located before morula developmental stage.[5] Secondly Pluripotent stem cells have capacity to differentiate into endoderm, ectoderm and mesoderm germ layers. These germ layers give rise to all organs and tissues of body. Pluripotent stem cells do not attain the potential to evolve into extra-embryonic type of tissues. That's one of the reasons there are ranked below totipotent stem cells.[6] Yamanaka (2006) with his team introduced the term of

induced Pluripotent Stem Cells (iPSC) and introduced a method to acquire pluripotent stem cells. Induced Pluripotent Stem Cells bear a maximum resemblance of their equivalent uripotent parts to embryonic stem cells.[7] However Multipotent stem cells could be found in each tissue and are imitative product of three germ layers. Tissue regeneration and homeostasis are one the main key components that are achieved through Multipotent stem cells.[8]

Stem cells also can be categorized into another three kinds i.e., embryonic, somatic and germinal. Germinal stem cells are derived through germinal layers of primary embryo. They firstly evolved into parent cells and then give formation to specific organ cells. However, somatic stem cells have limited rate of totipotency in comparison to Embryonic Stem Cells (ESCc) which forms from the inner cell mass of blastocyst. Although these have indefinite life span which made them omnipotent in nature. In contrast to that Adult Stem Cells (ASCc) are gained from bone marrow. The Adult stem cells are mesenchymal stem cells (MSCs), Multipotent Adult Progenitor Cells (MAPCs) and Heamopoietic Stem Cells (HSCc).[9]

Primarily, due to cellular heterogeneity skin stem cells are differentiated into various kinds and are sub-classified into:

a) Follicular stem cells
b) Melanocyte stem cells
c) Sebaceous gland stem cells
d) Mesenchymal stem cells. and
e) Hematopoietic stem cells and epidermal stem cells

Follicular Stem Cells

Mature stem cells reside in hair follicles termed as Hair Follicular Stem Cells (HFSCs) which are located in region of arrector pili muscles, also known as Bulge, they also contain melanocyte stem cells and epithelial stem cells. Except that HFSCs could also be found in Outer Root Sheath (ORS) region, that region is also called as “Bulge”. [10] Follicular stem cells are located at location of follicle bulge and have ability to differentiate into epithelium of hair follicle which also contains inner, outer root sheath and hair shaft. Follicular stem cells, special cell marker are said to be CD200, K15, CD34, NFATC 1 , K19 etc.[11] Dermal Papilla Cells (DPCs) are also type of stem cells present in hair follicle which are formed from dermal condensation which also considered as beginning stage for development of hair follicle. They play an essential feature in hair growth and osteocytes regulation and induction, plus also have ability of conversion in pluripotent cells.[12]

Melanocyte Stem Cells

Melanocyte Stem Cells are found in the region of hair germ and at region of follicle bulge, its essential markers include Dct, Sox and Pax3.[11] Melanocytes are known to be as melanin producing cells consisting 5-10 percent of humans body’s skin cells. Every melanocyte resides on epidermis basal layer and five keratinocytes immediately surrounds it. For formation of an epidermal melanin unit, melanocyte via several dendritic extensions made a linkage with 35- 40 additional keratinocytes. There is thought to be a symbiotic relationship in between of associated keratinocyte and melanocyte in epidermal melanin unit. This homeostatic ratio is maintained by melanocyte throughout its lifespan.[13] Until now Mesenchymal Stem Cells (MSCs) present in hair follicle are studied mostly and have been used in mouse models. Various kinds of stem cells are located in bulb (secondary hair germ) and bulge area of hair follicles. MSCs and Hair Follicle Stem Cells (HFSCs) are mostly could be found in these niches of stem cell in a normal hair follicle. During the development of hair follicles, from bulge cells secondary hair germ cells are derived. These are also being closely linked bulge cells extension.[14] Melanin pigment in skin surrounds skin keratinocytes and arranged them into an armor around nucleus to provide protection to genomic DNA against hazardous reaction of UV light. Melanocytes produce pigment in hair follicles which are incorporated later into growing hair and hence help in determination of mammals coat color. Melanocyte maintenance depends upon Melanocyte Stem Cells (MelSCs) population which is an inert population located in hair follicle bulge regin niche.[15] and also functions as reservoir for melanocyte. MelSCs produced differentiated melanocytes which give rise to pigment production.[16] In mature hair follicle, in melanocyte lineage there are said to be three linked compartments namely, melanocyte progenitor cells, terminally differentiated cells and melanocyte stem cells.

Sebaceous Gland Stem Cells

Sebaceous glands found in almost all human body other than soles of feet and palms of hand. They are said to play an important role in antibacterial skin properties, in cutaneous vitamin E, hydration of skin surface and in

other antioxidant synthesis including production of stratum corneum lipids. They are produced through excretion on skin surface of a waxy oily compound known as Sebum which is an end product of sebocytes secretion holocrine.[17] Sebaceous gland stem cells are type of stem cells which could be found near infundibulum and sebaceous glands. However, Blimp 1 are known to be their specific marker.[11] Stem cells that produce sebaceous glands are identified in hair follicle region above bulge region of CD34+/K15+. There is also a population of Lgr6+ located which produces sebaceous cells and the said population is multipotent in nature.[18]

Mesenchymal Stem Cells

Mesenchymal Stem Cells (MSCs) are located near skin dermis region and could be differentiated into mesodermal and neural cell types derivatives. Specific cell markers for mesenchymal stem cells are CD70 and CD105.[11] MSCs are multipotent stem cells originally have the ability to differentiate into tri-lineages including adipocytes, osteoblasts and chondrocytes. MSCs are determined on the basis of tri-lineage differentiation ability and surface markers positivity including CD73, CD105 and CD90. Mesenchymal stem cells could be found from dental pulp, adipose tissue and bone marrow. These are located in bone marrow stroma with adipocytes, endothelial cells (ECs), osteoblasts, monocytes, osteoclasts and Haematopoietic Stem Cells (HSCs).[19]

Hematopoietic Stem Cells and Epidermal Stem Cells

Hematopoietic Stem Cells are located at follicle dermal papillae and could be divided into erythroid and myeloid lineages. They contain same markers as found in different tissues and organs. Between all these types of skin stem cell sub-classification, epidermal stem cells are linked to tissue repair and skin regeneration. Epidermal stem cells are dividing cells in nature which produce short life span differentiating cells that play crucial role in regeneration of epidermis. Epidermal stem cells located at epidermis basal layer, sebaceous glands base and air follicle bulge region.[11,20]

Stem Cell Natures and Their Characteristics

Stem cells consists of two important key characteristics that differentiate them from other several cells found in body. First feature includes having ability of their maintenance of their number of cells for long span time period. Secondly, stem cells have capacity to differentiate into specific type of cells with specialized functions like skin cells, heart .[21]

Stem cells represents cells which are consistent and multiplied without distinction for a long period of time. They form mature cell types which have various characteristic features with specific functions. An essential feature of a stem cell is plasticity. “Transdifferentiation” term is interlinked with “plasticity” and represents a character of adult stem cells to distinct into tissues as comparison to their ancestor cells from they originated. For instance, adult bone-marrow derived MSCs multiplication into different skin cell types.[22]

Normal Adult Stem Cells and Tumor Stem Cells

Normal adult stem cells could be found mostly in somatic tissues from where they give arise the basis of cellular information for tissues related to their repair, homeostasis and maintenance.[3] These are tissue specific rare stem cells which also accounts for two most important features of a stem cells including self-renewal f differentiation into specific cell types contains main origin of tissue.[23]

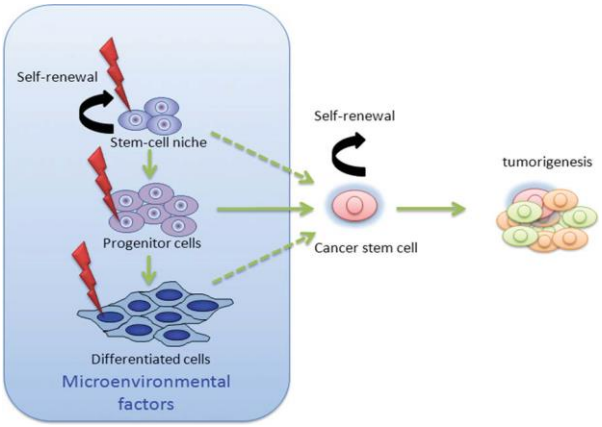

Figure 1. This figure shows representation comparison between Cancer Stem cell (CSC) and normal cell when expose to radiation.[24]

General Features of Skin

In human body skin is known to be substantial organ of body constitutes 15-20% of body mass, with 2 m2 surface area. Human skin conduct various function of body including sensory perception, protection from dehydration and infection, thermoregulation and mainly excretion and absorption. But momentarily skin perform as a physiochemical barricade in opposition to environmental stress for instance pathogens, exogenous

chemicals and ultra-violet rays. Mainly it be could be said that skin mainly work as a barrier to protect the human body against the physical factors and external environmental parameters which also play role in metabolic proceedings. Skin contains two forms of primary layer which are epidermis and dermis. The epidermis is a non-vascularized external layer which consist of special collection of cells called as keratinocytes. Keratinocytes are compactly linked to each other through tight junctions and desmosomes, they are also characterized via aspect of cytokeratins. During cell division process epidermal keratinocytes by Keratinocyte stem cells reside in stratum basale (basal layer) go through prearrange differentiation as their migration happens thoroughly to the skin surface to form tightly connected undamaged cells which provide barrier of epidermal coating .[25]

Its main function is to produce threadlike long protein keratin which play role as a protective layer. Epidermis is from ectodermal derivation which is outermost skin layer that have direct link exposure to environment. It's also known to be first line of defense in odds with pathogens and it's also helpful in different immunological activities and thermoregulatory functions. [26]

On other hand dermis is known to be connective tissue of skin which composed of dense large fibrous sections formed by fibroblasts.[27] Dermis mainly originates from mesoderm which lies beneath epidermis layer and helps to anchors various cutaneous structures including sweat glands, nerves, sebaceous glands. They also constitute mass of fibroblasts and immune cells that expressively play role in different physiological activity in skin. Dermis is a middle layer composed of structural proteins called collagen. It's also contains a small portion of fat cells called as lipocytes. Thickness of dermis layer is considered to be dependent upon anatomy of body and geographic location. [28]

About Skin Cancer

In people occurrence of skin cancer has been growing with passing of each day. Main reason for increasing incidence of skin cancer is because of extended exposure to UV radiation which depleting of ozone layer to earth surface. Skin cancer have two main types known as Non-malignant melanoma and Malignant melanoma. Non-malignant melanoma is further subdivided into Squamous cell carcinoma (SCC) and Basal cell carcinoma (BCC). These both mainly happen cause of exposure to UV sunlight. On other hand Malignant melanoma (MM) happens because of intense sun burn. 80-85% non-melonama type of skin cancer are Basel cell carcinoma (BCC) and Squamous cell carcinoma (SCC) but SCC is said to more lethal in comparison and may cause deaths. It is said that 80% of all skin cancer are BCC and 16% are SCC, Melanoma skin cancer comprise only 4%. At early-stage skin cancer could be detect easily through plain techniques or procedures but skin cancer at advanced stage could not be cured efficiently via any medications.[29] Similar to various other cancer, environmental conditions are play role in skin cancer. Skin cancer extent level also increase with passing age due to main cause of latency in between cancer itself and exposure of carcinogen [30]

Nonmelanocytic Skin Cancer and Malignant Melanoma

Squamous cell carcinoma and basal cell carcinoma (BCC) are collectively known as Non-melanoma skin cancer (NMSCs).[31] Basal cell carcinoma (BCC) initiate from skin cells which are located at epidermis basal layer and from epithelial structure consist of adnexa. BCC metastasis known to happen rarely, hence it's also reported to be spread to regional nodes through lymphatic paths and also to neck and head through way of bloodstream.[32] Squamous cell carcinoma (SCC) could be formed in various tissues which constitute of mouth, esophagus and skin by squamous epithelia. Meanwhile, cutaneous SCC biology are different in comparison to SCCs that are found in other sites. Cutaneous SCC have rare metastases (2-6%) and gradual relative behavior. Cutaneous metastasizes usually happens via lymphatics to nodes region which also mainly involves cervical and parotid nodes. Cutaneous SCCs originate chronically in skin when long term exposure occur to sun happens and mostly the occurring site for SCC is neck and head region.[33] One of most common malignant cancer type is NMSC. Approximately 2-3 million cases every year are recorded worldwide. USA consider to have 1-3 million each year on top. Canada, Asia. Europe and Australia NMSC level up 3-8% annually. Etiological factor for this is considered to be certain carcinogens, UV light and radiations. Its increasing globally by 10% annually and usually found in younger women and older man.[34]

Skin Stem Cells

Skin is a diverse biological organ including dermis, epidermis and adnexa (sweat glands, hair follicles and sebaceous glands) which when exposed to chemical, mechanical and environmental stress needs continuous self-renewal in order to continue performing its functions as a barrier etc. The multipotent skin cells which perform this self-renewal are called Skin Stem Cells (SCs). These are located in dermis, epidermis and hair follicles and they multiply rapidly and regenerate skin tissue in response to an external stimulus (e.g., wound).[35]

In-vitro culturing of primary culture of keratinocytes generates meroclones, holoclones and paraclones representing proliferative portion of human squamous epithelia. Among these clones, only holoclones possess epidermal SC features i-e long term regeneration and self-renewal. The term Holoclone itself describes proliferation ability of keratinocytes in-vitro and they can regenerate epidermis in-vivo. The other two types of cells i-e meroclones and paraclones lose their proliferation and self-renewal ability with the passage of time. Paraclones replicate up to 15 cell generations and then differentiate, whereas meroclones possess transition properties between SCs and differentiated cells similar to transient amplifying cells.[36, 37]

Stem Cell Niches:

Stem cell niches are the microenvironments where different stem cells reside in the body. It is proposed that this method is used to maintain and regulate different stem cell types.[38]

Skin stem cells located in specific units which surrounds the specialized microenvironment. These *niches* constitute various SCs along with supporting cells which helps in maintaining signals across different SC types. Human skin contains minimum five various SC niches i-e, HF bulge, basal layer of the epidermis, dermal papillae, dermis and base of sebaceous gland.[39] *Niche* defines the ancestry of stem cells, structure of foundation cells found around population of stem cells are located there. Stem cells resided in *niche* have a great effect on destiny of stem cells as they have linkages with cells exist within similar localized vicinity, also with their outside environment through the emergence of cell associations.[40]

Hierarchical Structure of Cancer

In the hematopoietic system, the cellular replacement and hierarchical tissue organization of stem cells was first described by Gilbert and Lajtha (1965). According to the studies of recent years, it is now agreed upon that all tissues contain stem cells, though their number or type differ in every cell or tissue.[41] On the other hand, cancer cells are the tumor cells that are said to be 'a wound that does not heal'. Cancer cells do not respond to the normal controls of cell growth and may also contain continuous cell renewal ability. Early studies of some solid tumors and leukemias indicated that only a small portion of cancer cells possess the clonogenic ability and thus are responsible for maintaining malignant growth.[42]

Cancer Stem Cells (CSC):

Cancer Stem Cells (CSCs) are the small number of cells present in tumors and are responsible for growth of cancer. When relocated into an animal model, these cells show tumorigenicity, differentiation and cell renewal capabilities. However, in respond to conventional therapies, they are resistant and escaped CSCs even after complete removal continue forming new tumor cells

Different cell surface markers are used to distinguish CSCs from other cancer cells. These markers include CD133, CD44, IL-6R, and ALDH.[43, 44, 45] Some of the recent studies showed that certain oncogenic, epigenetic and genetic mutations of cancer cells are inherited from normal stem cells thus forming tumors. Also, the self-renewal and continuous proliferation ability is also recognized to be taken from stem cells thus giving rise to "cancer stem cells".[46, 47, 48]

On the basis of these observations a cancer cell model has been generated which is based upon this concept that a small population of cancer stem cells is present which can proliferate and self-renew on its own and keep on growing the cancer cell mass. Thus, in this model reformation and metastasis of tumor may occur which is caused by residual chemotherapy resistant cells hence forming secondary tumors.[49]

In order to explain the connection between stem cells and cancer, a pre-tumor progression-based hypothesis was recently postulated. This hypothetical model is based upon stem cells in human colon crypts. According to this model, stem cells might accumulate genetic and epigenetic defects thus making a defective progeny which causes tumor progression and marks the transition from pre-tumor to tumor.[49, 50]

On the basis of new experimental evidences, a number of hypotheses have been proposed which identifies and explains the presence of CSCs in cancer and thus using it in future therapies. These studies suggest that genetic mutations might have occurred in the cancer cells causing them to behave like stem cells or CSCs might be the result of fusion of cancer cells and stem cells. In this case, introduced MLL-AF9 fusion protein was introduced into granulocyte-macrophage progenitors by (Krivtsov et al., 2006) in order to separate leukemia stem cells from acute myeloid leukemia. In this regard, the isolated leukemia stem cells had a gene expression profile similar to that of normal granulocyte-macrophage progenitors. However, a 'self-renewal' transcription program was activated in the leukemic stem cells, indicating that genetic changes can activate the self-renewal program in premalignant cells.[51]

Normal Stem Cells and Cancer Stem Cells

Cancer Stem Cells and normal stem cells possess same functions i-e excessive proliferation and the ability to self-renew. Also, most of the cell surface markers like CD29, CD44, CD133, etc are also shared by both types of cells. In solid tumors, however, specific cell surface markers are used to identify CSCs population.[52] A transformation is reported by some researchers which describes the formation of CSCs due to mutations in normal stem cells. This transformation is known to be associated with abrogated suppression of tumors and instability in the genome. Also, embryonic stem cells when exposed to environmental aberrancy form CSCs, characterized by resistance in apoptosis and spontaneous accumulation of DNA lesions.[53]

There is another type of cells called Non-Stem Cancer Cells (NSCCs) which can also lead to the formation of CSCs. In this case, the dynamic equilibrium is maintained between NSCCs and CSCs by interleukin-6, thus mediating tumor heterogeneity. Prostate cell lines, human breast tumors and breast cell lines are reported to show a change of NSCCs to CSCs. IL-6 mediates this type of conversion. Also, this transformation shows a change in expression of different microRNAs.[54]

Stem Cells in Epidermis

Human skin is exposed to various types of environmental stresses. Among these include carcinogens ad ultraviolet light which results in the induction of tumors in skin. A majority of skin cancers occur in epithelium which differs from each other in their biology, histology and genetics. Also, it is difficult to differentiate between different skin cancer types having mixed phenotypes and being monoclonal in genetic markers. This suggests two possibilities i-e formation of epithelial skin cancer from various cell types or stem cells of the epidermis being progenitors of cutaneous tumors. Also, differential phenotype of tumors is also originated from the interaction of epigenetic factors in this regard. Recent reports and studies have provided information with regard to the origin of cutaneous neoplasms, however, significant insight is obtained from genetic alteration and induction of skin cancer in mice models.[55]

Stem Cell Based Therapies

Stem cells possess rapidly emerging and promising therapeutic applications in the field of regenerative medicine where stem cells are used to treat many lethal and aggressive human diseases.[56] One extraordinary and challenging cancer in this regard is advanced metastatic melanoma which is resistant to conventional cancer treatment therapies. In case of conventional cancer therapies, tumor population in bulk is removed, which is known to have different properties as compared to MSC population. In cancer patients, CSCs are hypothesized to represent resistant cell pool.[57]

Specific target-based approaches which are designed to eliminate MSCs must be directed against cell surface antigens uniquely expressed by MSCs. As a result of these direct targeted approaches, several forms of net cellular effects can be observed i-e blockage of self-renewal, drug resistance reversal, anti-MSC immune response induction and differentiation therapy.

An important biomarker of MSCs which can be targeted in this case is ABCB5. This marker also provides possibilities of chemo-resistance. This involves the use of monoclonal antibodies against ABCB5 which can be used as a potential therapy.[58] Another approach which can be accessed includes inhibiting molecular pathways leading to stemness, however, this approach is still not evident.[59]

Various indirect therapies involving immune modulation and invasion are also effective strategies against MSCs. Immunotherapies relevant in this regard include the use of IFNα-2b and cytokines IL-2 as well as tumor vaccines and target specific induction of immuno-

tolerance to melanomas. In case of IL-2 therapy, production of T cells based immune invasion by melanoma stem cells causes suppression of IL-2 production. This cytokine suppression by melanoma cells results in re-activation of anticancer immune response.[60, 61]

Another particularly promising therapy against melanomas is anti-vasculogenic mimicry (VM) therapy which is an indirect strategy known to have no physiologic analog in adults or children, thus causing lesser effects on normal physiologic processes of the body. An effective anti-VM therapy is based on three aspects including blockage of molecular and biochemical signal pathways of VM, inhibition of tumor cell plasticity and remodeling of tumor microenvironment by remodeling ECM.[62, 63] DC based vaccines are also reported to show effective therapeutic effects against cancer stem cells which involves the use of CSC lysates as vaccines or CSC lines pulsed with DCs. In mice models of malignant melanoma, CSC lysates-pulsed DCs caused secretion of IL-4 and IFN which suppressed the growth of tumors and prolonged their survival.[64]

There are various future aspects in regard to the treatment of melanoma after gaining knowledge about MSCs. Specific cell surface markers of melanoma stem cells can be used as targets by using monoclonal antibodies. An antibody therapy (rituzimab) based on cell surface marker of MSCs namely CD20 is under clinical trials for the treatment of melanoma, causing regression in chemo-refractory melanoma.[65] Also, a monoclonal antibody produced against ABCB5+ MSCs resulted in tumor inhibition in mouse models.[66]

Knowing that IL-2 production can be blocked by MSCs through immune evasion, future therapies can focus on regulation of immune response. An example of this is the negative regulation of host T-cell by the combined activity of cytotoxic T-lymphocyte antigen-4 (CTLA-4) and its ligand B7-2 involving up-regulation of ABCB5 MSCs.[67]

Anti-CTLA4 monoclonal antibodies namely ipilimumab and tremelimumab are shown to have promising effects in patients of metastatic melanoma[68] in clinical trials.[69, 70] Another effective way was demonstrated by 15 patients in order to modify the microenvironment of the tumor. They showed that an inflammatory cytokine interleukin-6 which is released from differentiated melanoma cells caused reduction of self-renewal in MSCs and induced differentiation. On the other hand, an anti-inflammatory cytokine Interleukin-10 promoted self-renewal ability of MSCs. By causing blockage of the IL-10 receptor, sensitize MSCs into interleukin-6 has been done hence inducing differentiation of MSCs. Manipulation of these cytokine, caused a decrease in self-renewal capacity of MSCs and differentiated stem cells into an easily targeted phenotype.[68]

A number of treatment strategies can be considered for TSC/TAs. One strategy would be the activation of TSCs and differentiation of the whole TSC/TA population into a chemotherapy sensitive cell type. Another strategy would involve targeting multiple antigens against the TSC/TA population either by using target specific reagent antibodies or by immune system activation. Specific targeting of the CD133+ melanoma cells might destroy all TSC/TAs population thus needing additional approaches. A third strategy would be the specific targeting of a mutation or pathways activated aberrantly in TSC/TA population. But, this therapy might only kill active TAs, and thus require coupling with a reagent which can cause activation of quiescent TSCs making them susceptible. A fourth strategy would be to forcefully convert all TSC/TA cells into quiescent state thus hoping to prevent downstream tumor from further development. Long-term and suppressive therapies would then be required by these patients. And their TSCs will then be difficult to destroy due to inheritance of various protective properties. It is thus clearly known that any successful therapy will require various creative methods in order to eradicate the subpopulation of TSC together with removing all other cell types which have the capability of producing TSCs (TAs).[71]

A wide range of subpopulations of cells is present in case of a malignant melanoma and hence it's difficult to cure. Having subsequent knowledge about the presence of melanoma stem cells will be critically helpful in future in order to combat and treat melanomas. Future therapies can involve the use of different treatment options like targeting the cancer microenvironment, melanoma stem cell surface biomarkers of directly using stem cells as a method of treatment.[72]

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