"A Stochastic Model of Stem Cell Proliferation, Based on the Growth of Spleen Colony-Forming Cells" (1964) by James Till, Ernest McCulloch, and Louis Siminovitch [1]

By: Bains, Ajeet Keywords: Stem cells [2] Bone Marrow [3] Colony-Forming Cells [4]

In 1964, authors James Till, Ernest McCulloch, and Louis Siminovitch, published "A Stochastic Model of Stem CelProliferation [5], Based on The Growth of Spleen Colony-Forming Cells," which discusses possible mechanisms that control stem cell division. The authors wrote the article following their experiments with spleens of irradiated mice to demonstrate the existence of stem cells [6], had unknown properties. In their previous experiments, Till and McCulloch noticed that many similar-looking colonies of cells formed on the spleens of irradiated mice, but those colonies had a highly variable number of stem cells [6]. They could not explain why some stem cells [6] gave rise to many stem cells [6] while others only gave rise to a few. In the article, the authors propose an explanation for how stem cells [6] divide and renew, and provide both a greater understanding as to how cancerous tissues may arise due to unchecked stem cell division as well how stem cells [6] can aid in cancer therapy.

Stem cells are cells with the unique ability to develop into several specialized cell types such as blood or brain cells. Stem cells differ from somatic cells in that they are not specialized and can divide and renew themselves over a long span of time. There are two main types of stem cells [6], called embryonic stem cells [7] and adult stem cells [8]. Adult stem cells [6] are multipotent, meaning that they give rise to a number of varied cell types, but embryonic stem cells [7] are pluripotent and can give rise to any type of mature cell. Adult stem cells [6] are more specialized than embryonic stem cells [7] but they remain in a non-specialized state until the body needs to repair damaged tissue. Embryonic stem cells [6] are stem cells [6] located in the inner mass of cells within an embryo. Additionally, embryonic stem cells [7] can replicate over a longer span of time and develop into more than 200 cell types.

In 1957, McCulloch and Till joined the Ontario Cancer Institute in Toronto, Ontario, where McCulloch studied blood diseases and Till studied radiation [9] and its effects on cell development. From 1958 to 1963, they researched bone marrow cells and irradiated mice spleens that showed evidence that bone marrow cells have the ability to self-renew, divide, and specialize. In 1963, they collaboration with Siminovitch, who studied human genetics and the genetic roots of cancer at the University of Toronto in Toronto, Ontario. The authors determined key properties of stem cells [6], specifically their ability to self-renew and give rise to other stem cells [6]. Their findings provided the basis for research on how to isolatestem cells [6] and develop them for regenerative medicine [10], where stem cells [6] can replace damaged or diseased cells.

In the "Introduction," the authors divide the article into three main sections. In the first section, titled "Experimental Procedures," the authors describe the step-by-step process of the experiment used to count the colony-forming cells in spleens of irradiated mice. In the next section, titled "The Birth and Death Process," the authors seek to explain the odd results of the colony-forming cell counting experiment by observing the probability in which a cell is born or removed. In the final section, titled "Discussion," the authors summarize their thoughts in the article by restating the birth and death model while also calling for possible future research into the mechanisms, which control cell birth and death. They also state the significance of the model by revealing how it helps determine whether the production of specialized and unspecialized cells is under precise control from surrounding tissues.

In the first section, titled "Experimental Procedures," Till, McCulloch, and Siminovitch describe their experiment with colony-forming cells and irradiated mice. They tested for the relative number of stem cells [6], also known as colony-forming cells, by counting the number of mouse [11] spleen colonies. They tried to gather numerical data that would prove that differentmouse [11] spleen colonies have different numbers of stem cells [6] by the counting of mouse [11] spleen colonies. They prepared cell suspension from adult mouse [11] marrow or spleen tissue and an injected appropriate number of those cells into each of a group of recipient mice irradiated with a lethal dose of radiation [9] to prevent the host cells from forming colonies on their spleens. After ten days, the authors euthanized the mice, isolated their spleens, and tested for colony-forming cells within the spleen colonies.

Furthermore, the authors dissected each spleen colony from spleens containing a few well-separated colonies. They took cells from each colony, and injected the cells into other lethally irradiated mice then counted the number of colony-forming cells that developed. Only a percentage, p, of the injected colony-forming cells formed colonies on the spleens. For bone marrow cells, p is around seventeen percent. The authors used that information to obtain the number of colony-forming cells per colony. Overall, they tested eighty-nine spleen colonies and found an average of four point five colony-forming cells per colony and a variance of

eighty-one point four colony-forming cells per colony. The authors noted that the variance, which measures how spread out the numbers are from the average, was exceedingly high. Some colonies had very few colony-forming cells while others had many more colony-forming cells. The authors sought to understand why that variation occurred in order to determine if any sort of mechanism at the cellular level could control whether stem cells [6] divide to form other stem cells [6] or specialized cells.

In the following section, titled "The Birth and Death Process," Till, McCulloch, and Siminovitch propose the birth and death model to explain the varying number of colony-forming cells among the colonies. The model states that a single cell may give rise to offspring similar to itself, that is a stem cell that will go on to reproduce or a differentiated cell that will not reproduce or death and those two possibilities occur randomly. The development of a colony from a single cell produces a small number of new colony-forming cells and a large number of cells without the ability to form colonies. The differentiated cells are specialized cells within the colonies. Thus, many of the offspring of colony-forming cells lose the ability to form colonies because they become specialized and are no longer stem cells [6]. The loss of colony-forming ability with specialization considered a death process, and it contrasts with the self-renewal of colony-forming cells, which is a birth process. According to the authors, the number of colony-forming cells in a colony is the random probability that a colony-forming cell would self-renew into another colony-forming cell instead of specializing into other cell types. They claim that the birth and death process influences colony formation, which means that random chance determines whether an individual stem cell will divide. The birth and death process may not be a homeostatic or internal control mechanism that controls which individual cells will divide into stem cells [6] and which cells will specialize.

In the final section, titled "Discussion," the authors reiterate how stem cells [6] proliferate, and provide further rationale for the random birth and death process. The model of proliferation of cells during growth of spleen colonies has the following features every colony-forming cell may follow in one of two pathways. On one hand, the cell may divide and produce two new cells with the capacity to form colonies. On the other hand, the cell may specialize, and in doing so, lose the capacity for colony formation, although it may retain the ability to undergo several divisions, producing a number of fully specialized descendants.

The second feature of the model is that the two processes, the birth process, and the death process, occur at random in the population of colony-forming cells. The model implies that regulating the individual cells within the population is not precise. The question arises as to how relaxed regulation [12] can be reconciled with the orderly behavior of normal blood forming tissue. The authors use an analogy with the decay of radioactive nuclei to help explain how that can happen. According to the authors, if one studies a large number of radioactive atoms, one sees a very regular pattern of decay, following an exponential law. However, if one studies individual atoms, they decay in an unpredictable fashion at random. The authors state that it is possible their studies of the descendants of single cells display the random feature of hematopoietic function, while a study of large populations of cells reveals the orderly behavior of the whole system. It is the population as a whole regulated by signals from surrounding tissue rather than individual cells, and the authors suggest that control mechanisms act by varying the birth and death probabilities for an overall population of cells.

Because of the article's publication soon after Till and McCulloch's initial discovery of stem cells [6] in 1961, the authors were one of the first to question why stem cells [6] behave the way that they do. The authors proposed a birth and death model based on random chance, but still call for further research on what mechanisms control whether a cell is born or dies. Till, McCulloch, and Siminovitch's article provided a foundation for future experiments that predicted stem cell activity, including experiments that attempt to predict cancerous stem cell activity within tumors based on a similar probabilistic model that Till, McCulloch, and Siminovitch developed. The stochastic model allows for simulations of treatment scenarios and therefore improved treatment protocols for cancer treatment such as immunotherapy. Simulations may guide the choice of experiments to reduce the number of necessary experiments.

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