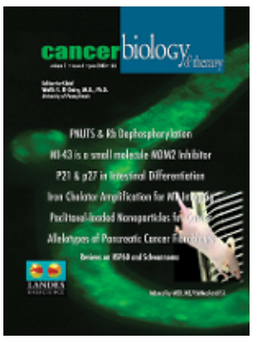

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Commentary

Static magnetic fields, blood and genes

An intriguing relationship

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It seems that humans are inherently fascinated by the effects of earth's magnetic field as was brilliantly narrated in the book "The Invisible Century: Einstein, Freud, and the Search for Hidden Universes" by Richard Panek, which begins with the vivid description of a very young Albert Einstein staring with amazement at his father's compass.[1] In recent days, with the advent of superconducting magnets, mainly used for diagnostic magnetic resonance imaging (MRI) and possibly for magnetically levitated trains, the biological effects of static magnetic fields thousands of fold more intense than earth's magnetic field, began to attract the interest of biologists and physicians. A simple textbook definition states that magnetic fields are generated by the movement of an electrical charge. A continuous electric current passing through a conductor creates a static magnetic field, while an electric current changing in time creates a variable magnetic field, which radiates electromagnetic waves spreading through a vacuum at the speed of light. Both types of magnetic fields enter living tissue, and are classified as non-ionizing radiation since they are relatively weak and unable per se to break molecular bonds. Metals in the body such as iron, zinc, manganese and cobalt, however, are sensitive to static and variable magnetic fields which may exert their effects on proteins and cellular components containing these metallic elements. Most of the papers in the magnetic field literature deal with the biological effects of variable electromagnetic fields because they are used extensively in telecommunication and information technology.

Perhaps because of this prominent interest in variable electromagnetic fields, the effects of static magnetic fields have received less attention, even though more than twenty years ago, the effect of a static magnetic field on the level of fibrinogen degradation products in rabbits with thrombosis was described.[2] All types of tissues are potentially affected by strong static magnetic fields such as those generated by devices for MRI, but it appears that the vascular system and blood are particularly sensitive. This might be due to the intrinsic rheological properties of blood and to the ability of the vascular system to remodel itself with precise tri-dimensional orientation in the ongoing process of angiogenesis. The paper by Strieth and colleague in this issue of *Cancer Biology & Therapy* deals just with these exciting issues: static magnetic fields, blood flow, blood cells and angiogenesis in the context of neoplasia.[3] In fact, many cancer patients undergo MRI during the process of diagnosis and follow-up, and in many instances, the study of the pattern of vascularization of their lesions is of critical importance in diagnostic and therapeutic decision-making. In their study, Strieth and colleagues demonstrate that, in a sort of biological application of Heisenberg's principle, the process of observation—in this case using a strong static magnetic field -modifies the observed object, i.e., in this case, it decreases the blood flow in tumour microcirculation and increases platelet adherence to endothelial cells.

Because evaluation of the characteristics of blood flow in tumours is critical in tumour diagnosis and staging, this observation is valuable in itself from an epistemological point of view. From a more practical point of view, however, these results raise the question of whether MRI is an appropriate diagnostic tool to evaluate blood flow, in particular, for the sluggish microcirculation of solid tumours. Interestingly, the effects of the static magnetic field used in this study appear to be selective on certain cell types involved in tumour microcirculation; thus, the reported data demonstrate that a static magnetic field reduces red blood cell velocity and increases platelet adhesion without affecting leukocytes or the smooth muscle cells of the vessel walls, as demonstrated by the lack of changes in mean arterial blood pressure and vessel diameters. If this selectivity of the effects of static magnetic fields is confirmed in other experimental systems, it follows that red blood cells and platelets, unlike leukocytes and smooth muscle cells, share molecules (presumably proteins at the plasma membrane, but other molecules could be hypothesized as well) that are modified by static magnetic fields.

The evolutionary implications are intriguing; in fact, all living beings (and consequently all types of cells) have evolved in the presence of a definite static magnetic field, but apparently, even within a clonal multicellular organism, some cells express genes ultimately leading to sensitivity to magnetic fields, whereas other don't. A whole genome approach to gene expression analysis in different cell

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types and in response to static magnetic field exposure could help clarify which genes are sensitive (or make cells sensitive) to static magnetic fields. This in turn could lead to the knowledge of their putative roles in evolution and possibly in tumour progression—if we consider the tumour itself as an unfortunate byproduct of evolution. In other words, such an approach should first identify which genes are expressed in magnetic field-sensitive cells (as red blood cells and platelets in this example), but not in non-sensitive cells (i.e., leukocytes or smooth muscle cells). Then, knowing the function of the proteins coded for by these genes, one could envisage a signalling mechanism responsible for the observed effects. There could even be two or more classes of genes involved: for example, there could be genes that are constitutively expressed in certain cell types that make them sensitive to the effects of static magnetic fields, and there could be other genes that are expressed (or whose expression is increased/decreased) following exposure. The products of these two classes of genes could be integrated in signalling mechanisms showing a significant degree of recursion; in fact, some genes (that could be termed "magnetic-sensitivity-conferring genes") could code for proteins that are modifiable by magnetic fields and, once modified, these proteins—perhaps through a signalling cascade that is not immune to the effects of magnetic fields—could affect the expression either of the same genes or of other genes. The genes of this hypothetical secondary response to magnetic fields could then code for other proteins that also are sensitive to the effects of magnetic fields and so on, approaching to arbitrary levels of depth in a manner that resembles the "typogenetics" described by Hofstadter.[4] Furthermore, proteins might not be the sole candidates for this role of sensory molecules: large and complex polymers like glycosaminoglycans, which show a precise array of electric charges on their surface, as well as small second messengers with stereospecific positioning of charges such as inositol 1,4,5-trisphosphate, might play a direct or indirect role in the cell response to static magnetic fields.[5,6]

The results reported by Strieth and colleagues, however, raise another interesting consideration concerning magnetic fields and genes: the cell types whose behaviour is modified in response to static magnetic field (i.e., red blood cells and platelets) have no nuclei. Therefore, whatever changes are induced by a static magnetic field, they are not due to alteration of gene expression or protein synthesis. The modification of pre-existing magnetic field-sensitive proteins or signalling molecules must be implicated and the effect is evidently up-stream of gene expression. But what could happen when the signalling cascade triggered by the static magnetic field reaches the DNA in nucleated cells? In answering this question, one should try to envisage the static magnetic field as a conventional ligand or signalling molecule that interacts with the same type of "receptor" in different cell types, but evokes different responses according to the peculiar signal transduction mechanism that is specific for each cell type and targets specific genes. In fact, a few years ago, it was demonstrated that a key proto-oncogene, c-*jun*, but not other proto-oncogenes (c-*myc* and c-*fos*) is expressed in response to a strong static magnetic field in HL-60 cells.[7] Although c-*myc* does not appear to be sensitive to static magnetic fields; there is an electromagnetic response element contained in a 900 base pair segment of its promoter, which contains eight nCTCTn sequences and is required for the induction of c-*myc* expression by variable (8 microT, 60 Hz) electromagnetic fields.[8] Thus even within the discrete category of nuclear oncogenes, it appears that some genes are sensitive to static magnetic fields and others to variable electromagnetic fields. Sensitivity to static magnetic fields is not limited to eukaryotic cells. For example, one study demonstrated that the expression of a superoxide-inducible soxS-lacZ fusion gene in *E. coli* was stimulated 1.4- and 1.8-fold when exposed to 5 and 9 T.[9] These latter results also suggest that strong static magnetic fields induce mutations through the elevated production of intracellular superoxide radicals in *E. coli*. This observation directly leads to the long debated, and not yet resolved, question as to whether or not electromagnetic field, particularly static magnetic fields, are genotoxic. Although the paper of Strieth and colleagues does not address the question, it logically follows from the Authors' suggestion to exploit the observed effects in combination anticancer therapeutic regimens. According to their suggestion, static magnetic field-induced deceleration of blood flow in tumour microcirculation could be utilized to facilitate delivery of cytotoxic molecules to the interstitial compartment of the tumour. Even though anticancer therapy commonly uses means that are per se mutagenic and tumour-inducing (from ionizing radiation to chemotherapeutic agents), knowledge of the possible genotoxic effects of a putative novel form of therapy would be appreciated. Unfortunately there is no definitive answer at this point. About ten years ago, a meta-analysis of a considerable number of studies led to the conclusion that the preponderance of evidence suggests that electric or magnetic fields have no genotoxic potential.[10] Nevertheless, the fact that researchers are reporting "novel" biological effects of static magnetic fields and that all papers invariably conclude that "further investigation is warranted", lead to the honest suspicion that we are not yet fully aware of the interactions between magnetic fields and biological systems. Our awareness of our own ignorance with respect to magnetic fields probably ensures that biologists and physicians will continue to be fascinated with magnetic fields in the years to come.

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