

Possible relationship between the somatic mutations and the formation of cancers

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Abstract. Cancer is one of the most life-threatening diseases and has been studied for more than 3 thousand years (earliest records of cancer research is 1500BC). But there are still insufficient number of efficient treatments for cancer. This is a review started with introducing the cancer and somatic mutations by explaining the hallmarks of cancer, followed by, the discussion of few types of mutations, which may be potential targets regarding to the therapeutic treatments. Also, some potential targets related to those mutations are listed, such as, pRb proteins with its two subunits (p130 and p107), reverse transcriptase telomerase (TERT), shelterin complex and so on. The statement “cancer is caused by accumulation of somatic mutations” can be supported by the positive correlation between cancer and age. In addition, some mutations, which have contribution on increasing mutation frequencies, has been proved to be the factors of cancer. For example, xeroderma pigmentosum, mutations on DNA MMR rep air and BRCA1 and BRCA2 mutations. This overview of the relationship between cancer and those somatic mutations, which may provide potentials for further cancer treatments.

Keywords: Cancer, Gene, Somatic mutations, Possible Targets

1. Introduction

The earliest recorded case of cancer was discovered from ancient Egypt in 1500BC, and evidence suggests that there is no treatment. (Sudhakar, 2009) As the technology developing, different types of cancer start to be found and the definition of cancer starts to be clarified. Cancer is classified in different ways. The simplest classification is according to the position where cancer grows on, e.g., breast cancer, lung cancer. Scientists found that most types of cancer are caused by mutations. (Ponder, 2001) Therefore, modern technology starts to classify cancer according to their genetic differences by FS methods. (Alhenawi et al., 2021) From this classification, targets are easier to be determinate. Thus, treatments which focus on specific mutated proteins can be applied on a group of patients rather than one patient.

Cancer is a group of cells grows uncontrollably in a certain section. (Sporn, 1996) There are six hallmarks of cancer that has been discussed in 2000. (Hanahan and Weinberg, 2000) These hallmarks are self-sufficiency in growth signals; insensitivity to anti-growth signals; tissue invasion and metastasis; limitless replicative potential; sustained angiogenesis and evading apoptosis. This suggests that to form a cancer, the growth and anti-growth signals are functional abnormally. For cancer grow uncontrollably, there are multiple ways to keep cell dividing. But in general, these mechanisms lead to the cells lost controlling of cell cycles by mistakes in signals.

(Golias et al., 2004) Also, telomerase is continuing to produce telomere repeats to let cell replicate without limit. In addition, apoptosis must be defective, so abnormal cells cannot kill themselves.

Somatic mutations are mutations which occurs after body development. Multiple factors lead to this type of mutations. For examples, radiations are one of the most obvious factors of somatic mutations. (Balmain, 2020) Somatic mutations might also occur during the cell divisions and some somatic mutations taken place spontaneously. (Martincorena and Campbell, 2015) Those somatic mutations change the DNA sequence. Sometimes, somatic mutations may occur on some important positions (e.g., DNA region coding for growth signals and anti-growth signals receptors, telomere section or DNA region coding for telomerase, etc.) and lead to the cancer.

2. Somatic mutations related to cancer

There are some examples of the somatic mutations which contribute for the cancer formation. Firstly, the insensitivity of anti-growth signals of cells may be caused by the genetic interruption on retinoblastoma protein (pRb) pathway. In the normal cells, during G1 phase, nearly all antigrowth signals are controlled by retinoblastoma protein (pRb) and its two relatives, p107 and p130. (Wang et al., 2019) The combination of oncogene c-MYC and

transforming growth factor TGF- α causes the loss of RB1 gene. This affects the pRb proteins with their two subunits and E2F family members thus the pathway is interrupted. (Di Fiore et al., 2013) Failure of antigrowth signals transmission leads cells dividing uncontrollably. Excess telomeres raise the limitless replicative potentials of cells. The length of telomere DNA is maintained by the reverse transcriptase telomerase (TERT). (Kelland, 2007) Mutations taken place on regulator proteins of TERT would leads to the raise of limitless replicative potentials. (Autexier, 2006) The regulator proteins are called multiprotein telomere complex, shelterin in shorts. Shelterin compound has six subunits (TRF1, TRF2, POT1, TPP1, TIN2 and Rap1), which is found at certain interstitial telomeric sequences. TRF1 and TRF2 would bind and interact with telomeres. POT1 is a protein connected TRF1 and TRF2 with TPP1 and TIN2. Rap1 only attaches with TRF2 and regulates several genes next to itself which act as a transcriptional co-regulator. (Schmutz and de Lange, 2016) (Schmutz and de Lange, 2016). In cancer cells, a mutation may take place on TRF1 causes the negatively regulated telomere length. Therefore, telomere lengths loss the ability of stopping DNA replicates which may facilitate the growth of cells without a limit. (Martínez and Blasco, 2010) Epigenetic silencing of death receptors and caspase-8 genes may lead to evasion of apoptosis. There are two signalling pathways of apoptosis, one is the death receptor (extrinsic) pathway and the other one is the mitochondrial (intrinsic) pathway. Epigenetic silencing of death receptors, overexpression of FLIP or epigenetic silencing of caspase-8 may occur and lead to pathway defection. Down the intrinsic pathway, overexpression of Bcl-2 proteins (anti-apoptotic proteins), Bax mutations or epigenetic silencing of Apaf-1 causes pathway failure. These mutations activate the anti-apoptosis mechanisms. (Fulda, 2009) Furthermore, oncogene MYC may be able to trigger apoptosis. High levels of MYC gene triggers robust apoptosis, which might be a potential for cancer treatment by increasing the MYC gene levels. (McMahon, 2014)

3. Factors lead to those somatic mutations

Cancer is a genetic disease, which means that cancer is caused by the genetic information damaging. (Wishart, 2015) Except special cases which some mutations are inherited, most of those mutations are somatic mutations. Normally, cancer requires multiple mutations to develop. This phenomenon can be supported by the relationship between aging and the chances of getting cancer. When people are getting older, the chance of getting cancer increases. From the investigation carried out by Brandon Milholland, it suggests that tumours of patients over 80 years old has relative higher mutation frequencies than patients under 20 years old (0.37(95% CI=0.30 to 0.43) and 2.21(95% CI=1.96 to 2.51)). (Milholland et al., 2015) On the cellular level, aging supposes make an accumulation of damages on cells leads to senescence and

loss of replicative capacity and potentially make the cells cancerous. (Irminger-Finger, 2007)

There are many types of mutational mechanisms which may lead to be the causative origins of cancer cells. Scientists mainly investigate these mutations by sequencing the cancer cell's genomes. The result the research taken by Morgane Macherets in 2015 suggests that over 40% cancers have mutation TP53 which is related to DNA repair and (or) checkpoint and the mutation of ATM is related to the DNA repair and checkpoint as well. (Macheret and Halazonetis, 2015) For example, the investigation carried out by A Petitjean in 2007 suggests that in 235 mutants which lead to the breast cancer, there are 160 of them are related to the TP53 mutation. (Petitjean et al., 2007) (Figure 1)

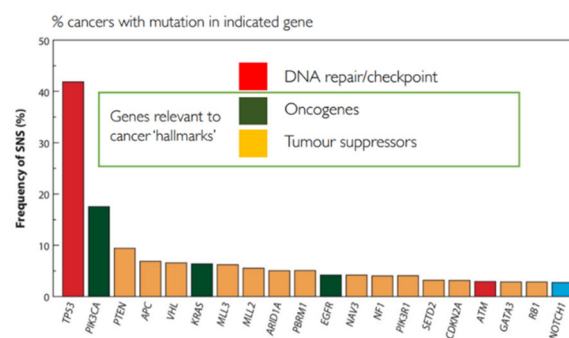


Figure 1. The results of sequencing cancer genome (Macheret and Halazonetis, 2015)

The accumulation of cancer often is affected by non-functional DNA repair system. To explain this idea more clearly, some examples are used to introduce these suggestions. When UV radiation hits the DNA strand, it may lead to certain mutations called TT-cyclobutane pyrimidine dimer. If this molecule is not repaired in time, these types of mutation may be accumulated in the cells. There is a disease called xeroderma pigmentosum (XP) affects the DNA repair mechanisms, which may contribute to the mutations accumulations and therefore increases the chance of getting cancer.

Xeroderma pigmentosum (XP) is a rare autosomal recessive disorder. There are eight groups of XP proteins related to eight genes (named XP-A, XP-B, XP-C, XP-D, XP-E, XP-F, XP-G and xeroderma pigmentosum variant XP-V). (Kniberg, 2015) One of those proteins group, called DNA polymerase eta, is required to replicate DNA containing unrepaired damage. (Veloza and Albuquerque, 2019) The polymerase eta is used to bypass those thymidine dimers with two adenine bases. However, the polymerase eta gene is mutated the polymerase eta with XP-V syndromes would be non-functional. Therefore, our cell loses the ability to replicate damaged DNA leading to mutations. (Lee and Pfeifer, 2008) As DNA damage (i.e. mutations) accumulates, the chance of getting cancer increases.

Other mutations affecting the DNA repair and checkpoint pathways may also allow the accumulation of mutations in cell's DNA. Lynch syndrome is a disease which affects the DNA mismatch repair (MMR) functions. This is an

autosomal dominant mutation which provides a greater chance to get colorectal cancer and endometrial cancer. The function of MMR is to repair a piece of unmatched DNA generated by a polymerase error by cutting a single strand of DNA out and refilling the gap with DNA polymerase. MMR involves the MutS protein which is detecting mismatches and MutL protein which repairing those mismatched DNA. In eukaryotic cells, there are at least six MutS homologues and four MutL homologues. Four of those subunits may be mutated in Lynch syndrome (MSH2, MSH6, MLH1 and probably MLH3). These mutations lead to MMR being non-function. (Bhattacharya and Patel, 2021) Therefore, some mismatched DNA may be replicated causing the mutation to be made permanent. The non-functional MMR pathways are more likely to induces mutations, which increases the mutation frequencies and potentially increases the chance of getting cancer.

BRCA1/BRCA2 are also an important and common target regarding to cancer treatment. Mutations of BRCA1 and (or) BRCA2 may produce a higher chance of getting breast cancer, ovarian and pancreatic cancer. BRCA1 is assigned to chromosome 17 and found three years earlier than BRCA2 and linked with chromosome 13. These types of mutations affect the BRCA1 proteins and causes BRCA1 shortened and non-functional. (Varol et al., 2018) BRCA1/BRCA2 stimulates homologous recombination to re-join two pieces of DNA. (Anderson et al., 1998). If this protein is non-functional, cut DNA can only be corrected by nonhomologous end joining which may introduce errors. When those errors accumulated, it may increase the chance of getting cancer.

4. Conclusion

Discussing the relationship between the somatic mutations and the cancer origins, some examples were used in this review. Those examples were analysed, and few possible targets were suggested. The fighting with cancer still needs effort and there is still a long way to end. This overview only suggested few ideas of the treatment of cancers, but none of them can really 'solve the problem'. In my point of view, the combination of different treatments should be taken place to deal with cancer due to large number of mutations. The targets suggested above can only stop or 'kill' cancer cells in some extent, but the repairment of those healthy tissues are still the problems regarding to the cancer treatments. In addition, the types of cancer are varied. This even increases the difficulty of cancer treatment. For example, treatment for xeroderma pigmentosum can only dealing with certain types of skin cancers, and treatments for BRCA1/BRCA2 are only functions for few cancers and especially for breast cancer. From those starting points, more types of cancer treatments may be discovered. Then, combining those treatments may increase the possibility to treat the cancer properly.

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