HIGH SCHOOL EDITION
Journal of Student Research
Volume 11 Issue 4 (2022)

The Ribosome's Effect on Stem Cells and How Their Dysfunction Could Cause Cancer

Anika Chawla[1]

[1]Gifted Gabber

ABSTRACT

Recently, the importance of ribosomes has greatly increased. It was discovered that they play a large role in the functionality of stem cells. This is due to the ribosome's effect on translational efficiency. Without high translational efficiency, stem cells would lose the ability to differentiate into other cells. If stem cells become dysfunctional, whether it is due to malfunctioning ribosomes, lack of ribosomes, or other mutations, diseases could arise, and tumors may form. In certain conditions, the tumor can be malignant and generate cancer. As more research is done on these connections, alternate treatments for cancer may be discovered and scientists may be able to figure out a way to prevent certain cancers from forming by starting at its molecular source.

Introduction

Stem cells are known for their ability to renew themselves. However, it has been recently discovered what aids their renewal process. The ribosome, a macromolecule that is made from proteins and RNA, has been found to play a large role in the fate of stem cells. Ribosomes are involved with protein synthesis and translation, and because stem cells self-renew, they must have a high level of translational efficiency. Therefore, a ribosome's functionality is crucial for a stem cell's fate and its ability to function. Although it is now known that ribosomes affect stem cells, it is not entirely known what occurs when a ribosome negatively affects a stem cell and its fate.

This research paper will predominantly highlight the function of both stem cells and ribosomes, and how one affects the other, as well as examine the possibility of negatively affected stem cells' ability to cause diseases, such as cancer.

The Function and Formation of Stem Cells

Stem cells are considered to be the body's "master cells," meaning that they are essentially the key factors in our organs, blood, tissue, and immune system. These cells have the ability to self-renew and serve as a repair system to replace damaged cells in tissue. These impressive cells fall under two categories: pluripotent stem cells and somatic, or "adult," stem cells. Pluripotent stem cells have the ability to transform into any cell in the human body. Under this category falls embryonic stem cells, which supply new cells for embryos as they develop into newborns. These cells also have the ability to become any cell in the body. In contrast, adult stem cells, also said to be multipotent, can only transform to create specialized stem cells of the specific organ or tissue that they are found in, such as skin or blood cells (Mayo Clinic Staff, 2022). When stem cells replicate and divide, there are three outcomes: the first being that both daughter cells, the resulting cells from the division of a parent cell, may be stem cells, the second being that one daughter cell becomes a stem cell while the other daughter cell becomes a differentiated cell, and the last being that both daughter cells are more differentiated.

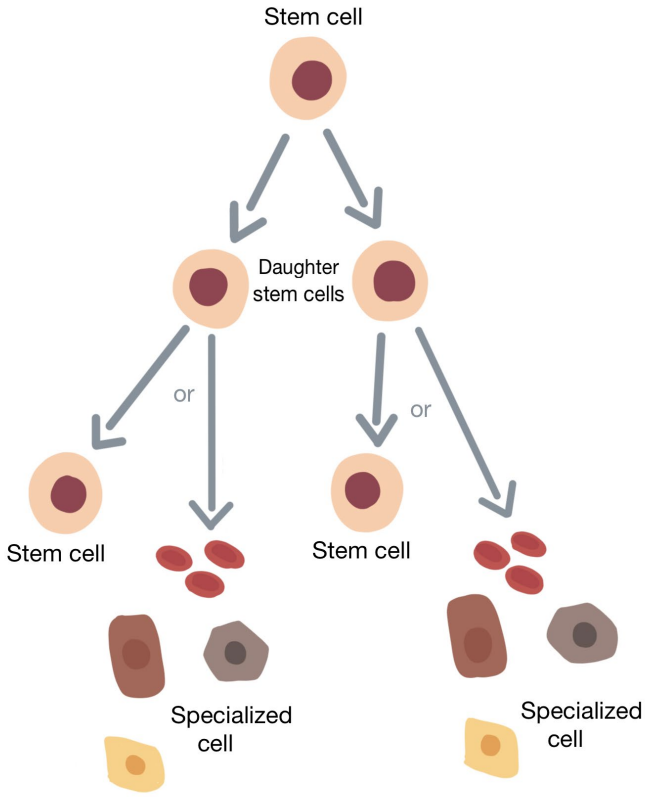

Figure 1. Stem cell differentiation. As seen in the figure, a stem cell splits into two daughter cells, which can then become either more stem cells or specialized cells.

Stem cell differentiation is the process of the cell transforming into a specialized cell. The regulation of the balance between the types of stem cell divisions, or the "potency," is crucial because if the ratio becomes imbalanced, the body will not be able to function correctly which could result in several types of diseases (Donatello et al., 2011). It is not yet known what exactly controls that regulation. Previously, research has focused on MUSASHI-2, an RNA-binding protein. It was found that when that protein is eliminated from specific stem cells, such as blood stem cells, those cells become more likely to become differentiated cells and not stem cells. However, a new study that focuses on METTL3, another RNA-binding protein, found that it is able to add methyl groups, or chemicals, to certain RNA nucleotides (Grisham, 2020). This is also known as methylation, and it ultimately aids in the regulation of RNA stability and in protein production efficiency. Therefore, RNA methylation and the METTL3 protein are believed to play a part in controlling how stem cells regulate their differentiation, but further research is necessary to identify the exact mechanism for stem cell differentiation.

The Function and Formation of Ribosomes

The ribosome is a 2-unit structure that is made from proteins and RNA. The two structures are the small ribosomal subunit and the large ribosomal subunit. The small ribosomal subunit is responsible for decoding the genetic information, while the large ribosomal subunit catalyzes the formation of the peptide bonds (Gregory et al., 2019). The ribosome as a whole is generally known for its vital role in the formation of proteins as protein synthesis occurs in the

ribosome itself. The ribosome reads an mRNA sequence and translates it into amino acids, which grow into a polypeptide chain. This chain is the primary degree of protein folding as it develops into a full protein. The ribosome also acts as a "docking station" for the tRNA that contains the amino acid that will be added to the growing polypeptide chain. The proper formation of the mature ribosome is crucial for its functionality. The process of the formation of the ribosome starts with the ribosomal RNA genes being transcribed by RNA Polymerase I into a single RNA precursor in the nucleolus. The 5S rRNA gene is transcribed separately in the nucleoplasm by RNA Polymerase III. Ribosomal protein genes are also transcribed in the nucleoplasm, but are done by RNA Polymerase II, and are then sent to the cytoplasm for translation. The ribosomal proteins and 5S rRNA gene are then imported into the nucleolus, where they will bind with the rRNAs that were transcribed there to form the small and large ribosomal subunits (Wang et al., 2014). These preassembled subunits are then sent to the cytoplasm through nuclear pores, a protein-lined channel that regulates the transportation of molecules to the cytoplasm. In the cytoplasm, they will develop further to become mature ribosomes.

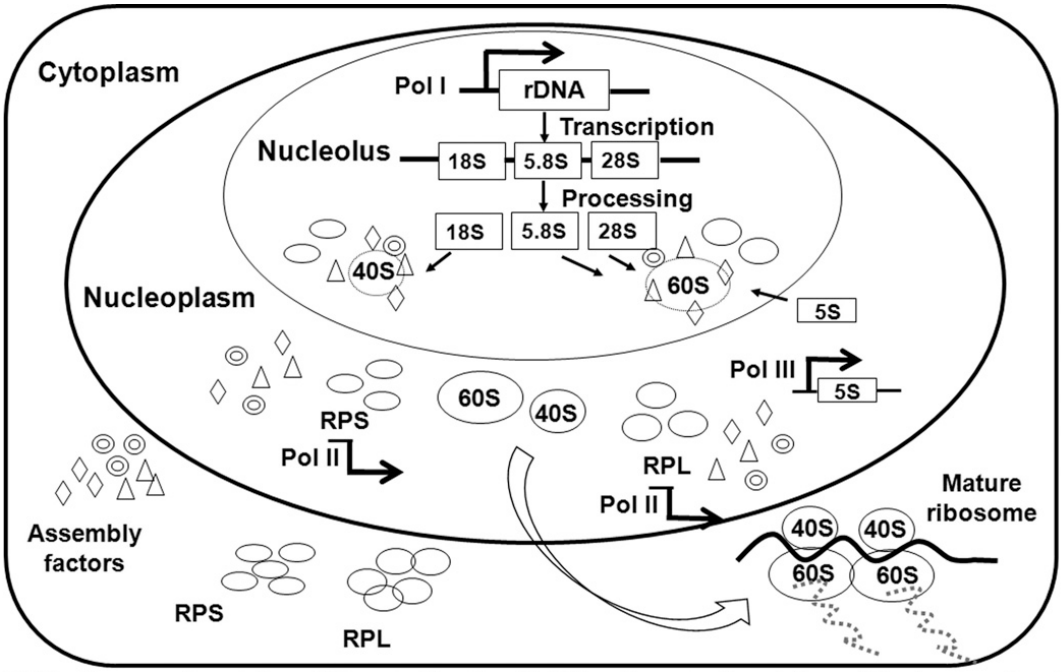

Figure 2. Ribosome Biogenesis. The figure depicts a visualization of the process of the formation of a mature ribosome in a eukaryotic cell (Wang et al., 2014).

In total, the two mature ribosomal subunits contain 4 different types of rRNAs, eighty different ribosomal proteins, three types of RNA Polymerases, and several other factors that are all required for the synthesis and final assembly of the mature ribosome. Therefore, it is crucial that each component works properly to ensure the proper functionality of the ribosome, as it affects other structures and functions in the body.

The Ribosome's Effect on Stem Cells

The Ribosome's Role in Translation

Recent studies have found that ribosomes play a large role in deciding the fate of stem cells, or how stem cells differentiate. This begins during protein synthesis. The ribosome is responsible for crucial steps of the translation process

including initiation, elongation, and termination. During initiation, incoming mRNA binds to the ribosomes to begin the process of translation. On the small ribosomal subunit, there is a "docking site" to which the mRNA and tRNA bind in order to allow the mRNA to direct the correct tRNA molecules to build the polypeptide chain. This is also considered the "A" site. During elongation, as the "A" site continues to bind the tRNAs to the ribosome, the "P" site is responsible for binding tRNAs that are carrying amino acids that have already formed peptide bonds to grow the polypeptide chain but are still attached to the tRNA. The peptide bonds are able to form because the ribosome contains an enzyme called peptidyl transferase (Tirumalai et al., 2021). At the last site, the "E" site, the tRNAs are released so that they can bind to more amino acids to continue to add to the growing polypeptide chain. All three sites are located on the ribosome and cannot work correctly without a functioning ribosome. During termination, stop codons are recognized at the "A" site and the peptidyl transferase is instructed to add a water molecule to the "P" site amino acid in order to make the tRNA detach from the amino acid and release the polypeptide chain or new protein. The small ribosomal subunit and large ribosomal subunit detach from the mRNA and each other and are sent to another translation initiation complex to repeat the process. Without a functioning ribosome, translation would not be able to properly take place. The ribosome is therefore vital for translational efficiency because it is responsible for how the process of translation occurs. With an increased speed of translation, ribosomes would be able to restart the process for another protein and bind to the mRNA much more quickly (Rodnina, 2016). However, finding the right speed is important because a translational efficiency that is too high could cause proteins to be made improperly and cause misfolding, but a low translational efficiency could hinder stem cell differentiation.

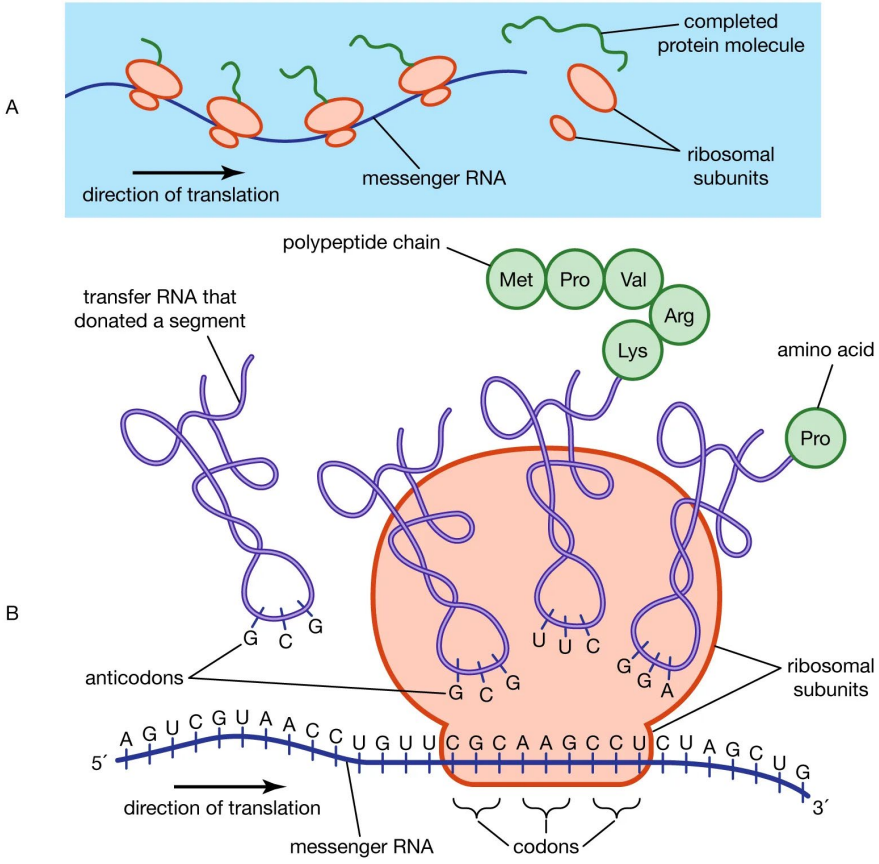

Figure 3. Translation. As seen in figure 3, the small and large ribosomal subunits are responsible for the process of translation in order to create a polypeptide chain, which will eventually become a protein (Jain et al., 2019).

Importance of Translational Efficiency for Stem Cells

Translational efficiency is crucial for stem cells because, with their ability to self-renew, they require protein to be made more quickly in order to differentiate into other types of cells. However, the regulation of the efficiency is also important because an efficiency that is too high, not only can proteins become misfolded, but it could cause too many stem cells to become differentiated, leaving not enough stem cells that are undifferentiated. This is also vital because stem cells need to preserve the capability to respond to signals concerning changes in cell identity by quickly altering gene expression (Gabut et al., 2020). So, the regulation of the translation process is crucial for stem cell fate decisions and differentiation. Researchers discovered that translational efficiency is two times lower in undifferentiated embryonic stem cells than in differentiated embryonic stem cells (Sampath et al., 2018). It was also found that the polysome density, the portion of actively translating ribosomes, was sixty percent higher in differentiated embryonic stem cells than in undifferentiated cells. This exemplifies that ribosome activity, and therefore translational efficiency, plays a large role in stem cell homeostasis and differentiation. Translational control is a key factor in regulating stem cell functions and responding to changes in stem cell fate.

How Stem Cells May Become Negatively Affected

Ribosomal heterogeneity is another important factor in the process of translation and the functionality of stem cells. It refers to ribosomes as varying in composition and specific function pertaining to translational control (Barna et al., 2018). Though physical evidence of ribosomal heterogeneity has been difficult to obtain in the past, researchers Naomi R. Genuth and Maria Barna have recently discovered that some actively translating ribosomes are lacking at least one ribosomal protein (Barna et al., 2018). Without this ribosomal protein, the ribosome is not able to function as it should. Small changes in the structure of the ribosome can cause translation to not occur properly and therefore affect translational efficiency. Furthermore, if the ribosomal proteins themselves are dysfunctional, translation may be affected. This is crucial for specialized ribosomes. If the ribosomal proteins become depleted or dysfunctional due to mutations or other circumstances, translation may become hindered, which will, in turn, prevent stem cells from differentiating properly. This may also cause the number of functioning ribosomes in a cell to decrease, also preventing important processes from taking place (Barna et al., 2018).

Not only do the internal mechanisms of a ribosome contribute to its functionality, but mutations can form which can cause the number of active ribosomes to decrease significantly. This can lead to stem cell dysfunction and eventually cell death. Without enough ribosomes, the translational efficiency decreases and therefore prevents stem cells from differentiating properly (Han et al., 2020). Noncoding RNAs have also been found to affect stem cell "fate." Noncoding RNAs are important regulatory components as they contribute to maintaining the functionality of stem cells (Hu et al., 2016). Additionally, rRNA processing is a critical part of the formation of a ribosome. One processing complex, SSUP, can reduce pluripotency and the effectiveness of translation if they are formed improperly (Han et al., 2020). Consequently, without the appropriate regulation of SSUP, the translational efficiency can decrease and can therefore hinder stem cell differentiation. If stem cells are unable to function and differentiate correctly, certain diseases could arise.

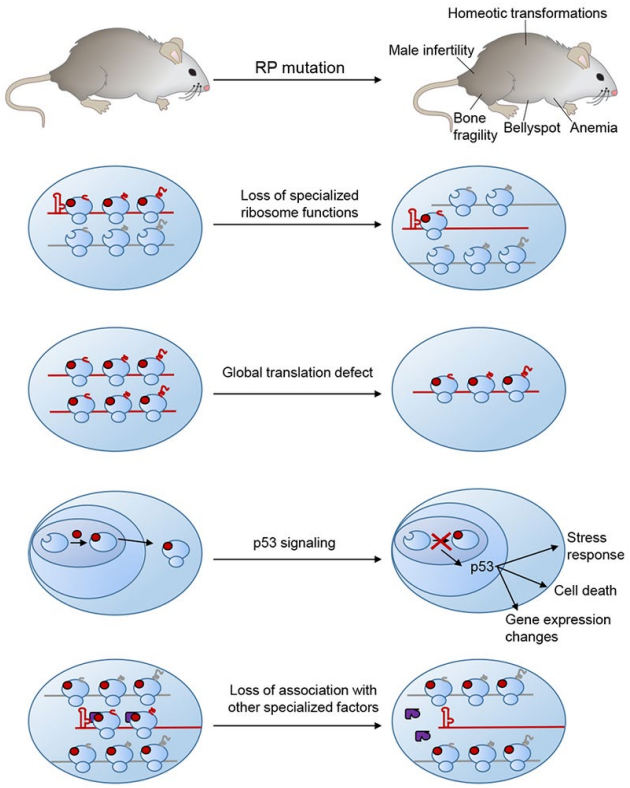

Figure 4. Effects of ribosomal protein dysfunction. This figure depicts the results of several types of scenarios in which ribosomal proteins do not function properly (Barna et al., 2018).

How Negatively Affected Stem Cells Could Cause Cancer

When stem cells lose the ability to control the regulation of their differentiation, they may become malignant, or show signs of malignancy. Because these stem cells live the longest in organs and tissues, they have a higher chance of becoming malignant and developing cancer. Once cancer develops, it is able to progress because of the shared ability to self-renew.

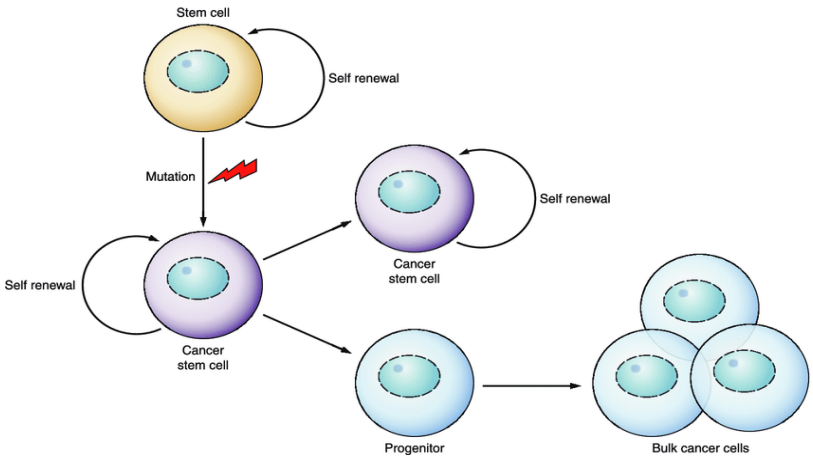

Figure 5. Renewal of cancer stem cells. Once a stem cell becomes a cancer stem cell, they will continue to self-renew and the cancer will progress (Clarke, 2012).

There are several ways that this may occur. The two most common ways can be displayed with models. In the first model, dysfunction and mutations occur in the stem cells themselves, preventing the stem cells from differentiating properly. This makes them more susceptible to additional triggers that could form malignant tumors. On the other hand, the second model describes how the initial dysfunction occurs in the stem cell, but final transformation into cancer only happens to the source of the specific cancer. Both of these models demonstrate affected stem cells' abilities to become cancerous. However, another factor has been discovered that also affects the initiation of this process. Chronic inflammation, slow and long-termed inflammation that lasts for prolonged periods of time, contributes to the formation of cancer stem cells. Chronic inflammation occurs because of delayed healing of wounds or continuous infection that maintains the activity of inflammatory cells. This environment triggers stem cells and causes cancer to develop (Afify et al., 2019). So, when stem cells are unable to differentiate properly, whether it is due to internal mechanisms or their environment, malignancy can form and cancer may develop. To treat this, a recent therapy that targets cancer stem cells can slow tumor growth and can cause regression.

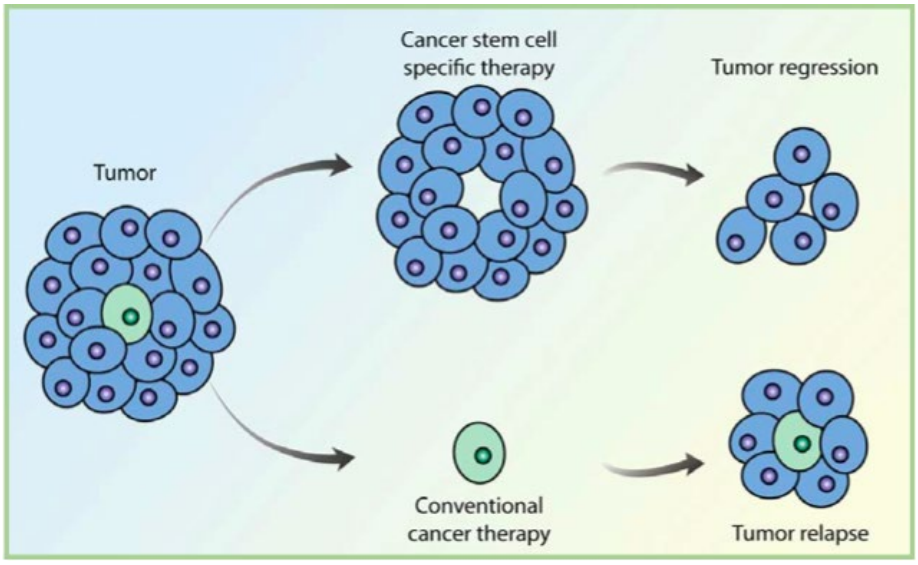

Figure 6. Therapy to induce cancer regression. Targeted cancer stem cell therapy can contribute to tumor regression.

Because most cancer treatments target large tumor masses, they often fail to eliminate the tumors that originate from just a few cancer stem cells. In addition to current treatments, targeted cancer stem cell therapy is more reliable for slowing cancer growth and generating tumor regression.

Conclusion

Ribosomes have been recently found to be critical in not only protein synthesis, but also the functionality of stem cells. With their responsibility of ensuring that translation happens correctly, they are also responsible for translational efficiency, or the speed at which translation occurs. This is vital because stem cells require a high translational efficiency to maintain the ability to self-renew. If the ribosome is unable to control translational efficiency, stem cells will not be able to differentiate properly. Ribosomal proteins also contribute to the dysfunction of stem cells because if they become dysfunctional themselves or depleted, the number of actively translating ribosomes will decrease, preventing stem cell differentiation from occurring appropriately. Without the ability to control the regulation of "fate" decisions, stem cells may become malignant. Because stem cells also last the longest in organs and tissues with their ability to self-renew, the chance of them transforming into cancer stem cells increases. Also having the ability to self-renew, cancer stem cells can cause tumors and cancers to progress. Chronic inflammation also creates an environment

that triggers stem cells because of inflammatory cells that maintain its activity. This can also lead to the development of cancer. However, a recent therapy was created to target cancer stem cells in order to promote tumor regression. In addition to other cancer treatments, this could become a part of the answer to eliminating cancer because instead of focusing on large tumor masses, it targets the cancer that may arise from just a few cancer stem cells, therefore slowing cancer growth and possibly regressing the cancer. In all, ribosomes and stem cells both play an important role in the health of our bodies and can play a large role in the formation of certain types of cancer. More research is needed in all areas in order to identify the exact mechanisms that control the direct cause of ribosome and stem cell dysfunction and the development of cancer. However, current research about these correlations can still be valuable in finding a more reliable treatment for cancer and preventing cancer.

References

Afify, S., & Seno, M. (2019). Conversion of Stem Cells to Cancer Stem Cells: Undercurrent of Cancer Initiation. Cancers, 11(3), 345. https://doi.org/10.3390/cancers11030345

Donatello, S., Hudson, L., Cottell, D. C., Blanco, A., Aurrekoetxea, I., Shelly, M. J., Dervan, P. A., Kell, M. R., Stokes, M., Hill, A. D., & Hopkins, A. M. (2011). An imbalance in progenitor cell populations reflects tumour progression in breast cancer primary culture models. Journal of Experimental & Clinical Cancer Research, 30(1). https://doi.org/10.1186/1756-9966-30-45

Gabut, M., Bourdelais, F., & Durand, S. (2020). Ribosome and Translational Control in Stem Cells. Cells, 9(2), 497. https://doi.org/10.3390/cells9020497

Genuth, N. R., & Barna, M. (2018). The Discovery of Ribosome Heterogeneity and Its Implications for Gene Regulation and Organismal Life. Molecular Cell, 71(3), 364–374. https://doi.org/10.1016/j.molcel.2018.07.018

Greenow, K., & Clarke, A. R. (2012). Controlling the Stem Cell Compartment and Regeneration In Vivo: The Role of Pluripotency Pathways. Physiological Reviews, 92(1), 75–99. https://doi.org/10.1152/physrev.00040.2010

Gregory, B., Rahman, N., Bommakanti, A., Shamsuzzaman, M., Thapa, M., Lescure, A., Zengel, J. M., & Lindahl, L. (2019). The small and large ribosomal subunits depend on each other for stability and accumulation. Life Science Alliance, 2(2), e201800150. https://doi.org/10.26508/lsa.201800150

Grisham, J. (2020, May 12). How Stem Cells Decide Their Fate. Memorial Sloan Kettering Cancer Center. https://www.mskcc.org/news/how-stem-cells-decide-their-fate

Han, Z., Zhang, Q., Zhu, Y., Chen, J., & Li, W. (2020). Ribosomes: An Exciting Avenue in Stem Cell Research. Stem Cells International, 2020, 1–12. https://doi.org/10.1155/2020/8863539

Hu, S., & Shan, G. (2016). LncRNAs in Stem Cells. Stem Cells International, 2016, 1–8. https://doi.org/10.1155/2016/2681925

Ribosome. (2022). Genome.Gov. https://www.genome.gov/genetics-glossary/Ribosome

Rodnina, M. V. (2016). The ribosome in action: Tuning of translational efficiency and protein folding. Protein Science, 25(8), 1390–1406. https://doi.org/10.1002/pro.2950

Sampath, P., Pritchard, D. K., Pabon, L., Reinecke, H., Schwartz, S. M., Morris, D. R., & Murry, C. E. (2008). A Hierarchical Network Controls Protein Translation during Murine Embryonic Stem Cell Self-Renewal and Differentiation. Cell Stem Cell, 2(5), 448–460. https://doi.org/10.1016/j.stem.2008.03.013

softCell e-learning | British Society for Cell Biology. (2020). softCell E-Learning. https://bscb.org/learning-resources/softcell-e-learning/

Stem cells and cancer. (2021). Harvard Stem Cell Institute (HSCI). https://hsci.harvard.edu/stem-cells-and-cancer

Stem cells: What they are and what they do. (2022, March 19). Mayo Clinic.
Tirumalai, M. R., Rivas, M., Tran, Q., & Fox, G. E. (2021). The Peptidyl Transferase Center: a Window to the Past. Microbiology and Molecular Biology Reviews, 85(4). https://doi.org/10.1128/mmbr.00104-21

translation | Description, Process, & Location. (2019). Encyclopedia Britannica. https://www.britannica.com/science/translation-genetics

Wang, W., Nag, S., Zhang, X., Wang, M. H., Wang, H., Zhou, J., & Zhang, R. (2014). Ribosomal Proteins and Human Diseases: Pathogenesis, Molecular Mechanisms, and Therapeutic Implications. Medicinal Research Reviews, 35(2), 225–285. https://doi.org/10.1002/med.21327

What Are Stem Cells? –. (2021). National Stem Cell Foundation.