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The Curses and the Blesses of E-Cadherin

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Abstract

E-cadherin is an evolutionary conserved molecule expressing from lower level animal to human. The principal role of E-cadherin is to maintain appropriate cell-cell connectivity at adherensjunction. Besides its role as cell-cell connector protein, E-cadherin is integrally involved in intracellular signaling as well as cytoskeletal remodeling. Proper spaciotemporal regulations as well as relevant specialized functions of E-cadherin are important for maintaining normal embryogenesis, cellular morphology and physiological function. However, defects in the expression and function of this gene products could become curses since numerous genetic and developmental studies have identified the critical role of this gene in path physiological conditions of multiple types of cancers leading to fatality. Recent study identified essential role of this gene product in stem cell biology including normal embryogenesis, induced pluripotent stem cell (iPSC) generation and stem cell differentiation. Currently iPSC has become a prime choice as starting material for regenerative medicine to treat many diseases; however the relevant technology has many shortcomings. Our lab and others have been exploiting this protein for successful application in regenerative medicine that made it a blessed molecule. Here, based on the latest available information, we are concisely presenting these agonies and advantages of E-cadherin.

Keywords: E-cad-Fc; Cell-cooking plate; Cell-recognizable biomaterial; Regenerative medicine

Introduction

The cell-cell adhesion is a fundamental phenomenon as well as intrinsic property of cell. Cell adhesion can be formed through four classes of junctions, *viz*., adherens junction, desmosomal junction, gap junction, and tight junction. The adherens junction and desmosomal junctions are mediated by cadherin and cadherin-like molecules that provide resistance to the shearing force to the neighboring cells [1-3]. The gap junction is formed by connexin channels that form conduits between partnering cells to transfer small molecules less than molecular weight 1 kD. The tight junctions are mediated by occludin and claudins, which provide a sealing barrier between two adjacent cells and involved in creating cell polarity resulting apical and basolateral surfaces.

The precise regulation of cell-cell contact mediated by cadherins is a critical issue in human health and disease. The human genome harbors more than 115 cadherin- and cadherin-like genes those are structurally classified into more than 30 families [4]. E-cadherin is the member of classical cadherin family with a long N-terminal extracellular domain (ED) with 5 IgG-like domains or cadherin domains, a transmembrane domain, and a cytosolic C-terminal [1-3]. Neighboring cadherins form homodimer on the cell surface *via* ED-2 domain-mediated *cis*-interaction. Such type of dimer or the furthest ED(ED-1) from opposing cells form Ca^{+2}-dependent homophilic binding and create the adherens junction. On the other hand, the cytoplasmic tail of E-cadherin interacts with either beta-catenin or gama-catenin, which is mutually exclusive for the E-cadherin-catenin protein complex; alpha-catenin, in turn, interacts with either the actin cytoskeleton or with beta-catenin or gama-catenin in a dynamic manner. Membrane proximal region of the cytoplasmic tail of E-cadherin binds with p120 catenin, which is linked with the stability and lateral clustering of E-cadherin on the plasma membrane [5,6]. Besides their role in cell adhesion, E-cadherin is also involved in critical intracellular signaling cascades *via* their cytosolic interacting partners leading to cellular responses spanning cytoskeletal remodeling-to-motility-to-cell death.

E-cadherin was first identified as a plasma membrane localized glycoprotein that is responsible for Ca^{+2}-mediated cell-cell adhesion during the morula compaction in mouse and chick embryo in early 80s [1,2,7,8]. The finding suggested important role of this protein in proper cell-cell connectivity leading to animal development. Over the years it has been recognized as a multifunctional and indispensable protein for human biology. Since E-cadherin is associated with the formation and maintenance of cell-cell connectivity and defects in compact cell-cell connectivity is related with the path physiology, for example, cancer metastasis therefore aberrant function or atypical expression of E-cadherin poses significant threats against healthy living. On the other hand, recent progress in biotechnology has been successfully exploiting E-cadherin for stem cell technology targeting application in regenerative medicine. Such advantageous achievements offer beneficial prospects of E-cadherin for the betterment of human health. The relevant bad impacts and good opportunities of E-cadherin on human health are described henceforth.

The Curses of E-cadherin

E-cadherin gene is mutation prone

Mutations for E-cadherin gene have been described associated with gastric, breast, ovary, endometrium, thyroid carcinomas etc. The mutations for E-cadherin gene reported to date span the entire gene including promoter region, and many of them have been reported lead to significant functional consequences. Many of these reported mutations necessarily generated specific phenotype *in vitro* similar to relevant path physiology [9]. In most cases, E-cadherin mutations are

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found in combination with loss of the wild-type allele.Oliviera et al. reported that, at the time point of their study, so far 141 probands have been identified those are harboring more than 100 different germlineE-cadherin gene alterations, mainly point mutations and large deletions [10].

E-cadherin in gastric cancer

One of the major effects for E-cadherin gene mutation has been established associated with the development of the autosomal cancer syndrome Hereditary Diffuse Gastric Cancer (HDGC). HDGC is the only Gastric Cancer (GC) syndrome with a proven inherited defect, which has been designated as and is caused by germline E-cadherin alterations. Other E-cadherin-associated hereditary disorders have been identified, encompassing HDGC families with or without cleft-lip/palate involvement, isolated early-onset diffuse GCs, and lobular breast cancer families without GC. The first germ line truncating mutation was first identified in 1998 from Maori kindred in New Zealand with family history of diffuse gastric carcinoma [11]. A recent study revealed that at the time of relevant publication there were 122 germ line mutations identified for the E-cadherin gene related with the incidence of HDGC [12]. Out of them, 72.1% were non-missense and 27.9% are missense mutations. The study further revealed that the frequency of such mutations related with path physiological conditions differs for geographical locations as well as ancestral lineages. It has also been reported that one third of all HDGC families described so far carry recurring E-cadherin gene alterations.

E-cadherin in breast cancer

Along with diffuse gastric carcinoma, frequent inactivating mutations have been reported in infiltrative lobular breast carcinomas [13]. The inactivating mutations detected for both tumor types are compatible with the typical scattered tumor growth with clear loss of cell–cell adhesion in relevant pathological tissues. Reportable that exon skipping is the predominant mutations identified related to the diffuse gastric carcinomas, and premature termination is the main mutation type identified associated with lobular breast cancer. Breast cancer is the second top cause of death due to prevalent metastasis in female cancer cases [14,15]. It has been understood over the last few decades that Epithelial–Mesenchymal Transition (EMT) most likely is the early stage of metastasis [16]. EMT is a complex and reversible process initiated by specific substances or transcription factors in such a way that epithelial cells acquire mesenchymal characteristics in cancer [17]. Loss of E-cadherin in relevant tissue is generally considered as one of the trademarks of EMT and a predictor of poor prognosis in many types of cancers [18]. E-cadherin in cell–cell junctions plays a key role in maintenance of characteristics of epithelial cells. Abnormal cellular distribution or compromised expression of E-cadherin usually results in EMT that promotes cancer progression to more aggressive phenotype [19]. An elegant study by Mani et al. showed that the induction of EMT in immortalized human mammary epithelial cells (HMLEs) resulted in the acquisition of mesenchymal traits [20]. These cells showed an increased ability to form mammospheres, which is a characteristic of mammary epithelial stem cells. A recent study with eleven common breast cancer cell lines revealed that mammosphere formation in breast carcinoma cell lines depends upon expression of E-cadherin, and suggested a close relationship between the EMT and E-cadherin in breast carcinoma cells [21].

One of the hallmarks for lobular breast cancer and diffuse gastric cancer is the typical appearance of diffusely growing rounded cells with scanty cytoplasm, which is suggesting a causal morphological effect of sporadic function of E-cadherin due to the mutations in the E-cadherin gene. Consistent with the fact, E-cadherin knock out murine model developed tumors reminiscent of human lobular breast cancer. It has been suggested that transcriptional silencing of E-cadherin gene might be associated with hypermethylation of CpG islands in the relevant promoter region or indirectly *via* the influence of transcriptional repressors of E-cadherin gene including Snail, Slug, E47, Twist1, Zeb1, Zeb2 (Sip1) etc [22,23]. Since E-cadherin is critically involved in EMT therefore, other factors those are indirectly affecting the transcription of E-cadherin, for example miRNA-200 family that affects ZEB transcriptional repressors, or associated with EMT have been reported linked with more aggressive clinical condition [23,24]. However, a recent study using 38 human breast cancer cell lines suggested that E-cadherin might not be so diabolically linked with the EMT process related to the development of relevant cancer path physiology [25].

E-cadherin in colon cancer

Tumor suppressor gene p53 relies on its quality to function as a potential sequence-specific transcriptional activator of some other proteins. Transactivation of E3 ubiquitin-protein ligase Mdm2 regulates p53 by a feed-back loop mechanism *via* ubiquitylation and proteasomal degradation of p53 [26,27]. Epidemiologycal study revealed that mutant p53-expressing tumors are aggressive and linked with poor prognosis. Several p53 mutants have been reported may acquire novel oncogenic function, which practically accelerate cancer progression by specifically regulating cancer invasion. A recent study with colon cancer cell line HCT116 revealed that the carcinogenic and metastatic role of mutant p53 is associated with the down regulation of E-cadherin, which is mediated by the elevated expression of the relevant repressor genes, *viz.*, Slug and Zeb1. The finding can explain the observation that the accumulation of p53 is accompanied with the decreased expression of E-cadherin in gastric carcinomas, and provides physiological significance of the interdependency of p53 and E-cadherin in cancer path physiology [28].

E-cadherin in gynecological cancer

Endometrial cancer (EC) and ovarian cancer (OC) are lethal gynecological diseases causing many premature deaths [29]. The normal risk of EC and OC is equal or greater than the risk of colon cancer [30]. E-cadherin has been reported linked with the gynecological tumors. Progressive behavior and deep myometrial invasion for type II EC has been established associated with the inactivation of E-cadherin, and the frequency for such association is significantly high (80-90%) [31]. One of the tissue OC thought to arise is the ovarian surface epithelium, and coincidently E-cadherin expression in this tissue is very low [32]. Defects in DNA mismatch repair and loss of E-cadherin expression has been known to linked with the gynecological cancers. Two major complexes Msh2-Msh3 and Msh2-Msh6 are involved in the recognition process of DNA mismatch repair. A recent study with knockout Msh2 and hemizygous E-cadherin developed EC-like path physiological tumors in the ovary, uterus and genital area [33]. These tumors were associated with complete loss of E-cadherin expression due to the relevant inactivating mutations. This data suggested a direct cooperatively of E-cadherin mutation and gynecological cancers.

E-cadherin in gall bladder cancer

E-cadherin has been found related with the gall bladder cancer (GBC). The study using more than 300 surgically removed tumor samples revealed that E-cadherin expression was abrogated in 67% of the tested samples diagnosed for GBC [34]. The expression of p53 gene was found high in 43% of these samples. Reportable that normal gall bladder as well as other gall bladder diseases, *viz.*, chronic cholecystitis

and xantho-granulomatous cholecystitis tissues did not over express p53, and E-cadherin expression was also found normal for these tissues. The loss of E-cadherin expression for the GBC tissues was observed suggested not to for mutation but due to some transcriptional repression mechanism that is suggesting similar relationship of p53 and E-cadherin recently reported for colon cancer [28].

E-cadherin in nerve-tissue cancer

E-cadherin has recently been shown associated with meningiomas. Meningiomas are among the most common human brain and spinal cord tumors that account for 15-20% of all central nervous system tumors [35]. They are usually derived from arachnoidal cells associated with brain menings. A recent study using 14 sporadic benign meningioma tumors with 3 normal arachnoidal tissue samples revealed that miRNA200a expression was down regulated by approximately 25 fold in meningioma tissues compare to the normal tissue. E-cadherin expression was also found abrogated in the relevant samples. Consequential functional study revealed that miRNA200a work as repressor for the transcription factor Sip1 and Zeb1, which in turn negatively regulate the expression of E-cadherin. However, miRNA200a has additional role on meningioma path physiology *via* regulation of Wnt-signaling and beta-catenin pathway. Since beta-catenin is an integral part of the C-terminal intracellular complex of E-cadherin therefore E-cadherin is indirectly involved in the relevant cancer-related pathophysiology [36]. A recent study using 60 meningioma tissues revealed sporadic E-cadherin expression in the tumors that further strengthen our understanding of the role of E-cadherin in meningiomas [37].

E-cadherin in pancreatic cancer

Pancreatic cancer (PC) is one of the worst cancers with morbidity to incidence ratio of approximately 0.83, mainly due to poor prognosis [38]. The median survival period for the patients with PC is about 4.1 months whereas the overall 5-year survival rate is less than 5% [39]. Since the diagnosis of PC is difficult therefore more than 85% patients were found in metastatic disease condition when detected positive for PC [40]. One of the Ras family homologs proto-oncogene, Kras, has been found mutated in 75 - 90% of PC incidence; $Kras^{G12D}$ is such a mutation found in PC [41]. Recent study with PC cell lines CD18/HPAF and ASPCI showed that the knockdown of $Kras^{G12D}$ allele directed to significant increase in the expression of E-cadherin both *in vitro* and *in vivo*. The study further revealed that such down regulation of E-cadherin by Kras in the relevant cell was mediated by altered regulation of E-cadherin repressor genes, *viz.*, delta-EF1, Snail and ETV4; albeit some other proteins were also found down regulated.

Besides these detrimental pathophysiological effects, some other pathophysiological consequences have been reported associated with abnormal expression and abrogated function of E-cadherin such as orofacial cleft and prostate cancer etc [42-45]. Nevertheless, the relevance of E-cadherin alteration in multiple cancers and developmental defects is well recognized, and established that the abnormal function of E-cadherin can become a curse for normal living of human.

The Blesses of E-cadherin

E-cadherin in stem cell biology

While altered expression or malfunction of E-cadherin could be very detrimental for healthy living, the normal expression and function is extremely important for natural development and physiology of animal. E-cadherin knock out mouse was reported embryonic lethal, suggesting prospect of application of this protein in stem cell biology and regenerative medicine [46,47]. Currently, stem cells, particularly, induced pluripotent stem cells (iPSCs) have become a popular choice as starting materials for regenerative medicine and tissue engineering field for the treatment of many physiological complicacies and developmental defects. Remarkably, E-cadherin has been established critically involved in many developmental and differentiation processes *in vivo* and *in vitro* systems comprising embryonic stem cells (ESC), induced pluripotent stem cells (iPSC), mesenchymal stem cells (MSC), and whole embryo [48-52].

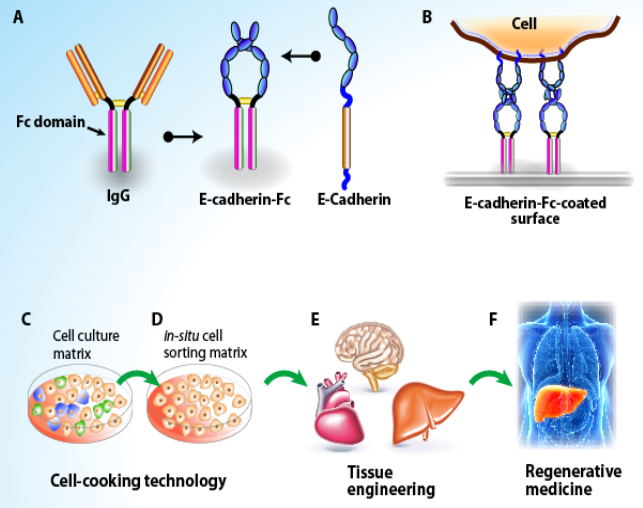
E-cadherin is an essential protein for supporting normal colony-forming phenotype of ESC and iPSC. However, recent studies revealed that over expression of E-cadherin can significantly stimulate efficiency of iPSC generation protocols [50]. Yet treatment with small molecules, which promotes E-cadherin expression, has been shown can enhance efficiency of iPSC generation [53]. The improved productivity for iPSC generation was effectively reproduced by application of C-terminal truncated form of E-cadherin that only has the extracellular functional domains. This finding indicated that the phenomenon was mainly exerted by the extracellular functional domains of E-cadherin [53]. Excitingly, E-cadherin has been reported was able to generate iPSC with only three Yamanaka factors - KLF4, SOX2, and c-MYC from murine fibroblasts excluding ectopic expression of OCT4 [50]. Recent studies revealed that where it was possible to skip other factors of Yamanaka cocktail for reprogramming of somatic cells to iPSC, however, OCT4 was not really dispensable [54-56]. This finding indicated that the spatiomechanical input exerted by E-cadherin has a critical role in driving somatic cell-fate to iPSC.

E-cadherin and cell-cooking plate

Our lab has realized the tremendous importance of E-cadherin in last decade and since has been endeavoring to exploit this fascinating protein for the regenerative medicine. The first successful application of E-cadherin in regenerative medicine was introduced little over a decade ago in the year 2002 [57]. Since E-cadherin exerts functional cell–cell coupling *via* EC domain therefore only the extracellular domain of E-cadherin was used that was fused with the Fc domain of IgG to make a chimeric protein E-cadherin-Fc (Figure 1). Interestingly, the chimeric protein E-cadherin-Fc retains the Ca^{2+}-ion dependent homophilic binding with the opposing E-cadherin catered by E-cadherin-expressing cells similar like native E-cadherin. This homophilic-interaction property of E-cadherin-Fc chimeric protein made it a very effective cell-recognizable biomaterial. On the other hand, the C-terminally fused IgG-Fc domain can bind with suitable surface, for example polystyrene, *via* hydrophobic interaction. Later it has been revealed that E-cadherin-Fc can bind directionally in such a way that the Fc-domain binds with the polystyrene surface extending the N-terminal E-cadherin towards outside to perform its normal interaction with the oncoming partners [58]. This unique property inspired to apply this as a plate-coating material for highly specific cell culture, which has been long sought for regenerative medicine protocol. Since these plates can offer selection of specific cells and also helps desired transition of experimental cells therefore they have been named 'cell-cooking plate'.

E-cadherin in hepatocyte culture

The application of E-cadherin as a novel cell-recognizable biomaterial was introduced by Nagaokaet et al. to improve the differentiation and maturation efficiency of hepatocyte in an *in vitro* system [57]. During then, several reports indicated that E-cadherin is essential for tissue morphogenesis, and is also required for maintenance



E-cadherin extracellular domain is fused with the Fc domain of IgG to generate E-cadherin-Fc biomaterial (A). E-cadherin-Fc N-terminal domains display homophilic binding with cell-resident E-cadherin while the Fc-domain binds with polystyrene surface *via* hydrophobic interaction (B). Cell-cooking plate technology has been successfully applied for desired cell culture (C) and *in-situ* cell sorting (D). Purified cells from the system can be applied for tissue engineering (E) and regenerative medicine (F).

Figure 1: Schematics of E-cadherin-Fc and its application in stem cell technology and regenerative medicine.

of matured tissues. It was earlier reported that hepatocytes could preserve their differentiated phenotypes in 3D spheroid assembly, or multi-layer cellular aggregates, which is most likely governed by E-cadherin-mediated cell-cell interaction [59]. It was also reported that culture of fetal liver cells at high cell density improved maturation of hepatocytes [60,61]; this phenomenon was attributed to E-cadherin. These findings suggested that cell-cell aggregation may directly stimulate hepatocyte maturation and maintenance of differentiated phenotypes. There was, however, no substantial evidence regarding the role of E-cadherin in these processes, and E-cadherin-Fc successfully applied as a tool to reveal the answer in a controlled manner.

The introductory application of E-cadherin-Fc as a cell-cooking biomaterial in hepatocyte differentiation study revealed that the differentiated hepatocyte was able to effectively bind with this chimeric protein-coated surface [57]. The adhered cells displayed low DNA synthesizing activity as well as conservation of Tryptophan Oxygenase (TO) expression comparable to those of spheroid-form hepatocytes. Such cell-cooking plate was also supportive to the differentiation of hepatocyte in culture there by suggested an essential role of E-cadherin-dependent matrix for the maintenance of differentiating and differentiated hepatocytes. Though it was fascinating to realize such kind of effective application of E-cadherin-Fc as biomaterial in regenerative medicine, however, the great prospect of this protein was recognized in 2006 when it was successfully applied as a defined matrix for stem cell culture that eliminated the importance of using unwanted feeder-cells in the relevant protocol [62].

E-cadherin in stem cell technology

The early protocol of stem cell culture used replication deficient mouse embryonic fibroblast (MEF) as a supporting material. Later it was realized that MEF does not only provide critically important cytokines for the stem cells but also provide supporting matrix for their survival and maintenance of pluripotency. MEF-conditioned medium (MEF-CM) was later used with matrigel to avoid the presence of unwanted cells in the stem cell culture condition. However, matrigel is a complex mixture of cell secretion without chemically defined composition, and therefore poses serious threat to the relevant protocol, particularly, if the target of the protocol is to apply the cells in regenerative medicine procedure. Recent reports stated that matrigel may contain unwanted pathogenic agent, and further strengthen the importance of using a completely defined chemical system for culturing stem cell. As mentioned earlier, Nagaoka et al. has applied the E-cadherin-Fc as a defined chemical substratum for successful culture of mouse ESCs without the necessity of any unwanted feeder layer or matrigel coating [62]. The study revealed that mouse ESC can preserve their pluripotency on E-cadherin-Fc-cooking plate for prolonged culture period. ESCs cultured on such cell-cooking plate were later successfully produced germ line-competent chimeric mouse [63]. A separate study using mouse MSC lines NIH3T3 and STO stably expressed E-cadherin as feeder-cell displayed greater level of stem cell marker expression with standard colony-forming phenotype compare to the cells cultured on normal MEF-feeder layer [64]. Several feeder-free culture protocols for ESC have been reported where ESC produce standard tightly-bound colony phenotype [65-70]. Such type of tight colony formation produces heterogeneous cell population within a colony, which potentially generates micro niche as well as affects homogenous accessibility of cytokines to these cells. As a result colony-forming stem cells differentiate heterogeneously that introduce several kinds of cells in the system as contamination along with the desired cells. This is one of the biggest limitations in stem cell technology and regenerative medicine field to resolve. Interestingly, E-cadherin-Fc matrix produced single cell phenotype for mouse stem cell [62]. This is a fascinating outcome for stem cell technology since it provides an exciting solution for overcoming the limitation of inherent colony forming phenotype-linked cellular heterogeneity. The stem cells cultured on E-cadherin-Fc-matrix bear all signs of pluripotent stem cells, and can form all three germ layers in a teratoma forming assay, as well as can generate germ line-competent chimeric mouse. Soon after, E-cadherin-Fc-cooking plate was successfully used for culturing human ESCs with milder enzymatic treatment during the cell dissociation and seeding steps [70]. Even MSCs also were successfully cultured on E-cadherin-Fc defined matrix. Interestingly, MSCs cultured on cell-cooking plate displayed higher level of E-cadherin and beta-catenin expression, which is suggesting better stemness of these cells compare to the MSCs cultured on other substratum.

E-cadherin in regenerative medicine:

Remarkably, ESCs cultured on E-cadherin-Fc-cooking plate require fewer amounts of cytokines for maintaining their pluripotency, which is significantly beneficial for cost effective culture of ESC, particularly, for bulk level culture. The ESCs with monolayer-type single cell phenotype was also showed higher proliferation and transfection efficiency compare to the standard colony-forming cells cultured on other matrices. Regenerative medicine protocols require lot of cells therefore such kind of improved proliferation ability of stem cell could be extremely beneficial for rapid amplification of iPSC on E-cadherin-Fc substratum. This may efficiently shorten waiting time of the patients to receive necessary cell therapy. On the other hand, the higher transfection efficiency of single cell phenotype stem cells obtained on E-cadherin-Fc matrix could be utilized for targeted delivery of preferred extracellular cargo, like genetic products or drugs, into these cells for improved expected effects. Reportable that E-cadherin-mediated cell-cell adhesion is frequently rearranged during early embryogenesis to regulate cell migration, cell sorting, and tissue function thus

suggesting a close relationship of stem cell maintenance, proliferation, and differentiation with E-cadherin [46,47,71-73]. However, there is no suitable system to study relevant signaling pathways to address these critical questions. E-cadherin-Fc cell-cooking plate, therefore, can be used as a suitable tool for obtaining single cell phenotype of stem cells, which will facilitate revealing relevant signaling pathways necessary for stem cell maintenance, proliferation, and differentiation. Another important application of E-cadherin-Fc-cooking plate was realized for non-enzymatic stress-free one stop *in-situ* purification of *de novo* hepatocyte from the mixtures of differentiating cells for targeted hepatocyte differentiation protocol. In fact, 92% albumin-expressing cells were harvested on E-cadherin-Fc-cooking plate without the necessity of harsh enzymatic treatment or mechanical cell sorting [74]. Collectively such kind of multidimensional benefits are exerting blessings of E-cadherin for effective advancement of stem cell technology and regenerative medicine towards application.

Summary

E-cadherin is involved in multiple pathophysiological conditions of different tissues and developmental defects. Anomalous expression or abnormal function of E-cadherin gene products due to point mutations and exon skipping have been reported for relevant disorders. Such type of mutations were reported harbored as genetic materials and carried over to the siblings and descendants. However, since the function of E-cadherin is exclusive and so far there is no other redundant gene product identified in human genome therefore atypical function of E-cadherin could be lethal for human life. On the contrary, cell-cooking plate technology has been established and recognized as a very advantageous tool for generation and purification of iPSC as well as a highly efficient defined matrix for *in vitro* iPSC culture, which is significantly propelling regenerative medicine field towards application. In would be great to achieve *in vivo* application of E-cadherin that may directly help fighting against the relevant pathological condition, for example, cancer metastasis or even developmental defects. Further interdisciplinary scientific and technological efforts are necessary to achieve new utilities of E-cadherin to push the balance from the cursed side to the blessed side that would ultimately benefit mankind.

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