

Commentary

The International Sepsis Forum's controversies in sepsis: how will sepsis be treated in 2051?

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Abstract

Great advances have been made in describing the intracellular pathways and genes that are activated by bacterial products. New definitions and therapies for sepsis will be based on such cellular and genetic alterations. In particular, in 2051 sepsis will no longer be defined simply as a clinical constellation of findings, but rather will be divided into different entities dependent on the intracellular cascades or genes activated. Similarly, therapies will be specifically directed at such functional genetic or biochemical alterations, thereby permitting more rational therapy of specific cellular abnormalities in infected patients. Supportive care will also have advanced by 2051, allowing for less iatrogenic harm to critically ill septic patients. Finally, a better appreciation of the cellular and genetic pathways that are activated in patients will permit an improved understanding of prognosis in critically ill infected patients, allowing more appropriate use of therapies.

Keywords genomics, nuclear factor- κ B, proteomics, sepsis

I do not think there will be something called 'sepsis' in 2051 because we will know much more about this entity than we do at present. Patients will still present in the same way (clinical evidence of infection with or without organ failure) but we will be able to determine very quickly (using polymerase chain reaction or other techniques) which organism the patient has been infected with, and hence the antimicrobials to use. We will also rapidly identify which pathways are activated in patients. Therefore, instead of discussing a syndrome (which is the problem with sepsis at the present time), we will be able to state which organism the patient is infected with and we will know why they have (or why they are likely to have) organ failure.

In 2051 we will not be talking about syndromes but rather about molecular definitions of and genetic predisposition to disease, as well as about activation of specific pathways that lead to organ dysfunction. Therefore, although two patients lying in beds next to each other may look alike, in fact

completely different pathways may be activated in them, and we will be able to recognise this. We will therefore move from vague diagnoses to specific descriptions of the patient's condition. For example, the oncologist may say that 'The patient has a B-cell lymphoma with a transposition of a certain chromosome', rather than simply stating that a patient has cancer; in 2051 we will be able to make an equally specific statement, enabling us to provide specifically targeted therapy.

Lessons from nuclear factor- κ B

One of the great advances over the past few years has been to elucidate the pathway that leads from Toll-like receptors to the acute inflammatory response by activating certain genes. This, of course, eventually leads to organ system dysfunction, and the prime candidates for activating these genes are transcription factors. One that is known to activate multiple proinflammatory genes is nuclear factor- κ B; we know that patients who have greater activation of NF- κ B tend not to survive.

Unfortunately, in 2051 we will still have to deal with endotoxin being released by *Escherichia coli*, but by then we will be able to determine who will do poorly and who will do well. By appreciating the patient's gene polymorphisms, including single nucleotide polymorphisms, we will know how they will react to endotoxin, because we will have deduced which of those polymorphisms leads to higher or lower expression of the molecules associated with organ dysfunction. Therefore, we will be able to identify at-risk patients early and treat them accordingly.

Remember, however, that it is not enough just to turn on genes; they must also be translated into proteins. By 2051 we will have developed techniques that will tell us within several hours, or even minutes, what pattern of proteins a patient has. Some recent data from my laboratory illustrate what happens when neutrophils are stimulated from a group of volunteers with lipopolysaccharide. We found that there are both high and low responders, with high responders being those who consistently produced more NF- κ B and the low responders being those who barely reacted to the endotoxin.

Therefore, the central dogma of this new field will probably be to gain an understanding of how proteins are expressed, because these are really the motors of cellular function and dysfunction in critically ill patients. DNA reflects our genomic predisposition and there will be changes in RNA that we can detect with chips, but what is probably most important is how proteins are expressed.

Detection

At present we can describe a patient's genetic make-up by looking at several thousand cells. However, the number of cells required has been dropping dramatically, and by 2051 we will need fewer than 10 cells (which could be achieved from a buccal rub) to determine a patient's genomic predisposition. This will tell us which genes are upregulated and which genes are downregulated. Currently, such procedures take hours, but without a doubt in the near future, and certainly before 2051, we will be able to do this in a similar time as routine laboratory tests require. Therefore, when a patient presents in the emergency department, we will be able to tell their genomic profile both quickly and easily.

Interesting though that may be, and as I allude to above, the real issue is to be able to assess the patient's proteomics. By 2051 we will be able to identify which proteins are being expressed, to what levels, how high or how low the protein levels are in various cell types, and how the proteins are modified after translation. This will enable us to identify those patients who will respond to various drugs. For example, if a patient upregulates the intracellular kinase Akt and has increased levels of this kinase, then we will be able to give them an anti-Akt therapy and thus improve their outcome.

Long before 2051 we will have created a database of proteins by taking them out of the cells, running them in a two-dimensional gel, visualizing the gel using an informatics system, and deducing which spots are upregulated proteins. As and when we find a previously unidentified spot we can sequence it using mass spectroscopy and therefore identify the protein. All this will be put into a database so that we will know what a pattern of proteins means in terms of disease severity and prognosis. Thus, by 2051, just as a blood transfusion may be given for a low hematocrit, we will know from the spots on the gel what the patient has in terms of their molecular disease and how to treat them.

Supportive care

Even if we do not have 'sepsis' and even if therapies are based on molecular mechanisms and signaling pathways, there will still be a role for supportive care. Some patients will be noncompliant and will present with relatively advanced disease and organ dysfunction. For these patients we will have to modulate activated pathophysiologic cascades that contribute to organ system dysfunction and death.

Our supportive care will be nontoxic. Tidal volumes are currently getting smaller and smaller, and by 2051 we will have no tidal volume ventilation; we are getting close to that now. We will have noninvasive monitoring of organ and cellular function, and so catheters will no longer be needed. We will have maintenance of tissue homeostasis through appropriate metabolic, nutritional, and cellular support. We will also have more accurate outcome prediction, leading to appropriate levels of support.

By being able to identify cascades and intercellular mechanisms, we will also be able to identify those patients in whom it does not make any sense to intervene. Through prophylactic care we will be able to increase how long our patients live, as well as improving their quality of life. If and when the patient suffers a catastrophic event we will look at the intercellular picture and make one of two choices; either the patient is amenable to therapy or this is a terminal event. The patient will have lived a long and healthy life because of prophylactic therapies; they will have received gene therapy, because their genetic polymorphisms will have been identified; and they will have received appropriate vaccines – at this point there is nothing else that can be done. At this point we will still need to talk to families – we are still physicians, we are still health care providers, and we will be better able to inform the family about the prognosis and to better tailor and choose therapies at that time.

Competing interests

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