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Review

Evidence supporting a role for dormant bacteria in the pathogenesis of spondylarthritis

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ABSTRACT

Spondylarthritis is still viewed as a reaction to infectious agents, as opposed to an infection by persistent bacteria, for several reasons: (a) an infection is considered proven only when the organism can be cultured; (b) no studies have identified dormant bacteria in the tissues targeted by spondylarthritis; (c) the bacterial persistence hypothesis has no therapeutic implications at the time being, since antibiotics are effective neither on dormant bacteria nor on the manifestations of spondylarthritis; and (d) the high prevalence of borderline disorders combining features of spondylarthritis and of psoriatic arthritis, or even rheumatoid arthritis (RA), would indicate a role for dormant bacteria in these last two diseases. However, recent data on dormant bacteria have rekindled interest in the bacterial persistence hypothesis. Dormant bacteria cannot be cultured, because they express only a small group of genes, known as the regulon, which includes genes for transcription factors that block the expression of the usual bacterial genes. Certain forms of cell stress, such as molecule misfolding, promote the entry of bacteria into a state of dormancy, which induces the low-level release by the host cells of cytokines such as TNF. Whether HLA-B27 misfolding facilitates the persistence of dormant bacteria within spondylarthritis tissue targets remains to be determined. If it does, then treatments that reactivate dormant bacteria might make these organisms susceptible to appropriate antibiotics and might therefore serve as useful adjuncts to non-steroidal anti-inflammatory drugs and TNFα antagonists. TNFα antagonists rarely reactivate dormant bacteria, with the exception of *Mycobacterium tuberculosis*, which, together with metastatic cells, is the most extensively studied latency model to date.

1. Certain bacteria are capable of hibernating

Certain bacteria can survive in a dormant state for long periods (up to 26,000 years) [1]. Neither negative culture results nor lack of efficacy of antibiotics eliminates the existence of dormant bacteria. For instance, staphylococcal osteitis can relapse many years after an apparently full recovery.

A role for persistent dormant bacteria in the pathogenesis of spondylarthritis has been suggested. Until recently, however, spondylarthritis was viewed as a reactive disease, for five main reasons:

- culturability is widely viewed as a prerequisite to pathogenicity, according to the concept put forward by Koch;
- to date, no studies have identified dormant bacteria in the tissues targeted by spondylarthritis (entheses, joints, eye, gastrointestinal and urinary tract epithelia, and skin);
- at present, proving the bacterial persistence hypothesis would have no therapeutic implications, since antibiotics fail to eradicate dormant bacteria, and can even promote their persistence;
- many patients have borderline conditions combining features of spondylarthritis with features of psoriatic arthritis or even of rheumatoid arthritis (RA), and the bacterial persistence hypothesis would therefore have to apply to these last two diseases;
- TNFα antagonists are beneficial in patients with spondylarthritis, despite their ability to reactivate certain intracellular bacteria. Nevertheless, recent data have rekindled interest in the potential role for dormant bacteria in spondylarthritis.

1.1. Dormancy is not the only modality of bacterial persistence

"Viable but non-culturable" (VBNC) is a term often used to designate dormant bacteria. However, the two are not synonymous. In addition to many strict anaerobes, VBNC bacteria include L-phase variants (which lack a complete cell wall [2] but are not in a state of dormancy) and spores. Under highly unfavorable conditions, spores composed of bacterial DNA surrounded by a strong outer membrane can develop in the cytoplasm of certain bacteria (*Clostridium*,

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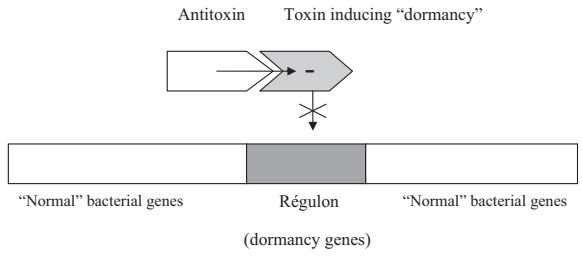

Insufficient toxin inhibition may lead to activation of the regulon genes. The regulon contains genes that inhibit the transcription of non-regulon bacterial genes: the bacterial cell then enters a state of latency and subsequently of dormancy characterized by exclusive or nearly exclusive expression of the regulon genes.

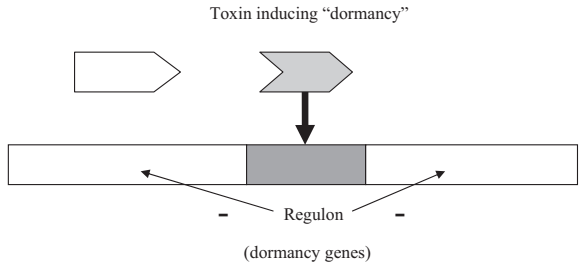

Fig. 1. For the vast majority of bacteria in a colony, "antitoxins" inhibit "toxins" (present in the environment or produced by the bacteria), which can activate the regulon genes that induce and perpetuate a state of dormancy.

Bacillus, *Coxiella*, *Actinomycetes*, and some mycobacteria) [3]. Calcium dipicolinate within the core confers resistance to extremely harsh environmental conditions and to the passage of thousands of years. When conditions become more favorable, the spores can give rise to viable bacteria.

The non-culturability of dormant bacteria is related to the expression of only a small number of genes (about 300), known collectively as the regulon. The regulon includes genes for transcription factors that inhibit the expression of the usual bacterial genes (except those encoding the heat-shock proteins, which promote dormancy [4]) (Fig. 1). Regulons differ substantially across species [5], and detailed characterization of the regulon is needed to enable studies of the dormancy of a bacterial species. At present, such detailed information is available only for *Mycobacterium tuberculosis* and some *Nocardia* species [6]. However, evidence of regulon expression is not sufficient to confirm profound dormancy, as a continuum exists between the latent state and the dormant state (Fig. 2).

Long-lasting infections are characterized by the development of biofilms (bacteria aggregates adhering to a surface and secreting a protective matrix). Biofilms are resistant to antibiotics both by virtue of their matrix and because they often contain dormant bacteria, which are less effective in activating the immune system compared to culturable bacteria, although they induce low-level release of TNF, IL-1, and IL-6 [7].

1.2. Mechanisms and circumstances that promote cell entry into dormancy

Entry into dormancy is due in part to chance. Although the cost to the colony is insignificant (with about one in 10^3 to 10^6 bacteria becoming dormant), the human body harbors about several thousand to several millions dormant bacteria [8]. Dormant *M. tuberculosis* organisms capable of undergoing reactivation in the event of immunosuppressive therapy are found in two billion individuals worldwide.

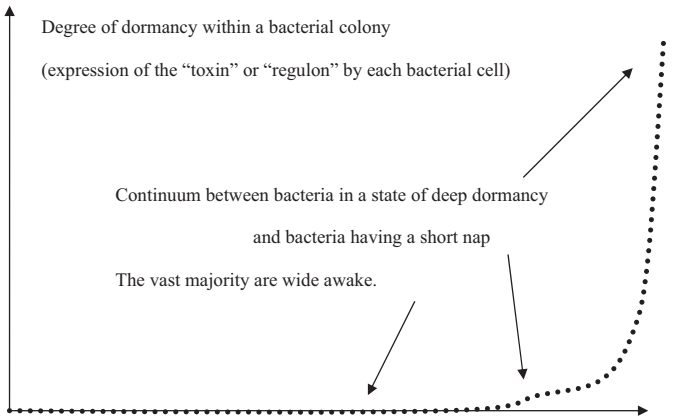

Fig. 2. Dormancy does not follow the all-or-nothing rule: among bacteria in the same colony, a continuum exists between a brief nap and a very deep and lasting sleep.

Entry into dormancy is also governed by exposure of the cells (bacteria and also some eukaryotic cells) to stressful factors [9] including:

- conditions that are unfavorable to survival (e.g., hypoxia, deficiencies in essential nutrients such as iron and tryptophan, excessive colony density, pressure due to antibiotics or chemotherapeutic agents, and certain immune response modalities such as interferon gamma secretion);
- the need to avoid depleting the stores of certain cells (hematopoietic stem cells) early in life;
- terminal maturation of certain epithelia or misfolding of various proteins within the cytoplasm.

This last factor deserves special attention, as the predisposition to spondylarthritis conferred by the HLA-B27 gene may result chiefly from the tendency of the HLA-B27 molecule to fold incorrectly, particularly within the mucous membrane epithelia [10]. In addition to the number of exposed cells in the bacterial colony, the level of stress affects the subsequent *duration* of dormancy.

1.3. The use of dormancy as a survival strategy varies across bacteria and tissues

Entry into dormancy has been documented in most enterobacteria (*Enterobacter*, *Escherichia coli*, *Klebsiella* [11]) and *Helicobacter pylori* [12]. However, dormancy may play a more decisive role for certain types of organisms, such as *M. tuberculosis* [13], whose tendency to acquire a dormant phenotype is most marked in lipid-laden macrophages and in adipocytes, including those located around lymph nodes [14]. Dormancy of spirochetes occurs preferentially within astrocytes, whereas *Borrelia* can become dormant within joints. Thus, a case of arthritis due to Lyme disease occurred after autologous cartilage transplantation in a patient who had been bitten by a tick 15 years earlier [15].

1.4. Underlying molecular mechanisms

The transcription factors involved in regulon expression and dormancy may differ according to the nature of the stress. These factors are often called "toxins" and described as regulated by "antitoxins". "Toxin-antitoxin" systems may contribute to cause suicide of the bacterial colony under certain conditions [16].

Most "toxins" seem to be proteases. In *E. coli*, they consist of the long-form filament molecule (Lon) and several m-RNAses [17] such as the RelE toxin, which is antagonized by the RelB antitoxin [18].