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# Xenobiochemical interconditioning in recombinant DNA technology: theoretical and applicative aspects

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***Abstract***

In the technology of recombinant DNA, as a specific domain of genetic engineering, the obtainment strategy involves the use of two different fragments of DNA known currently with the denominations of vector and passenger. The xenobiochemical peculiarities of recombinant DNA formation explain the transgenesis process, specific for the recombinant DNA technology. The consequence of transgenesis consists in the modification of genotype and subsequently, of the phenotype. At the level of molecular biology it can be discussed as a phenomenon that influences the series of processes replication-transcription-translation. This series reveals that, at the end, the protein synthesis is also influenced. In modern biotechnologies these aspects can explain (positive and negative) effects induced by transgenesis in the conditions of a xenobiochemical conditioning. In this frame – approaching xenobiochemical aspects (regarding foreign DNA) – it becomes possible in recombinant DNA technology to discuss about genetically modified organisms (GMO) and the necessity to extend investigations over the polyheteronucleotidic sequences from DNA's macromolecule.

***Keywords***: recombinant DNA – xenobiochemical interconditioning

## Introduction

In the domain of contemporary biosciences is observed a continous tendency of extent for the applications of modern biotechnologies. These are based on the possibility of deoxyribonucleic macromolecules (DNA) to realise recombination at genes' level.

The concept of biotechnologies leads to the idea of interdisciplinarity in this domain focusing on the integration of biosciences (mainly biochemistry and molecular biology) and engineering sciences (mainly technologies) to applications - on organisms or some of their molecular components.

This kind of interdisciplinarity led to the procedures that generated the so called „genetic engineering" based on the applications of „recombinant DNA technology".

In this manner, starting from the problems of genomics and proteomics, through biotechnologies can be obtained molecular analogues that subsequently are used in the domain of products and services.

At the level of the actual knowledge it is considered that biotechnology developed four directions in function of the appliance domain: a) green biotechnology - with applications in the agrarian domain; b) blue biotechnology - with applications in the marine and aquatic domain; c) red biotechnology - with applications in the medical domain; d) white biotechnology - with applications in the industrial domain.

For the obtainment of results in biotechnology is used genic recombination considered as a phenomenon that leads to the appearance of new genes in cells related to the parental heritage.

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A special domain in modern technologies is represented by „transgenic organisms", generically named „genetically modified organisms" (GMO).

Transgenicity, specific for genetically modified organisms, involves the presence of natural genes - for interest in biochemistry, but also of foreign genes – for interest in xenobiochemistry. Thus, the idea of xenobiochemical interconditioning in the organisms modified by transgenesis.

## 1. Genic recombination at the interface with xenobiochemistry

Mainly, between biotechnologies and genetic engineering are notable differences. Biotechnology is practiced since millenia and genetic engineering since some decades (Batista and Oliveira, 2009). Genetic engineering includes a series of techniques that allow genic manipulation of the organisms by introducing, modifying or eliminating some specific genes (Jaenisch, 1988; Rogers and Parkers, 1995; Conner, 1999).

Genic recombination is an expression of the modification that appear in the genome as a consequence of „foreign gene" transfer (transgenesis) with inherent effects over the genotype and the phenotype. The presence of „foreign gene" in recombinant DNA technology brings into the attention the aspects of xenobiochemistry.

The study of gene recombination shows that the modification of the genome can take place on natural ways (spontaneously) or on experimental ways (based on technologic processes). In this acceptance there are distinguished:

a) natural genic recombination (NGR) realised on „natural biochemical pathways" that represent a specific domain of molecular biology in general, and of molecular genetics in special. The problems of NGR are of interest for eredobiology;

b) technologically mediated genic recombination (TMGR) is realised on „mediated chemical pathways". The method is specific for modern biotechnologies and is based on the use of microorganisms (viruses, bacteria, yeasts, micelles etc.) and of cell cultures (vegetal and/or animal ones).

### 1.1. Natural genic recombination

In literature NGR is discussed distinctly for viruses, prokaryotes, eukaryotes.

#### 1.1.1. Genic recombination in viruses.

The genetic material of viruses is represented by a genome constituted of «coreal nucleic acid» (RNA or DNA) present in the core of viruses. The viruses with impact over the human, animal, vegetal and bacterian organisms have the property to replicate autonomously (Bryce, 1985; Griffiths et al., 2000). This autonomous replication is realised in the host-cell (recipient-cell) and it has as consequence the lysogeny (in case of temperate viruses) or the lysis (in case of virulent viruses).

Viral genic recombination has been studied mostly in case of bacterian viruses (bacteriophages) following sometimes situations when the host-cell was simultaneously infected with two or more viruses with a different genome.

#### 1.1.2. Genic recombination in prokaryotes

In prokaryotes there is generally just one genophore (with similar attributes of the chromosome in eukaryotes). The prokaryotic (bacterian) genophore is constituted of a single circular dc-DNA macromolecule. Although being disposed in a nucleoide (without nuclear envelope), the bacterian genophore is attached to a cellular formation named mesosome.

Beside the genophoral DNA, in bacteria is also found DNA with genetic role localized in plasmids. Plasmids contain plasmidal DNA that topologically is dc-DNA (Alberts et al., 1983; Darnell et al., 1986).
In bacteria, the genome has a more complex constitution. Genic recombination takes place with specific mechanisms during the processes of: 1) transformation; 2) conjugation; 3) sexduction; 4) transduction.

Details are presented in treatises of cellular and molecular biology (Darnell et al., 1986; Garban, 1998).

### 1.1.3. Genic recombination in eukaryotes

The eukaryotes as multicellular organisms, have a more complex genotype. The genetic biologic information is found in the chromosomes that are present in the cell nucleus. Natural genic recombination in eukaryotes had a lot of difficulties due to the structural complexity of genes' DNA. It is known that deoxyribonucleoside-phosphates (dNMP) from genes' DNA forms „reiterative sequences" and „unique sequences" (Micklos and Freyer, 1990; Sittman, 1994).

The reiterative (repetitive or redundante) sequences intervene during regulation processes and the unique sequences represent structural genes.

In eukaryotes, beside chromosomal DNA is also found DNA in cell organites: mithocondria and chloroplastes. Mithocondria contain mithocondrial DNA (mt-DNA) that has autonomy because stays at the origin of the biosynthesis of some proteins from the internal limiting membrane of the mithocondria. Plastids contain also a specific DNA i.e. chloroplastic DNA (ct-DNA) with the molecular weight ranging $0.7 - 1.8 \cdot 10^8$ Da and with functional autonomy. Chloroplasts contain chlorophylle and take part in photosynthesis.

A general presentation of the problems refering to natural genic recombination assures the understanding of the particular aspects regarding the applications in the study of artificial (technologically mediated) recombination.

## 1.2. Technologically mediated genic recombination

Implementation of biochemistry and molecular biology in recombinant DNA technology allowed a development of modern biotechnologies after 1970. By means of biotechnologic methods important results have been obtained with biomedical interest, e.g. vaccines, interpherons; pharmaceutic interest, e.g. hormons, antibiotics, vitamins etc; food interest, e.g. aminoacids, food proteins, enzymes (needed for fermentation of beverages, cheese etc.); agricultural interest, e.g. „genetic reprogrammed organisms" for amelioration (plants, animals) known by the denomination of genetically modified organisms; industrial interest, e.g. in chemical industry (acetone, methanol, ethanol, solvents) and in energetic industry (e.g. biofuel, inferiour alcohols).

The problem of technologically mediated genic recombination (TMGR) needs the approach of two subjects: a) operating means for recombinant DNA technology (enzymatic systems, action mechanisms etc.); b) stra-tegy of recombinant DNA obtainment (role of vector and passenger), principles of nucleic acids manipulation named in some treatises ‹‹genetic genius››, engineering of new genotypes.

### 1.2.1. Operating means for recombinant DNA technology

The central problem of this topic is the use of specific enzymes that act on nucleic acids. These enzymes are considered as „tools of recombinant DNA" (Emery, 1884; Sittman, 1994; Garban, 2005). They allow DNA and RNA manipulation. There are usually discussed:

α) *restriction and modification enzymes* respectively restriction-modification systems (R-M systems). These systems can be distinctly discussed as two components.

- restriction systems – characteristic for bacteria, limit the infectious capacity of bacterial viruses. Produced enzymes are endonucleases with high specificity, generically named restriction enzymes;
- modification systems – present in bacteria, assurethe producing of enzymes which modify the own DNA protecting it of self – asimilation. The enzymes that take part are named methylases and generically, modi-fication enzymes.

β) *enzymes from the group of ligases*. Are known as polynucleotid-synthetases or DNA-ligases. Have the role to catalyze the formation of the phosphodiesteric covalent bonding between nucleotides proding the elongation of DNA chains.

γ) *enzymes from the group of DNA-polymerases*. Diverse polymerases intervene in the formation of recombinant DNA by binding the fragments with coesive ends. Such enzymes are DNA polymerases-DNA dependent and DNA-polymerases-RNA dependent.

### 1.2.2. Strategy for obtainment of recombinant DNA

In the strategy for obtainment of recombinant DNA it is operated with the concepts: vectors (a) and passengers (b).

a) Concept of vector – defines a detached fragment of a DNA molecule having the property to replicate independently of the originating chromosome (autonomous replication), property that is maintained even if a foreign DNA fragment is included. In the current practice many types of vectors can be used: α) *plasmids* - mainly plasmidal DNA, specific for bacteries; β) *bacteriophages* (bacterial virus) - mainly coreal DNA from the core of viruses, e.g. λ bacteriophage; γ) *cosmides* - artefacts constituted of DNA fragments with the role of vectors.

b) Concept of passenger - defines a fragment of a DNA molecule with a certain sequence of nucleobases that represents the carrying gene of biologic information needed for the biosynthesis of a certain product e.g. hormons, enzymes, diverse proteins.

The passenger also named „passenger DNA" or „target DNA" has the property of integrating into an adequate vector generating the so called recombinant DNA. Under these conditions replication can take place in host cells maintaining the information that assures the biosynthesis of the proposed product.

## 2. Molecular forms of recombined DNA

The obtainment of the vector (i.e. vector DNA) and passenger (i.e. passenger DNA) as biologic-interactive formations represents precursor steps of recombinant DNA synthesis.

Obtainment of recombinant DNA is presented in Figure 1, starting from a vector represented by plasmidal DNA of a prokaryotic (bacterian) cell and a passenger originating from a fragment of chromosomal DNA of an eukaryotic human cell.

Generally, the vector can be represented by plasmidal DNA, coreal DNA (of the bacteriophage) or cosmidal DNA and the passenger is represented by chromosomal DNA (from vegetal / animal cells). The formation of the vector and of the passenger is realised by the action of restriction endonucleases (Garban, 1998).

The restriction enzymes determine the „molecular clivage" followed by the release of sectioned plasmidal DNA, respectively fragments of chromosomal DNA.

In the case of chromosomal DNA fragments the so called DNA libraries are constituted represented by numerous fragments. One of these fragments represents the passenger DNA i.e. the selected gene named, generally, interest gene. This one competes at the formation of recombinant DNA.

Interactions between vector and passenger takes place under the action of the enzyme DNA-ligase and is followed by the formation of recombinant DNA. Further on follows a step of transformation and transfection in bacterial cells of E. coli. Thereafter cloning and multiplying is realised.

After the formation of recombinant DNA, cloning is realised. In molecular biology – in the context refering to recombinant DNA – the concept of clone refers specifically to identical host-cells that carry identic molecules of recombinant DNA.

Generally it is stated that there is cloning strategy (Sittman, 1990). There can be observed three distinct steps: α) formation

of recombinant DNA molecules, β) insertion and propagation of recombinant DNA in the host cell (possible nowadays both in the eukaryotic and prokaryotic cell); γ) selection of transformants and transfectants made in the succession: γ') selection of all cells that are transformed or transfected; γ'') selection only of that cells that overtook recombinant DNA (in which specific DNA integrated – by transgenesis).

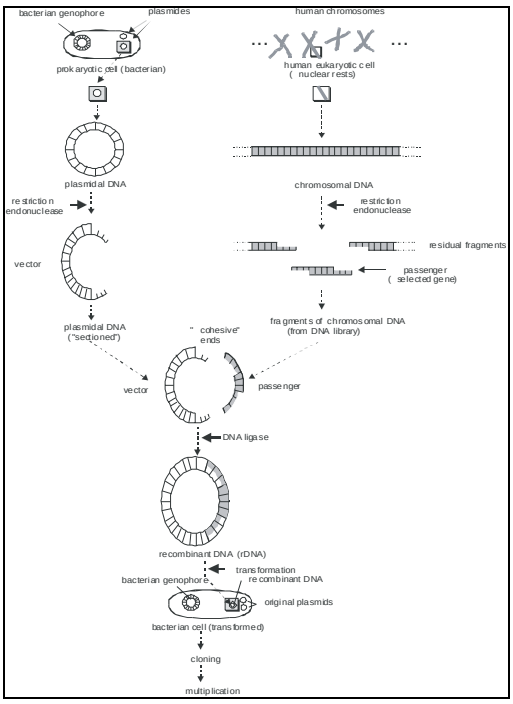


**Fig. 1-1.** Mechanism of recombinant DNA formation by the interaction of plasmidal DNA and a fragment of chromosomal DNA (Garban, 1998)

## 3. Xenobiochemical peculiarities of transgenesis

The applications of molecular biology based on the concepts of genetic engineering assure – as it was shown - the

use of an assembly of methods and techniques for the handling of genetic information at molecular and cellular level, in order to obtain new genotypes.

Implementation of methods specific for molecular biology, more precisely, for recombinant DNA technology, focus also the modern biotechnologies from agriculture and zooculture (Griffith et al., 2000; Cockburn, 2002; Faust and Glenn, 2002; Taski-Adjukovic, 2009).

Due to the methods used in genetic engineering became possible the interference with the „genetic inheritance" of vegetal and animal cells (Kendrew, 1994; Koldziejczyk, 1998; Griffith et al., 2000; Rerart, 2002).

There are to ways on which one can intervene in the genome of an eukaryotic cell (vegetal or animal one): a) introduction of one or more genes named „interes genes"; b) modification of the expression of one or more genes that exist in the cell.

Operating on these ways involves gene transfer. Genes transfered by means of genetic engineering are known as „transgenes".

As a result of the modifications of cell genome by introducing one or more genes that originate from other organisms takes place the process named „gene transfer" or „transgenesis".

## 4. Xenobiochemical approach of the relation genotype - phenotype

The concepts of genotype and phenotype allow the defining of genetic characteristics at molecular level and of visible features at the level of organisms.

On the genotype and phenotype can act physical, chemical and biological agents that can induce modifications. Such modifications are generated through mutations and respectively through genic recombination.

### 4.1. Concept of genotype.

Genotype is defined by the totality of genetic material represented by genes (constituted of nucleic acids). An explanation of this concept becomes possible defining the notions genome and genetic background accredited in molecular biology and genetics.

The genome – in the acceptance of actual knowledge – can be circumscribed rigorously: to viruses by coreal nucleic acid (present in core); in prokaryotes by

genophoral DNA and extragenophoral DNA; in eukaryotes by chromosomal DNA and extrachromosomal DNA. The genetic background defines the totality of genetic information included in the genotypes of all individuals of a population, constituting its hereditary inheritance.

### 4.2. Concept of phenotype

Is defined by the totality of morphologic, functional, biochemical and behavioral characteristics that are visible for an individual. In molecular biology in the case of modified phenotypical aspects is used the expression „modified attributes" (in case of recombinant DNA technology applied to GMOs). In the individual genotype and on a large scale in the populational genetic background one can intervene (in plants and animals) by means specific for selection. Thus the phenotype can be influenced by: a) natural selection – regarding the survival of individuals with genotypes biologically necesary for the considered population; b) artificial selection (practiced by man) – following the maintainment of individuals (animals, plants, microorganisms) with genotypes that are usefull under economic, social or biomedical aspect.

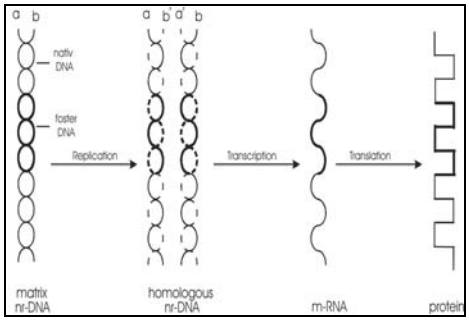


**Fig. 2**. Biosynthesis of a protein of nr-DNA (after natural genic recombination)

### 4.3. Modifications induced on the genotype and phenotype

Among the modifications induced at genotypic and phenotypic level – as it was shown – can be mentioned the natural recombination and the biotechnologic mediated recombination. By biotechnologic mediated recombination can be realised a transgenesis process obtaining recombinant DNA.In the acceptance of the „central dogma of biology" it is known that genetic information exists in genes, thus in DNA molecules, and takes part at the processes of replication-transcription-translation.During natural genic recombination, natural DNA (matrix nr-DNA) is constituted of „native DNA" and a „foster DNA" fragment (fig. 2). From the primary molecule homologous nr-DNA is formed and thereafter messenger RNA (m-RNA) and, finally, the protein.During technological mediated recom-bination (fig. 3) technologic DNA (matrix tr-DNA) is formed of a fragment of „vector DNA" and a fragment of „passenger DNA". Further on takes place the synthesis of homologous tr-DNA, of messenger RNA (m-RNA) and, at the end, of the protein synthesis.

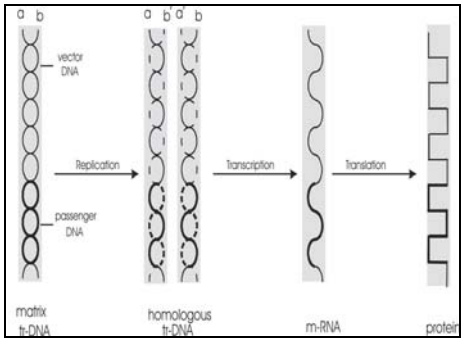


**Fig. 3**. Biosynthesis of a protein induced by tr-DNA (after technological mediated genic recombination)

In the second case can be spoken about a recombination with xenobiochemical conditioning knowing that passenger DNA is represented by genes that are „foreign" for the organism (that could be considered xenogenes). In this case is currently spoken about GMOs. This transgenesis realised by biotechnologies using genes from different species can have applications in the agricultural and medical domains.

During genes disemination by selling products originating from GMOs, diverse opinions have been vehiculated, some of

them favourable, ascertaining the idea that GMOs do not present a danger for human health and there is no risk for dis-semination, and others unfavourable suggesting caution regarding genetic pollution of environments.

The approach of the GMO problem in nutrition (Schubbert et al., 1998; Zhu et al., 2004; Cassidy, 2006; Whitman, 2009) like the use of synthesis additives in food processing (Hutson et al., 1992; Garban, 2004) reveals the importance of xenobiochemistry

Xenobiochemical aspects regarding the interaction of DNA with various chemicals has been studied more detailed in the biogenesis of adducts with small molecules. These small molecules are xenobiotics of food interest beside nutrients. For example, among organic compounds, one can mention mycotoxins (e.g. aflatoxins), polycyclic aromatic hydrocarbons (e.g. benzopyren) and among inorganic compounds the ions of some heavy metals with toxic potential (e.g. Hg, Cd, Sn).

Also, interactions with adduct formation can be generated by some chemotherapeutic drugs with cytostatic action (e.g. cys-platinum, cyclophosphamide).

The problem of xenobiochemistry in recombinant DNA technology peculiar aspects because the interactions lead to the integration of passenger DNA molecules in vector DNA molecules resutling recombinant DNA. In this case, as well as in case of adducts, it can be considered that there is an interaction between native DNA and a foreign DNA that is represented by the xenobiotic.

Under this aspect, the result of the interaction, characterising transgenesis, leads to recombinant DNA for which exploring is imposed as an investigation method for the implications of genetic engineering.

In case on GMOs this complex approach was imposed by the fact that some products are of nutritional use (Jonas et al., 2004; König et al., 2004; Batista and Oliveira, 2009).

Such studies are extended nowadays being important to elucidate aspects regarding molecular biology and food safety.

## Conclusive aspects

In natural genic recombination can be observed the existence of important differences conditioned by the the specificity of genic fragments (DNA fragments). Thus in case of natural genic recombination take part fragments of „native DNA" and of „foster DNA" as a formation belonging to the own genome.

In case of technological mediated genic recombination take part „vector DNA" and „passenger DNA" that compete to the formation of recombinant DNA, mentioning that the DNA fragments belong to different biological entities. This last situation explains the transgenesis and puts into evidence the xenobiochemical interconditioning consecutive to DNA formation.

Out of these reasons, in modern biotechnologies based on the obtainment of recombinant DNA, the processes of replication-transcription-translation lead to the modification of the genotype and inherently, of the phenotype. Effects are distinguishable in case of GMOs with implications on the appearance of modified attributes such as: insect resistance, viral resistance, herbicide tolerance, plant reproductive sterility, delayed ripening / softening etc.

Appearance of modified attributes originates in a xenobiochemical inter-conditioning that explains transgenesis and validates the genotypical specificity of the new organisms.

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