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Review Article

Overview in Cancer Reversion: Targeting PKC Signaling as a Therapeutic Strategy in Rhabdomyosarcoma.

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Abstract

Cancer remains a complex disease, and conventional therapeutic approaches often fail to achieve a cure. Cell reprogramming has emerged as a promising approach in cancer management, highlighting the concept of controlling cancer cell plasticity. While cancer is generally considered irreversible due to genetic mutations, cancer cells can revert to a normal phenotype in certain microenvironments. This phenomenon, known as cancer reversion, has been observed in various types of cancer.

Skeletal muscle cancer, such as rhabdomyosarcoma (RMS), is a rare but aggressive tumor that primarily affects children and young adults. Despite advances in treatment, RMS remains a significant clinical challenge, and new therapeutic strategies are needed. Recent studies have implicated the dysregulation of muscle cell differentiation in RMS development, suggesting that promoting differentiation could be a promising approach to counteract tumor growth.

Signaling pathways, particularly the phospholipase C (PLC)/protein kinase C (PKC) pathway, play a role in regulating muscle differentiation. While PLC/PKC signaling is essential for differentiation, distinct PKC isoforms exhibit dual roles in either promoting or repressing myogenesis. Elucidating the molecular mechanisms underlying cancer reversion in skeletal muscle cells may lead to the identification of novel therapeutic targets, including the PKC family.

This review highlights the significance of cancer reversion in skeletal muscle and emphasizes the need for further research into the underlying molecular mechanisms. By understanding how to restore normal cell behavior in cancer cells, researchers may uncover new opportunities for the development of effective and targeted cancer therapies.

Keywords : cancer reversion, differentiation, rhabdomyosarcoma, PLC/PKC.

OVERVIEW OF CANCER REVERSION

Cancer is a multifactorial and complex disease for which conventional therapeutic approaches often fail to achieve a cure. Classically, the cancer treatment involves surgery and the tumor cells destruction with chemotherapy or radiation or more recently, focusing on activating the patient's immune system [1]. In that sense, cell reprogramming signifies an important progress in cell biology and has potential in cancer management [2]. However, although there is an increasing investigation aiming at optimizing cancer cell reprogramming so that it can be used as therapy in humans, it remains technically and ethically challenging to fully apply in clinical trials. But it establishes an important concept regarding the cancer cell, which is the possibility of managing its plasticity. Plasticity refers to the cells´ skill to acquire diverse phenotypes through differentiation programs. It is an integral feature of biological systems that is regulated by changes in gene expression. However, the cellular plasticity allows tumor cells to modify their behavior, simplifying their evasion from terminal differentiation and conferring tumor cells the ability to change in response to their environment, leading to increased tumor variety and treatment resistance.

Tumor cells progressively acquire essential biological traits, known as "hallmarks," that allow for tumor establishment and progression[3,4]. These characteristics include the activation and maintenance of proliferative signals, evasion of growth-suppressing mechanisms, resistance to cell death,

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replicative immortality, promotion of angiogenesis, activation of invasion and metastasis mechanism through disruption of the Wnt-β catenin signaling pathway; also are include the reprogramming of energy metabolism and immune system evasion [3,4]. Genomic instability and mutations play a crucial role in acquiring these hallmarks, generating genetic variations responsible for these unique capabilities. Additionally, inflammation, by introducing bioactive molecules into the tumor microenvironment, becomes another contributing factor to tumor development [3,4]. Despite the various causes and forms of progression of this disease, the different types of cancer share certain general characteristics such as uncontrollable cell proliferation and division, and loss of cellular and molecular architecture [5,6]. Also, the ongoing investigation of cancer has brought significant observations such as the constant presence in tumors of a subpopulation of cells with stem-like properties, known as cancer stem cells (CSCs)[7]. This subpopulation of cells is characterized by enhanced ability to initiate tumor growth, proliferate, invade, migrate, and resist routine treatments [8]. Remarkably, CSCs can transdifferentiate to different cell lineages, to acquire a more aggressive and therapy-resistant phenotype [9]. This heterogeneity among cancer cells within the same tumor could be due to genetic changes, environmental variances, among others. Interestingly, lower in the hierarchy, differentiated cancer progenitor cells form most of the cancer cell population and do not generate tumors [10]. What are the molecular mechanisms in differentiated cancer progenitor cells that prevent tumors? The response implies the knowledge of the signaling pathways that underlie the physiology and the differentiation capacity of the CSCs and represents potential therapeutic targets [11]. Whatever the cause of the tumor cellular heterogeneity, the possibilities of controlling signal transduction mechanisms and their regulatory points responsible for the presence of different cell types, make us think about the possibilities of modifying the aggressive behavior of tumor cells; and they remind us of those studies whose objective is to restore normal behavior and eliminate tumoral characteristics. The concept of cancer reversal is not new [12].

How cells become malignant has concerned scientists for over a century, and at the same time, they have asked themselves the opposite question: are cancer cells able to revert their malignant behavior?. If we start from the basis that cancer is generally triggered by genetic modifications that cannot be reversed, such as somatic mutations of oncogenes or tumor-suppressor genes, then tumorigenesis is considered irreversible. However, there are evidences of tumors without cancer-associated gene mutations [13]; for example, containing changes in the DNA methylation state and not in its sequence [14]. Moreover, as was mentioned above, actual scientific evidences demonstrate that cancer is not simply a genetic disease but rather a complex system, involving a heterogeneous group of normal and cancer cells, being their interactions as well as their epigenetic state, fundamental for the pathogenic process. In agreement, it has been observed that cancer cells in normal microenvironments or under certain conditions revert to nonmalignant cells [6]. Certainly, cancer reversal is a topic that has been under investigation for a long time. **Table 1** summarizes experimental evidence showing the cancer reversal process.

Table 1. Experimental evidence of cancer reversion.

Tissue Involved	Ref.
Ovarian Teratoma	[15]
Crown Gall	[69]
Testicular Teratoma	[70]
Teratocarcinoma Cells Injected Into Blastocysts	[72]
Murine Lung Cancer	[73]
Liver Cancer Cells	[74]
Human Breast Cells	[75]
Human Melanoma Cells	[76]
Melanoma cells	[77]
Human Colorectal Cancers	[24]
Breast Cancer Cells	[78]
Hepatocellular Carcinoma	[79]
Acute Promyelocytic Leukemia Cells	[80]
Rhabdoid Tumors	[81]

As already pointed out, evidences indicate that the Interaction between tumor cell and its microenvironment plays a crucial role in determining the actions of the tumor and, as observed, the microenvironment provided what was necessary to achieve non-malignant cellular behavior [15,16,6,17]. It is relevant to determine what is the cause, the agent or the mechanism within that microenvironment that is able to take control of a tumor and govern its behavior.

The microenvironment is heterogeneous in its cellular composition; additionally, to cancer cells, there are also no-tumor cells, secretory proteins, blood vessels that surround and support the growth of the tumor [18] and the called extracellular matrix found on the lateral and basal surfaces of cells, that include insoluble complex of proteins and carbohydrates [19]. The exchange or interaction between the components of the microenvironment is important. So, tumor cells can modify the nature of the microenvironment, and conversely, the microenvironment can affect the tumor behavior [20]. Namely, it has been shown that mechanical interactions between cancer cells and extracellular matrix can accelerate neoplastic transformation [21]. Also, altering extracellular matrix structure, through MMP3/stromelysin-1 (Str1), in normal tissues contributes to cancer generation [22].

In consequence, due to the relevant effects of the interaction

tumor-microenvironment, it is central to elucidate the factors, signaling pathways or entities involved in such interaction, not only for the restoration of the malignant phenotype to normal cell behavior but also to ensure that the reversal lasts over time.

Cancer reversion implies reprogramming of cancer cells into normal or normal-like cells. These reverted cells reached a normal phenotype and also lost malignant behavior. As was mentioned, genetic alterations are irreversible, but some attempts to experimentally repair altered gene activity have been investigated for cancer reversion. For instance, it has been shown that Adenomatous Polyposis Coli (APC) tumor suppressor loss is strictly required for the development of colorectal cancer [23]. In agreement, the APC restoration promotes disease regression in the small and large intestine and restores homeostasis in the intestinal crypt [24]. In addition, somatic mutations are found in healthy cells throughout life, and these mutations do not change cell behavior and accumulate passively [25]. This is consistent with evidence indicating that cancer reversal is possible without the need to act on the affected genes. Indeed, molecular targets that can induce cancer reversion without gene restoration were identified [26]. Such as, a methyltransferase was recognized which depletion converts stem-like colorectal cancer cells into postmitotic cells and reestablishes normal morphology in patient-derived colorectal cancer organoids [27]. Coincidentally, studies have shown that the initiation of tumors shows that normal differentiated cells carrying oncogenic mutations remain in a nonmalignant condition until they experience cellular reprogramming and shift to a stem or progenitor-like state [28]. This dedifferentiation, previously mentioned here or also known as tumor cell plasticity, implies that tumor cells lose their specialized properties and take on less differentiated phenotypes reminiscent of early embryonic development [29]. Loss of differentiated state is linked with increased tumor cell invasiveness, immune system evasion capacity and drug resistance [30]. The differentiation state of cancer cells has been linked to their potential for proliferation and ability to metastasize, that is to say, their aggressiveness [31]. Moreover, neuroblastoma and breast cancer are two tumor forms where the tumor cell differentiation concept is used in the clinical prognostic [32].

Differentiation process is essential during the embryonic and postnatal development of an organism, as well as in the renewal and repair of tissues. It is highly regulated by a combination of intrinsic genetic signals and environmental factors. In general terms, differentiation denotes the developmental process whereby cells gradually acquire more specialized functions, changing the phenotype and acquiring specific morphological, biochemical and functional characteristics, establishing differences between cells. This process was considered as unidirectional, but the information available in the context of cancer indicates that the cells can dedifferentiate. The bidirectionality of this process is irrefutable, and it is the basis for a new prototype of reversal therapy as an alternative to current cancer treatments.

SKELETAL MUSCLE DIFFERENTIATION AND CANCER

Skeletal muscle comprises approximately 40 - 50% of body mass [33] but is infrequent that this tissue develop cancer [34], may be due to its low turnover compared to other highly proliferative tissues that develop tumors more frequently[35,36]. In general, the primary tumors developed in skeletal muscle include rhabdomyosarcoma (RMS) and rhabdomyoma (RM) [37]. The secondary skeletal muscle cancer is also rare [34].

Even though we have vast information about this RMS [38], advances in identifying new therapies have been lacking. Incomplete understanding of the disrupted molecular machinery of RMS is crucial reason for the slow advancements. RMS incidence is nearly four new cases per million children under the age of 20, without a specific geographical tendency[39]. RMS represents the most common pediatric soft tissue sarcoma and involves a group of cancers that affect connective and supporting tissues such as muscles, nerves and blood vessels [40,41]. These tumors are located in the head and neck region, genitourinary tract, and extremities, can really occur anywhere in the body, with believed origin in skeletal muscle due to its myogenic phenotype.

Most cases of RMS are sporadic; however, the disease can be associated with other syndromes [38]. Although still debated, studies suggest that RMS derives from the mesenchymal cell lineage, which is typically fated to become skeletal muscle tissue. The onset of RMS is similar to the development of skeletal muscle but differs from it in that there is a slowdown or arrest in normal skeletal muscle development [42]. It is observed that the PAX3–FOXO1 fusion protein is a key actor arresting myogenic differentiation, which is related to the RMS cells´ proliferation potential [43]. Indeed, the PAX3-FOXO1 fusion protein, resulting from the stable reciprocal translocation of chromosomes 2 and 13, is a recurrent chromosomal rearrangement found in RMS [43].

Through myogenesis, pluripotent mesodermal precursor cells commit to the myoblast lineage, proliferate, differentiate, and fuse into multinucleated myotubes, maturing to form myofibers. This process is controlled by a family of conserved basic helix-loop-helix (bHLH) and myogenic regulatory factors (Mrfs), Myogenic Differentiation 1 (MYOD1), MYF5, MRF4 (MYF6) and Myogenin [44]. Interestingly, RMS cells express Mrfs, yet fail to execute terminal muscle differentiation. Generally, RMS contains MyoD but its transactivation activity has been compromised; it fails to bind the corresponding target genes and the cells do not reach the mature state [45]. Numerous signaling cascades have been involved in the process of non-

differentiation, all of them agreeing on having MyoD and myogenin as the central points of the process [46].

On the other hand, there is some evidence indicating that RMS can also arise from endothelial progenitors, which suggests a mechanism for tumors that originate in areas that are devoid of skeletal muscle tissue (salivary gland, gallbladder, prostate and bladder) [47]. This non-muscle origin is explained by the occurrence of transdifferentiation of endothelial progenitors into myogenic cells due to hyperactivation of the Sonic hedgehog signaling in development.

Based on microscopic analysis, two subtypes of this cancer have been defined or established: alveolar or embryonal RMSs. These two variants, alveolar and embryonal, are, respectively, associated with translocations of chromosomes 2 and 13 and deregulation of genes in chromosome region 11p15.5[48,49]. The alveolar variant constitutes 20-25% of RMS diagnoses and is characterized by smaller, rounder cells similar to pulmonary alveoli. This subtype is more aggressive than other RMSs. The other variant, embryonal, involves a heterogeneous population of cells in different stages of differentiation towards a skeletal muscle phenotype [50]. This classification has been further refined by the identification of 'fusion positive´ RMS (FPRMS) and ´fusion negative´ RMS (FNRMS), due alveolar variant usually containing a balanced chromosomal translocation generating oncogenic PAX3-FOXO1 or PAX7-FOXO1 fusion transcription factors that are absent in embryonal RMS [50]. In addition, as the fusion protein has biological and clinical effects and not all alveolar RMSs present a fusion protein (the remaining 20% are classified as fusion-negative ARMS), the classification as FPRMS or FNRMS is better accepted. It is important to mention that although these two variants are the best studied, since 2013, other subtypes have been recognized, such as pleomorphic and spindle cell or sclerosing RMS and, new advances in molecular biology have refined this classification, identifying novel subtypes such as MYOD1-mutated RMS, VGLL2/NCOA2-rearranged RMS, and TFCP2-rearranged RMS [51,52].

In terms of molecular features, the embryonal subtype cells present nuclear localization of β-catenin in addition to its classic cytosolic and proximal membrane localization. They also express high levels of N-cadherin and integrin-α9, both of which are positively regulated by the Notch pathway. These molecular characteristics imply more aggressiveness, and the maintenance of an undifferentiated state within the tumor [53].

Respect treatment, currently is multimodal, combining surgery, when feasible, to completely remove the primary tumor and chemotherapy to control disease spread, even without evidence of metastasis, because most patients present with spread cancer cells. Radiotherapy is used to treat most high and intermediate-risk patients as well. Chemotherapy and radiotherapy, particularly in children, may cause complications and low quality of life [38].

Regards Rhabdomyoma, the other tumor type developed in skeletal muscle, is a benign tumor of myocyte lineage that represents the most common primary cardiac tumor of youth and infancy; and in adults is an unusual neoplasia which has a predilection for the head and neck region [54]. In younger individuals, most cases are associated with the genetic disorder Tuberous Sclerosis Complex (TSC) [55].

Since the 2010s, various investigations have suggested the effectiveness of an inhibitor of the mammalian target of rapamycin(mTOR)calledeverolimustotriggertumorregression in neonatal patients with cardiac rhabdomyoma[56-58]. Although those works evidence the rhabdomyoma shrinkage, they do not fully explain the molecular mechanism underlying tumor regression, and even less so if malignant cells revert towards a more normal state. However, everolimus is known to be an apoptotic agent; therefore, the tumor regression is probably due to the apoptotic process rather than the restoration of a normal phenotype.

In the context here descript, muscle cell differentiation, known as the transition to a mature muscle cell phenotype, could represent a map showing the various paths that lead to these pathologies, that is, the knowledge of the underlying molecular mechanisms and the control points of the differentiation process, arises as a key events to counteract uncontrolled tumor proliferation and increase the possibilities of treatments. For example, the cytokine interleukin-4 (IL-4) that acts as a myoblast recruitment factor to induce mature myotubes throughout mammalian muscle growth [59], is upregulated in RMS, suggesting that the IL-4R signaling pathway represents a target for avoiding tumor progression.

Regards muscle differentiation signaling, has been descript a role of PKC demonstrating that its activity is crucial for the differentiation process of both C2C12 and mouse primary myoblasts. Precisely, blocking with specific siRNA, atypical protein kinase C was involved in the myogenic process, regulating the cyclin-dependent kinase 5[60]. On the other hand, due PLC activation results in the production of DAG and calcium ion through inositol triphosphate release, it is very likely that also conventional PKC play any role in the mentioned process, since was evidenced that PLC signaling is required for the activation of cyclin D3 promoter in C2C12 cells and in differentiation of the murine myoblasts cell line leads to the up-regulation of cyclin D3[61,62]. The evidence supporting the role of the PLC/PKC pathway in skeletal muscle differentiation [61] makes it a potential target for studies on tumor reversion in that tissue. Recently, Milanesi´s group demonstrated that staurosporine, bisindolylmaleimide, and neomycin sulfate (direct or indirect protein kinase inhibitors) induce differentiation in C2C12 and RMS cells[63]. Therefore, these data imply that the PLC/PKC pathway prevents muscle differentiation. In agreement, the calcium-

regulated classical protein kinase C β (PKCβ) as a repressor of myogenesis has been identified [64]. The evidence of Milanesi and Nasipak, is opposite to that suggesting a role for PKC in muscle differentiation. It should be noted that, using specific inhibition with siRNA, atypical PKC was involved in myogenesis, while Milanesi as well as Nasipak involved conventional PKCs. Regards Faenza´s works, they use U-73122 inhibitor then they do not inhibit PKC directly; since it is known that activation of PLC would involve the activation of classical or conventional PKCs, they suggest that the effects observed could also involve PKCs. However, PLC inhibition would not imply the inhibition of PKC, since the existence of PLC-independent PKC activation mechanisms has been demonstrated [65]. Compatible with these observations, it has been demonstrated that PKC downregulation results in increased myogenesis in C2C12 cells as measured by creatine kinase activity and myogenin expression [66]. Interesting, they involved PKC alpha.

Other studies, using short hairpin-RNA (shRNA) to specifically knockdown PKC theta expression in C2C12 cells, reported that PKC theta regulates myoblast differentiation and fusion [67]. Perhaps the induction of muscle differentiation observed by Milanesi et al. may be favored by a potentiation of the atypical and novel PKCs functions due to classical PKCs inhibition.

The existing evidence strongly suggests that the PKC family and the molecular events regulated by it are points of interest for the development of muscle cancer reversal therapies. In addition, a mechanism of PKC isoforms cross-regulation seem a logical plausibility and could explain the different roles of each PKC isoform in muscle differentiation or in process related to RMS development; for example, using RNA interference, have established that PKC iota also has a role in alveolar rhabdomyosarcoma anchorage-independent growth and tumor-cell proliferation [68].

CONCLUSIONS

Despite rapid advances in targeted therapies, high drug costs, undesirable collateral effects, implying patients with poor life quality, are concerning aspects of today's cancer management. In this context, tumor reversion represents an exciting field of investigation.

Although cancer reversion was first documented over a century ago and substantial biological evidence has since been amassed, its underlying mechanisms remain largely unresolved, and a comprehensive systems-level analysis has yet to be undertaken.

Cancer cells are frequently undifferentiated, which means they lose the specialized characteristics of normal cells. Cellular differentiation, marked by the acquisition of mature muscle cell characteristics, is pivotal in impeding tumor growth and enhancing sensitivity to treatments.

There are to be many possible mechanisms of cancer reversion, just as there are many mechanisms of tumorigenesis. Regards RMS, muscle cell differentiation emerges as a crucial mechanism to counteract tumor proliferation. Among all the emerging evidence on this topic, here, we wanted to highlight the role of intracellular signaling pathways, focusing on the PLC/PKC signaling pathway, especially the activities of distinct PKC isoforms, which play dual roles in either promoting or repressing myogenesis. While atypical PKCs support differentiation, classical isoforms such as PKCβ and PKCα appear to hinder it. The divergent effects among PKC types, along with the potential for isoform cross-regulation, position this kinase family as a promising target for reversing muscle tumor phenotypes and guiding RMS therapy development.

Advances in emerging technologies have significantly deepened our understanding of the molecular mechanisms governing processes such as cell differentiation. This expanded knowledge enables the identification of specific molecular aberrations that hinder the acquisition of a normal, fully differentiated phenotype. By pinpointing the signaling pathways and molecular messengers involved, we can strategically modulate their activity, either by inhibition or activation, to restore physiological differentiation and achieve maturation toward a normal cellular phenotype.

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