Molecular Biology in the Development of Cancer

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Cancer is one of the most frequent causes of death in the U.S. and in the Federal Republik of Germany; each year about 210,000 persons die of cancer in the FRG. The death rate in the U.S. has not changed since 1971, as is shown in an epidemiological study being carried out since then. Despite the fact that epithelial types of cancer occur more often in old age and that life expectancy has risen, - even in statistics adjusted to allow for the aging of the population this is valid still. There have been advances achieved in some types of cancer, e.g. infantile leukaemia or leukaemic reticuloendotheliose, however these subgroups are so small that they are irrelevant when doing statistical comparisions. During the years of the study the proportion of the different types of cancer has changed only slightly. It has to be taken into account as well, that, thanks to improved diagnostic research, cerebral tumours are more easily detected, so that it seems, that this type of cancer has increased overproportionally.

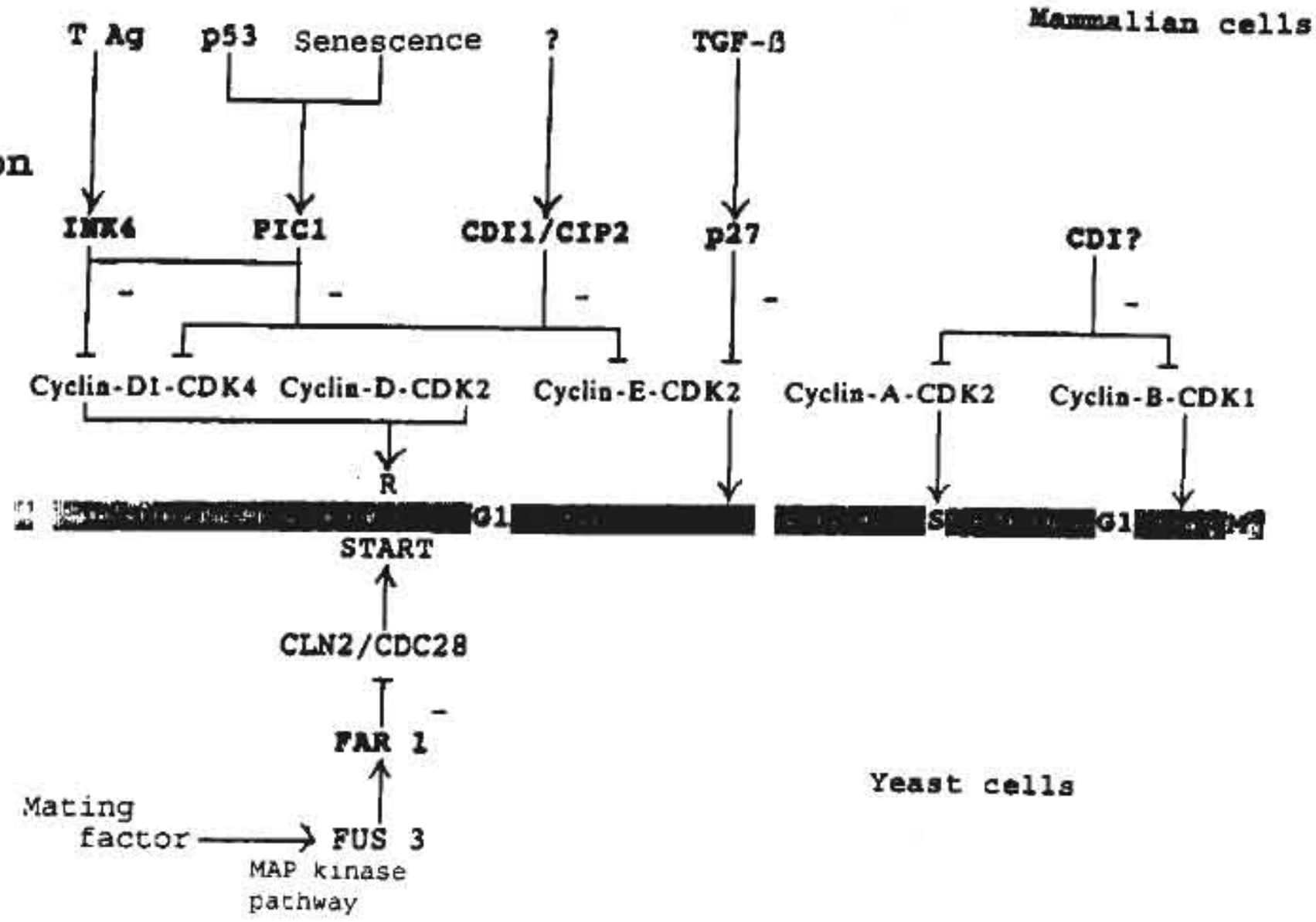
More than the clinical results those achieved through *in vitro* experiments and models provide us with the some fitting pieces in the puzzle. Here, the different molecular-biological processes in the primary stages of cancer development, which occur in every healthy organism as well, are to be described. To be left aside is the detection and elimination of degenerated cells - immunology in the widest sense.

Theories concerning cancer development have changed considerably in the course of this century. 30 years ago Warburg predominated with his opinion, that environmental factors cause modifications in metabolism and that these changes, especially the aerobic fermentation of cells, cause cancer. The changed proportion of cAMP and cGMP is only an indication of a changed metabolism and not its cause; other factors cause this change. Today the scientific world takes the view that environmental factors and genes together trigger off cancer and that the change in metabolism is not a cause but a consequence of cancer.

Environmental factors and genes have to be seen alongside with the cell cycle (see figure): The G_0 phase, from the biochemical point of view, is the most active phase of the cell, where it is able to continue to differentiate itself. Fully differentiated cells cannot revert to the cell cycle. The cell cycle continues, passing from the G_1 phase to the S phase, during which the replication of the DNA takes place. After a further G phase the chromosomes condense and separate themselves during mitosis, the M phase. In the *E.coli* the cell cycle lasts for about 20 minutes, in fast-

growing, human tumours from 24 to 72 hours. Cells don't seperate synchronously, in most cases all stages occur at the same time.

Cell Cycle of Eukaryotes with Regulation Points



First the environmental factors, which can trigger off cancer were investigated in experiments. Included among these were chemical substances, which modify the DNA and above all the bases, e.g. nitrite, which can be formed from nitrate taken in with the food. Among these factors you also have to count the substances which may bind to the nucleic acid strand and would disturb the transcription. In a broader sense ionizing radiations whose energy is used in forming high reactivity free radicals also belong to this group. With a low dosage nucleic acids are changed in a way which can cause cancer, with a high dosage nucleic acids are changed so much that neither transcribing nor replication is possible any more. This is why chemotherapeutic substances, which react according to this principle and which are used in treating cancer, at a low dosage trigger off cancer, as well.

Ionizing radiations are not the only cause leading to the formation of radicals; radicals are also an intermediate product of the respiratory chain, of the obtainment of energy. As an intermediate product of the respiratory chain they are not dangerous, but there are always a certain number of unwanted side effects. When the amount of energy which is required rises, as in manual work, the number of radicals increases. Every cell, but mainly the mitochondria, have to protect themselves against the radicals produced with the help of certain factors, the antioxidants. There is a sufficient amount of them in natural food, but due to storage, precooking and overlong cooking some of these substance are destroyed, which is why

the addition of antioxidants, e.g. beta carotene (provitamine A), vitamine C and E and selenium provide protection against cancer, as well. The preventive effect of vitamin A against cancer has now been proven in large-scope studies and epidemiological experiments.

In bacteria there is a semilogarithmic dependency between the dose of a modifying agent and the time, which is necessary to trigger off reactions. It was concluded from these results, that each of these steps had to be prevented, because it leads to a mutation and, as a consequence, may cause the development of cancer.

Apart from the triggering off of cancer by chemicals, viruses were considered to be a different factor for triggering off cancer. The process common to both became obvious with the discovery of the oncogenes or protooncogenes: the cancer viruses contain oncogenes, gene sequences which stimulate cell multiplication. In the cells there are very similar inactive, dormant predecessors, the protooncogenes, which can be easily transformed into oncogenes by chemical modification. A multitude of oncogenes were found which partially contained growth factors and their receptors as genetical products. However with oncogenes the problem of cancer was not to be solved neither theoretically nor in its treatment in a clinic.

In mammalian cells it is not as easy to trigger off mutations as it is in bacteria. Part of the differences is due to the fact that the eukaryotic cells contain many more membranes, e.g. the karyotheca. This means that the diffusion conditions differ to those in prokaryotes. They are also able to maintain differing concentration gradients with the help of ionic pumps. The amount of DNA and the number of genes is higher in mammals and there are posterior control and repair mechanisms, which stop cell multiplication so that repair mechanisms can intervene. This, above all, has an effect on the cell division rate.

An example for such a repair mechanism is given by a hereditary disease, the xeroderma pigmentosum. The persons affected by this disease easily develop cancer, especially on those parts of the skin that are exposed to light. UV-light leads to the formation of a covalent bond between two adjacent thymidine bases of one nucleic acid strand. As a consequence there are no free valencies that would enable them to combine with the second nucleic acid strand. During replication this section acts as a gap, which may lead to the insertion of wrong bases and therefore to the formation of nonsense codons or incorrect transcribing and, finally, to the development of tumours. Normally there is a repair mechanism which intervenes: it detects these defects of the double helix, removes them and supplies the correct complementary section. The patients suffering from xeroderma pigmentosum either lack this repair system or it

is not very active, hence these defects cannot be effectively eliminated. The risk is extremly high for fair-skinned persons and it increases with the increase in high energy radiation on the skin and on the ground. Apart from the repair of thymidine dimers, further control proteins, the cyclin-inhibiting proteins have been found. They stop the cell cycle if there are changes or defects in the replication of the DNA.

The actual euphoria about soon finding an universal cancer therapy, is due to the research of the suppressor genes, which inhibit cell proliferation. There are more than 20 suppressor genes in one cell, seven of which have been characterized in detail. A series of suppressor genes change the activity of the cyclin-dependent protein kinases (CDKs) and hence the mayor control points of cell multiplication (see figure)

Research on the suppressor genes and their function led to the discovery of the importance of the apoptosis, the programmed cell death: the number of (cancer) cells rises not only due to the activation of cell division but also due to the inhibition of cell degradation. Oncogenes inhibit this degradation, suppressor genes stimulate this apoptosis. Apoptosis enables the organism to protect itself against viruses by sacrifying infected cells, and it enables the thymus to eliminate "wrong" T cells. This is why intense research is being carried out on the mechanisms of apoptosis.

In the suppressor genes it was found that, although the human has got a diploid genome, sometimes only one gene is transcribed actively. This phenomenon has been found in some growth factors and their receptors: It is always the paternal gene of the insulin-like growth factor II (IGF II) and the maternal gene of the corresponding receptor that are transcribed. If a child has only two of the paternal gene of the growth factor, the risk of developing Wilms' tumour is 700 times more than average. The two genes may be distinguished one from another through their varying degree of methylation.

As Hermann Hesse once said "*All knowledge and every increase in knowledge does not end with a full stop but with a question mark. More knowledge means more questions and each of them is being continuously replaced by newer questions.*" Regulation of cell multiplication and cell degradation is a complex interaction, we know very little about. Summing up, in clinical application this means that research has provided *much knowledge and little cure*. We should still aim at helping the organism to regulate itself. Therefore treatment methods, which have proven worthwhile should be kept, even if they cannot be explained yet.

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