

Short Article

Biomedical Science and Clinical Research

Symbiont Conversion Theory

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Abstract

Symbiont Conversion Theory is a new scientific theory, summarizing and generalizing efforts that have been made by various researchers in the past years; it could even be perceived as a new scientific paradigm. This theory states that microorganisms and cells which are commonly considered to display parasitic behaviour can be "educated" and transformed into symbionts. This is not just a hypothesis but a theory since there is already evidence that proves that this is possible. The primary motivation for developing this theory is the failure of classical approaches to therapy of cancer and infectious diseases that follow the paradigm "destroy and kill". It is common knowledge about medical doctors that chemotherapy and radiation therapy have detrimental side effects on healthy, functional tissue, and also that antibiotics can harm benevolent cells. These negative side effects can possibly be avoided by the new approach of treating parasitic diseases by converting the culprits into symbionts of which the human organism profits. Another motivation for developing this theory is that some researchers have suggested bacteria and other microbes have certain innate rights themselves [1].

1. Motivation and Goals

Symbiont Conversion Theory is the statement that parasites can be converted into symbionts, and it explains by a couple of examples how this can be done. There is both a practical and an ethical motivation for the development of this theory. Some may dismiss the ethical dimension as being unimportant; after all, who empathizes with microorganisms, except perhaps some crazy people.

However, even if you dismiss the ethical component, Symbiont Conversion Theory has a practical value: it is just too well-known a matter of fact that chemotherapy, radiation therapy and antibiotics can have harmful side-effects which are better to be avoided.

The long-term goal is to create organisms, most of all humanoid organisms, that have an improved immune system. Instead of destroying and killing intruders, the immune system of this post-human species should educate the parasites and convert them into symbionts. This, of course, is only a long-term goal. It requires synthetic biology to reach a level that allows to create artificial immune systems. It also requires artificial life and computational systems biology to be far more developed than now, so that synthetic organisms can be simulated on a computer before the modifications are actually implemented, to avoid mistakes. This may sound more like fiction than science, but it actually is science. Moreover, this is only the long-term goal. The short-term goal is to make new treatments of cancer and infectious diseases possible

by means of signalling cascades triggered by hormones and by modification of microorganisms using synthetically engineered bacteriophages that do not kill bacteria but rather alter their behaviour.

2. Microorganisms Acting as Pathogens

In the 19th century Robert Koch made the discovery that certain diseases are caused by infection with microorganisms. Since then, it has become common knowledge that infectious diseases may be caused by bacteria or other types of microorganisms, such as protozoa or fungi.

While symbionts are microorganisms that live in us and from which we profit, parasites harm us while taking advantage of our organisms. Bacteria are known to be both parasites and symbionts, for instance in the intestinal flora there are bacteria that act as symbionts, while pathogens that cause diseases are to be considered parasites.

The harmful thing about bacteria is primarily their toxins, which are chemical compounds synthesized and secreted by them that interfere with the metabolism of the host organism and thus affect it in a negative way. However, one must not forget either that the actual symptoms of bacterial infections are most of all caused by the way the immune system reacts to them, i.e. by inflammation. We notice pain, see the doctor, and the doctor makes the diagnosis pharyngitis, laryngitis, pneumonia etc. Then the doctor concludes that the cause of the inflammation is the bacteria and he or she

is most likely to prescribe antibiotics to destroy and kill these invaders. From a strictly scientific point of view, it is of course not true to say that the direct cause of the inflammation is bacterial infection; it is just an indirect cause. The actual "culprit", so to speak, is the human immune system.

We must, however, not make the mistake to believe that the immune system were a bad thing and that the patient would profit from disabling the immune system entirely. It is easy to observe in immune- deficiency syndroms such as AIDS what negative effects on health a heavily suppressed immune system may have. The actual problem is not the immune system per se but inflammation. Many doctors prescribe cortisone to suppress inflammation and treat some infectious diseases this way, partly in addition to antibiotics. However, cortisone is a bad thing since it not only suppresses inflammation but also the immune system as such. What would be more desirable would be suppression of inflammation while sustaining the other mechanisms of immunity such as phagocytosis and antigen-antibody reactions. According to my late mentor Uwe Rohr, this can be achieved by means of the so-called adiol (androstenediol and androstenediol). The adiol is a steroidal hormone just like cortisone. Uwe Rohr proposed that giving the patient high doses of soy isoflavones would lead to a conversion of other steroidal hormones into adiol and thus inflammation would be suppressed while at the same time the other functions of the immune system would not be hampered but, on the contrary, would be boosted [2].

While being a loyal disciple of Uwe Rohr, I would like to go even beyond that. It is not desirable from an ethical point of view that the immune system destroys and kills bacteria and other cells that have a detrimental effect on the host organism. After all, these pathogens are living things as well, so they should also have a right to life. That is why I propose a mechanism to "educate" and convert pathogens to cells that are beneficial for the host organism.

3. Cancer

What applies to microorganisms goes for cancer as well, at least to some extent. Cancer is a potentially deadly disease caused by cells of the host organism that have undergone mutation and behave in a manner that harms the host organism. Why should it not be possible to convert these cancer cells back into normal, functional tissue?

Uwe Rohr has in particular dealt with cancer. He shared Rudolf Virchow's view that cancer cells are basically cells that "have lost the ability to convert themselves into functional epithelial tissue". He proposed a method to resolve this, for which he adopted the term "Modify and Repair", which had originally been coined by researchers from Harvard Medical School and MIT in context of repair of blood capillaries in a malignant tumor [3]. In Uwe Rohr's opinion, this process could be undergone by application of steroid hormones that have previously been blocked. Isoflavones such as daidzein, which share biochemical similarities with a particular group of steroidal hormones known as adiol, modulate stem cells in plants where they have been derived from, such as soy and red

clover, and this effect can apparently be obtained in the human organism as well [4]. In pregnancy, adiol and 2- methoxy-estradiol stabilize membranes and convert stem cells into differentiated functional cells [5-7]. This, according to Uwe Rohr, could be used to treat cancer in humans effectively without aiming to destroy or kill the malignant cells.

4. Reprogramming of B Cell Leukemia Cells

A paper that takes the same line as Uwe Rohr has recently been published by James Scott McClellan and his team [8]. It states that BCR-ABL1+ precursor B-cell acute lymphoblastic leukemia is "characterized by a block in differentiation due in part to the somatic loss of transcription factors required for B-cell development" and that the authors "hypothesized that overcoming this differentiation block by forcing cells to reprogram to the myeloid lineage would reduce the leukemogenicity of these cells". This could be achieved "by exposure to myeloid differentiation- promoting cytokines in vitro or by transient expression of the myeloid transcription factor C/EBP alpha or PU.1". According to the authors, "[t]he resultant cells were clonally related to the primary leukemic blasts but resembled normal macrophages in appearance, immunophenotype, gene expression, and function".

The paper also refers to a publication by Nowak which gives an overview of several other hypotheses regarding the possibility to treat leukemia by stimulating the differentiation of the malignant cells [Nowak], but it also states that "[t]o date, [...] differentiation therapy has only been used routinely in a subtype of acute myeloid leukemia, namely, acute promyelocytic leukemia (APL)".

Furthermore, the authors refer to work by Graf and coworkers, which "has demonstrated that immature B cells can be reprogrammed to apparently normal macrophages although enforced expression of C/EBP alpha" and has "also demonstrated that a human B-ALL cell line can be induced to reprogram into macrophages" [9]. In contrast to these older publications, McClellan and his co-authors "report here the first example to our knowledge of myeloid reprogramming of primary human BCR- ABL1+ B-ALL cells occurring in samples from multiple different patients" and "demonstrate that myeloid reprogramming can be accomplished through the action of soluble cytokines without genetic manipulation of leukemic cells".

However, there is still an unsolved problem: "Even after a second round of sorting and culturing B- ALL blasts in reprogramming conditions, a population of residual blasts remains." The authors "speculate that our culture methods are not yet optimized for maximal reprogramming".

Another recent publication on the reprogramming of cancer cells has been authored by Akihiro Fujikawa [10]. This paper states that targeting a receptor-type protein tyrosine phosphatase called PTPRZ "inhibits stem cell-like properties and tumorigenicity in glioblastoma cells".

Moreover, an Israeli group around Anna Shteinfer-Kuzmine has published a paper that deals with selective induction of apoptosis

in cancer cells [11]. Although apoptosis is generally considered to be a form of cell death, according to Uwe Rohr the same processes that initiate apoptosis may also lead to differentiation of stem cells into functional tissue.

5. Reprogramming Bacteria

In a recent study by Liao et al., it was found that adding an acetyl tag to the histone HU modified both "the thermal stability and DNA binding kinetics of HU" [12]. "Accordingly, this modification likely destabilizes the chromosome structure and regulates bacterial gene transcription. This work indicates that acetyllysine plays an important role in bacterial epigenetics." In their conclusions, the authors point out that "[i]ntroducing two mutations into E. coli HU alpha converts a commensal strain into an invasive form, so it is likely that post-translational modification of HU may exert similar effect" [13]. Moreover, "[s]uch molecules may modulate the transcription- activation profile of pathogen and eliminate the virulence without killing the bacteria, thereby preventing the emergence of drug resistance" [14,15].

6. Summary and Conclusions

This paper marks only the beginning of the new scientific paradigm of Symbiont Conversion Theory. In this paper, several publications have been cited which demonstrate that it is possible to "transform", "convert" or "reprogram" malignant cells as well as intruders (i.e., bacteria) into differentiated, functional cells that actually have a beneficial effect for the host organism. Thus, it has been shown that parasites can be "educated" to become symbionts. This makes Symbiont Conversion Theory not just a hypothesis, but a theory. My own contribution is that I have generalized several novel attempts at treating various forms of disease and pointed out what they have in common, i. e. that their mechanism is to convert parasites into symbionts.

A final note: Originally I wanted to call Symbiont Conversion Theory simply Symbiosis Theory. But then I realized that there is another theory, namely Serial Endosymbiotic Theory, coined by Lynn Margulis, which would also deserve to be called Symbiosis Theory. I therefore propose that the term Symbiosis Theory should be used as an umbrella term for the two of these theories.

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