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Apoptotic genes which are involved in stem cell division: Their mutation and effects

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Abstract
The regulation of stem cell division is crucial for tissue development, maintaining homeostasis, and repair of injury. Apoptotic genes play a pivotal role in maintaining proper stem cell division through the controlled elimination of damaged or unwanted cells. Mutations in these genes can disrupt the delicate balance between self-renewal and differentiation, leading to profound effects on tissue function and development. This abstract explores key apoptotic genes such as p53, Bcl-2, and CASPASE family members, highlighting their significance in stem cell division and the consequences of mutations. The protein p53 acts as a "guardian of the genome" by monitoring DNA damage and regulating gene transcription. Its expression increases in response to DNA damage and interacts with various genes like p21/waf1, mdm2, and BAX. Another gene family under scrutiny is Bcl-2, originally identified in lymphoma patients due to chromosome translocation. Bcl-2 proteins play a role in apoptosis regulation, divided into apoptosis suppressors (e.g., Bcl-2, Bcl-X_L) and promoters (e.g., BAX, Bad). BAX and Bad promote apoptosis, while Bcl-2 and Bcl-X_L inhibit it. Thus, these genes' expression is involved in maintaining the balance between cell survival and cell death in many different cell types throughout the body. Two models suggest that apoptosis regulation involves interactions between these proteins, with either pro-apoptotic BAX being suppressed by hetero-dimerization or apoptosis-suppressing proteins offering dominant survival signals. Understanding the interplay between the expression of apoptotic genes and stem cell biology is essential for unraveling the molecular mechanisms that underlie developmental disorders, aging, and diseases like cancer.

Keywords: Apoptotic genes, mutation, stem cell division, apoptotic suppressors

Introduction
In the fields of developmental biology and regenerative medicine, stem cell division is a vital process. It is essential to the upkeep and development of the body's many tissues and organs. These cells have the unusual capacity to divide and self-renew, producing distinct cell lineages as well as identical offspring cells. (Li *et al.* 2010) [1]. Since the stem cells have the ability to replace damaged or defective cells, this process has tremendous potential for therapeutic applications in the treatment of degenerative diseases and injuries (Orford *et al.* 2008) [2]. The subtle balance between self-renewal and differentiation is governed by a complex interplay of regulatory systems that govern stem cell division. A number of intrinsic and extrinsic elements, including as genetic programmes, signalling pathways, and microenvironment choreograph this delicate equilibrium. (Watt *et al.* 2013) [3]. One of the striking strategy that has been adopted by stem cells is to preserve their population and diversity is asymmetric division, in which one daughter cell keeps its uniqueness of being a " stem cell "that is to maintain its trait that differentiates stem cells from other types of cells in the body) (Morrison *et al.* 2006) [4]. This review provides a comprehensive understanding of the intricate relationship between apoptotic genes and stem cell division, shedding light on their roles in tissue homeostasis and repair. Stem cell division is regulated by a complex interplay of genes and signalling pathways a few of which are listed in Table 1.

Table 1: Genes involved in stem cell division with pivotal functions

Genes	Functional Importance	Reference
p53	Regulation of the cell cycle and prevention of tumors	(Orford *et al*. 2008) [2]
NOTCH1and HES1	Controls the equilibrium of self-renewal and differentiation	(Weng *et al*. 2006) [34]
WNT3a	Controls the self-renewal and differentiation of stem cells.	(Weng *et al*. 2006) [34]
BMI1	Maintaining the self-renewal capacity of adult stem cells.	(Seifert *et al*. 2015) [6]
SOX2	Maintenance of totipotency of embryonic stem cells.	(Seifert *et al*. 2015) [6]
OCT4	Regulates pluripotency and self-renewal of stem cells.	(Pesce *et al*. 2001) [7]
NANOG	Stabilization of embryonic stem cells.	(Orkin *et al*. & 2011 Sancho-Martinez *et al*. 2016) [9, 8]

Genes such as PIK3CA control the PI3K/AKT pathway, which affects metabolism and cell survival. Mutations can impair the maintenance of stem cells and the regeneration of tissue. (Mosner *et al.* 1994) [13]. In a nutshell it can be underlined that the mutations in the genes encoding stem cell division can disrupt the perfect equilibrium between differentiation and self-renewal thereby resulting in tissue regeneration to be hindered and possibly even contributing to the onset of illness. To effectively promote tissue healing and restore normal cellular homeostasis, specific therapeutic interventions must be developed, which requires an understanding of these genetic processes.

Defects in apoptotic pathway

Apoptotic pathway defects are common in tumours and may result in treatment resistance. The goal has been to improve the tumour cells' response to chemotherapy by restoring these abnormalities and inducing apoptosis in them. Although there are research that back up this theory, there are also differing views. (Kumar *et al.* 1996) [16]. Wyllie *et al.* 1980 [17]. have shown that medication resistance in lymphomas is influenced by the apoptotic inhibitor Bcl-2 oncoprotein. (Wyllie *et al.* 1980) [17]. A research group revealed that drug sensitivity in cancer cell lines is not significantly impacted by the amounts of essential cell-death components. (Mashima *et al.* 2005) [18]. Literature study reports, deletion of p53 or components of apoptosomes can postpone chemotherapy-induced cell death, although this does not always translate into longer life. (Schmitt *et al.* 2000) [19]. It has been observed that clonogenic assays have limits since they are conducted under harsh conditions that are not present *in vivo* -the idea that targeting abnormalities in the apoptotic pathway is a promising avenue for cancer treatment is bolstered by the discovery of multiple medicines that block anti-apoptotic proteins. G3139 (Genasense / Oblimersen), an antisense oligonucleotide that has shown promise in mitigating Bcl-2 overexpression and bettering patient outcomes. (Svingen *et al.* 2004) [20]. Bcl-2 antisense oligonucleotides are being tested in ongoing clinical trials to see how well they work against different types of tumours. Several strategies are being researched to disrupt Bcl-2 activity in cancer cells, such as the creation of BH3-exclusive protein peptide analogues and small-molecule Bcl-2 inhibitors. (Brown *et al.* 1999) [21]. The recently discovered Bcl-2 inhibitor ABT-737 shows remarkable activity as a single drug molecule mechanism-based *in vivo* tumour regression. (Nahta *et al.* 2003) [22]. When cells treated with 5-aza-2-deoxycytodine (decitabine), a DNA-methyltransferase-1 protein inhibitor that incorporates into DNA at cytosine residues and prevents further DNA methylation (Oltersdorf *et al.* 2005) [23]. Table 2 gives an idea about the role of different genes and the resultant mutation effects on the cell

Table 2: Common gene and their mutation effects

Genes	Mutation Effects	Reference
p53	Mutation of this gene increases the risk of cancer development.	(Levine *et al.* 2016) [14]
bcl-2	Anti-apoptotic Bcl-2 protein can promote cell survival, and inhibit apoptosis.	(Michael *et al.* 2001) [25]
BAX	Leads to autoimmune diseases and neurodegenerative disorders.	(Michael *et al.* 2001) [25]
Bad (bcl-2 associated agonist of cell)	Associated agonist of cell death) - disrupts the balance between prosurvival and prodeath signals.	(Yoo *et al.* 2006) [29]

Effects in gene mutation on apoptosis both in pro-apoptotic and anti-apoptotic pathways

Apoptosis is a closely controlled process of programmed cell death that is essential for preserving tissue homeostasis and halting the growth of cancer. Gene alterations can have a significant impact on this process. Mutations can cause dysregulation of apoptosis by affecting both pro- and anti-apoptotic pathways. The following pathways can throw much light on how gene mutations affect both pathways:

1. Pro-apoptotic Pathways

Apoptosis is promoted in part by pro-apoptotic genes. The Bcl-2 family, which contains both pro-apoptotic members like BAX, BAK, and BID, is one well-researched group. Changes in these genes can cause alterations in cell survival by disrupting the poise between pro- and anti-apoptotic members. For example it was cited that increased mitochondrial permeabilization can result in the release of pro-apoptotic factors like cytochrome c, which can be caused by mutations that promote the overexpression of pro-apoptotic components like BAK and BAX. This starts the apoptotic cascade and activates caspase. BAX-deficient animals showed increased carcinogenesis and decreased apoptosis, according to one study (Yin *et al.* 1997) [31].

2. Anti-apoptotic Pathways

By blocking the permeabilization of the mitochondrial membrane and the release of cytochrome c, anti-apoptotic genes like bcl-2 and bcl-xl limit apoptosis. Even when apoptotic signals are present, apoptosis can be inhibited due to mutations in these genes that increase their anti-apoptotic activity. An often observed mutation in cancer is the

overexpression of bcl-2, which prevents cell death and increases cell viability. This can contribute to tumour development and resistance to chemotherapy (Tsujimoto *et al.* 1989) [32]. Furthermore, the balance of pro-to-anti-apoptotic factors might be indirectly impacted by changes in apoptotic regulatory proteins like as p53. By upregulating pro-apoptotic genes, wild-type p53 induces apoptosis; however, mutant p53 can become inactive or even strengthen anti-apoptotic pathways, which prolongs cell life. A study has shed light on the function of p53 in the control of apoptosis. (Vousden *et al.* 2009) [27]. It can be inferred that gene alterations can cause aberrant cell survival and play a role in illnesses like cancer by upsetting the delicate balance between pro- and anti-apoptotic pathways. Additional information about how these mutations affect the regulation of apoptosis can be found in the references given.

Conclusion

In conclusion, the proper regulation of genes involved in stem cell division is crucial for maintaining tissue homeostasis and preventing diseases. Mutations in these genes can disrupt the delicate balance between self-renewal and differentiation, leading to abnormal cell growth, and tissue dysfunction, and potentially contributing to cancer development. Understanding these genes' roles and the consequences of their mutations enhances our ability to harness the potential of stem cells for regenerative medicine while minimizing the risks associated with genetic anomalies. Ongoing research in this field promises to uncover more insights, paving the way for innovative therapies and personalized treatments in the future.

Conflict of Interest

The authors have no potential conflict of interest.

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