

- cells accelerate recovery of acute renal injury and prolong survival in mice. *Stem Cells*. 2008;26:2075–2082.[PubMed]
45. Falanga V, Iwamoto S, Chartier M, Yufit T, Butmarc J, Kouttab N, Shrayder D, Carson P. Autologous bone marrow-derived cultured mesenchymal stem cells delivered in a fibrin spray accelerate healing in murine and human cutaneous wounds. *Tissue Eng*. 2007;13:1299–1312.[PubMed]
 46. Weiss ML, Medicetty S, Bledsoe AR, Rachakatla RS, Choi M, Merchav S, Luo Y, Rao MS, Velagaleti G, Troyer D. Human umbilical cord matrix stem cells: preliminary characterization and effect of transplantation in a rodent model of Parkinson's disease. *Stem Cells*. 2006;24:781–792.[PubMed]
 47. Sanberg PR, Willing AE, Garbuzova-Davis S, Saporta S, Liu G, Sanberg CD, Bickford PC, Klasko SK, El-Badri NS. Umbilical cord blood-derived stem cells and brain repair. *Ann N Y Acad Sci*. 2005;1049:67–83. [PubMed]
 48. Chung DJ, Choi CB, Lee SH, Kang EH, Lee JH, Hwang SH, Han H, Lee JH, Choe BY, Lee SY, Kim HY. Intraarterially delivered human umbilical cord blood-derived mesenchymal stem cells in canine cerebral ischemia. *J Neurosci Res*. 2009;87:3554–3567. [PubMed]
 49. Chang YS, Oh W, Choi SJ, Sung DK, Kim SY, Choi EY, Kang S, Jin HJ, Yang YS, Park WS. Human umbilical cord blood-derived mesenchymal stem cells attenuate hyperoxia-induced lung injury in neonatal rats. *Cell Transplant*. 2009;18(8):869–86. [PubMed]
 50. Ortiz LA, Gambelli F, McBride C, Gaupp D, Bad-doo M, Kaminski N, Phinney DG. Mesenchymal stem cell engraftment in lung is enhanced in response to bleomycin exposure and ameliorates its fibrotic effects. *Proc Natl Acad Sci USA*. 2003;100:8407–8411. [PMC free article][PubMed]
 51. Haller MJ, Viener HL, Wasserfall C, Brusko T, Atkinson MA, Schatz DA. Autologous umbilical cord blood transfusion for type 1 diabetes. *Experimental Hematology*. 2008;36:710–715.[PMC free article] [PubMed]
 52. Willing AE, Lixian J, Milliken M, Poulos S, Zigova T, Song S, Hart C, Sanchez-Ramos J, Sanberg PR. Intravenous versus intrastriatal cord blood administration in a rodent model of stroke. *Journal of Neuroscience Research*. 2003;73:296–307. [PubMed]
 53. Chang JW, Hung SP, Wu HH, Wu WM, Yang AH, Tsai HL, Yang LY, Lee OK. Therapeutic Effects of Umbilical Cord Blood-Derived Mesenchymal Stem Cell Transplantation in Experimental Lupus Nephritis. *Cell Transplant*. 2010 [Epub ahead of print]
 54. Hwai-Shi Wang, Shih-Chieh Hung, Shu-Tine Peng, Chun-Chieh Huang, Hung-Mu Wei, Yi-Jhih Guo, Yu-Show Fu, Mei-Chun Lai, Chin-Chang Chen, Mesenchymal Stem Cells in the Wharton's Jelly of the Human Umbilical Cord, *STEMCELLS*2004;22:1330n1337www.StemCells.com

SOME POINTS IN MECHANISM OF LIVER REGENERATION (REVIEW)

Elena Mocan, Natalia Boaghie, Oleg Slivca, Viorel Nacu

Laboratory of Tissue Engineering and cell cultures

The State Medical and Pharmaceutical University “Nicolae Testemitanu”

Summary

In a healthy adult liver, only ~1 hepatocyte in 20,000 (0.005%) is in the cell cycle. The rest are quiescent, in the G₀ state. This article is focusing on the early events occurring in liver after partial damage (chemical or hepatectomy). Understanding of signaling pathways that allows hepatocytes to maintain most of their homeostatic functions and important capacity to complete restitution of lost or damaged tissue will propose new strategies to treat liver disorders.

Rezumat

Anumite aspecte a mecanismului regenerării hepatice (Review)

Într-un ficat adult sănătos numai o hepatocită din 20.000 (0.005%) există în ciclul celular în stare de diviziune. Restul sunt pasive în stare G0. Acest articol se axează pe evenimentele anticipate care au loc în ficat, după deteriorarea parțială (chimică sau prin hepatectomie). Înțelegerea căilor de semnalizare, prin care hepatocitele permit menținerea capacităților homeostatice și funcțiilor importante pentru restituirea completă a țesutului deteriorat sau pierdut, propune noi strategii pentru tratarea afecțiunilor hepatice.

The liver plays a central role in metabolic homeostasis, as it is responsible for the metabolism, synthesis, storage and redistribution of nutrients, carbohydrates, fats and vitamins. The liver produces large numbers of serum proteins including albumin and acute-phase proteins, enzymes and cofactors. Importantly, it is the main detoxifying organ of the body, which removes wastes and xenobiotics by metabolic conversion and biliary excretion [6, 12, 16, 19].

Liver regeneration has been recognized by scientists for many years and was even described by the ancient Greeks, who mentioned liver regeneration in the myth of Prometheus. *Having stolen the secret of fire from the gods of Olympus, Prometheus drew down on himself the anger of Zeus, the ruler of gods and men. Zeus punished Prometheus by chaining him to Mount Caucasus where he was tormented by an eagle. The eagle preyed on Prometheus' liver, which was renewed as fast as it was devoured (Bulfinch's Mythology)* [16].

It is known adult hepatocytes are long lived and normally do not undergo cell division, they maintain the ability to proliferate in response to toxic injury and infection. After a partial hepatectomy (removal of a section of the liver), liver cells reenter the cell cycle and replicate until the liver recovers its lost mass, within a precision of 10% [9, 12, 16, 19]. There is now a very phenomenal capacity that in liver regeneration does not require the recruitment of liver stem cells or progenitor cells, but involves replication of the mature functioning liver cells. However, it was proved the existence of facultative stem cells in the liver which are undifferentiated cells as typical stem cell and found in the system of bile canals (Hering canals). Its nearest precursors, oval cells can give rise to several cell lines, including hepatocytes and biliary epithelial cells [9, 16]. The regenerative process is compensatory because the size of the resultant liver is determined by the demands of the organism, and, once the original mass of the liver has been reestablished, proliferation stops [1, 11]. The reasons for initiating the regeneration stage, up to now finally be resolved. One theory suggests that hemodynamic overload, which is subjected to the remainder of the liver after its resection, activates inducible nitric oxide synthase (iNOS) and cyclooxygenase-2, which leads to increased production of nitric oxide (NO) and prostaglandins [9, 13]. It stresses the importance of preserving portal blood flow and the consistency is maintained by the hepatic arterial buffer response [17].

Although numerous studies have investigated the molecular mechanisms of liver regeneration, including the roles of cytokines, growth factors, matrix remodeling, and metabolic signals [3, 7, 9, 15], any basic questions remain. What are the signals that trigger the early events in the regenerative process? What role plays stem cells in liver regeneration?

Investigators have begun to answer these questions by using molecular and genetic approaches to identify the important regulatory pathways that control the regenerative process. There are different models of study the process of liver regeneration. The most important are model using chemical administration of hepatotoxic chemicals (e.g. carbon tetrachloride) and surgical model (technique of partial hepatectomy) [6, 9, 19]. Of course the initial response reactions are different depend of the nature of damage. For example, during the injury to the tissue results in disruption of capillary vascular networks and extravasation of blood, accompanied by local release of coagulation factors, platelets, growth factors, etc. [7, 15]. There is considerable literature suggesting that the early hemodynamic changes after partial hepatectomy are important of all aspects of liver regeneration. The importance of the hemodynamic events and the change of relative proportion of portal to arterial blood are the least

studied and least understood. The one of theories suggests that hemodynamic overload after the liver resection activates inducible nitric oxide synthase (iNOS) and cyclooxygenase-2, which leads to increased production of nitric oxide (NO) and prostaglandins [2, 7, 9, 13]. NO and prostaglandins sensitize macrophages to the liver secondary inductors of inflammation, especially to the endotoxin of gram-negative intestinal microflora, whose level in serum after liver resection increases. It is related to bacterial translocation from the gut due to a violation of local immunity, changes in the composition of flora and increase its permeability, and with a decrease in the absolute number of Kupffer cells and inhibition of their function [6, 7, 13]. Sensitized macrophages produce tumor necrosis factor α (TNF- α), which is a multifunctional cytokine, transmitting signals through two types of receptors: TNFR-1 (p55) and TNFR-2 (p75) [5, 15]. It acts as a mediator of acute-phase response in the liver and has a cytotoxic effect by the amplified DNA synthesis (phase S), reaching a maximum between 24 and 48 hours after resection. The peak of DNA synthesis of biliary epithelium cells has observed after 36-48 h, Kupffer and stellate cells - after 48 h and, finally, the endothelial cells of sinusoids - after 96 h of surgery [11, 14, 16]. The conversion through the phases of the cell cycle is modulated by the interaction between cyclins, cyclin-dependent kinases and its inhibitors. After 7-10 days after the hepatectomy the liver regeneration stops [14].

In a healthy adult liver, only ~1 hepatocyte in 20,000 (0.005%) is in the cell cycle [23]. The rest are quiescent, in the G₀ state. After partial hepatectomy, hepatocytes reenter the cell cycle by going from the G₀ state to the G₁ phase. Cells in the early G₁ phase progress, driven by growth factors, through the G₁/S restriction point, after which cells are committed to progress to mitosis, even in the absence of the G₁ growth factors. However, cells in early G₁ phase that have not reached the restriction point can return to quiescence in the absence of growth factors [11, 15, 16]. Fausto and Riehle have considered three subpopulations of hepatocytes: quiescent cells (Q), primed cells (P), and replicating cells (R) [2]. In the priming phase of liver regeneration, multiple immediate-early genes such as *c-fos* and *c-jun* are induced [11].

Early events occurring in liver after partial hepatectomy

The partial hepatectomy induces rapid induction of more than 100 genes not expressed in normal liver [11, 15, 19]. These genes relate directly or indirectly to preparative events for the entry of hepatocytes into the cell cycle. The functions served are several and many of these genes (e.g., *IGFBP1*) appear to play an essential role. One of the earliest observed biochemical changes is increase in activity of urokinase plasminogen activator (uPA) [1, 10]. The relationship between increase in uPA and the hemodynamic changes discussed above is not clear, but there is literature documenting increase of uPA in several cell types including endothelial cells following mechanical stress associated with increased turbulent flow [2, 15]. Urokinase is known to activate matrix remodeling, seen in most tissues during wound healing and also in liver regeneration [1].

Overall regulation of extracellular matrix during liver regeneration is a very complex process, involving metalloproteinases and tissue inhibitors of metalloproteinases (*MMP9*) [9, 15]. Hepatic extracellular matrix binds many growth factors. Prominent among matrix binding growth factors in the liver is hepatocyte growth factor (*HGF*) [8, 15].

A key endpoint of liver regeneration is the restoration of the total number and mass of hepatocytes, the main functional cells of the liver responsible for delivering most of the hepatic functions important for body homeostasis. Hepatocytes are the first cells of the liver to enter into the cell cycle and undergo proliferation, and they produce mitogenic signals for other hepatic cell types [15-17]. Quiescent hepatocytes in normal liver express a variety of growth factor receptors. These include receptors for PDGF, VEGF, fibroblast growth factor receptors, c-kit [1, 6, 15]. Many growth factors and cytokines have been implicated in regulating liver regeneration. The growth factors include hepatocyte growth factor (HGF), epidermal growth factor (EGF), transforming growth factors (TGFs), insulin and glucagons. And the cytokines include tumour necrosis factor TNF α and interleukin IL-6. There are several individual transcription factors or

proteins that are required for normal liver regeneration but have not yet been associated with specific growth-factor- or cytokine-regulated signal-transduction pathways [3, 6, 8, 15].

The studies with hepatocytes in primary culture however have shown that despite the expression of many mitogenic receptors, the only mitogens for hepatocytes in chemically defined serum-free media are *HGF* and ligands of the EGFR (EGF, TGF α , amphiregulin, HBEGF, etc). These ligands are direct mitogens [9,15].

Hepatocyte growth factor (HGF)

The view of HGF as an initiator of liver regeneration is bolstered by the fact that it is a direct mitogen for hepatocytes, it activates its receptor very early, and it can induce most of the changes occurring during the liver regeneration (including massive hepatic enlargement). HGF levels in plasma increase 10- to 20-fold after hepatectomy [9, 15]. HGF injection in portal vein of normal rats and mice causes proliferation of hepatocytes and enlargement of the liver [10, 11]. HGF in liver is produced predominantly by the stellate cells [15], but also by hepatic endothelial cells [8].

Tumor necrosis factor (TNF)

TNF is a protein known to have a variety of effects on many cells and tissues. Contrary to what its name implies, TNF can often have promitogenic effects on cells, depending on conditions which regulate activation of NF κ B [6, 15]. TNF is not a direct mitogen for hepatocytes. The enhance the mitogenic effects of direct mitogens such as HGF, both *in vivo* and in cell culture [9] and is mitogenic for hepatocytes with transgenic expression of TGF α [10, 18]. TNF increases in plasma after partial resection. Its cellular source is considered to be the hepatic macrophages (Kupffer cells) but production by other cell types has not been excluded. TNF should not be viewed as the initiator of liver regeneration, but rather as one of the many concurrent and contributory extracellular signals that all together orchestrate the early events of the response. TNF is also a regulator of iNOS [13], and mice with deficiency in iNOS have defective liver regeneration [9, 25].

Epidermal Growth Factor (EGF) and Transforming Growth Factor α (TGF- α)

These two factors belong to the EGF family and share a common receptor (EGFR). EGF is mitogenic for a variety of epithelial cells, hepatocytes, and fibroblasts, and is widely distributed in tissue secretions and fluids. In healing wounds of the skin, EGF is produced by keratinocytes, macrophages, and other inflammatory cells that migrate into the area. TGF- α has homology with EGF, binds to EGFR, and shares most of the biologic activities of EGF. The "EGF receptor" is actually a family of four membrane receptors with intrinsic tyrosine kinase activity [5, 9].

Interleukin 6 (IL-6)

There is abundant literature documenting the crucial role of IL6 in initiation of the acute phase response in hepatocytes. This is a rapid increase in production by hepatocytes of many proteins which assist in controlling acute or chronic inflammation [3, 4]. IL6 is produced by hepatic macrophages. IL6 is not a direct mitogen for hepatocytes and does not enhance the mitogenic effect of other growth factors. It is, however, a direct mitogen for biliary cells [11, 15] and it has important effects on integrity of the intrahepatic biliary tree by regulating production of small proline-rich proteins by cholangiocytes. IL6 does increase in plasma following hepatectomy. IL6 is probably a factor contributing to optimizing processes of the early stage of liver regeneration, but it should not be viewed as the initiator of the process [16].

Signaling mechanisms in hepatocyte growth

Molecular studies of gene-expression cascades in the regenerating liver have provided insights into the signalling pathways that are rapidly activated in the remnant liver post-

hepatectomy. More than 100 immediate-early genes have been identified, which are activated by normally latent transcription factors at the transition between G0 and G1, before the onset of de novo protein synthesis. The advent of microarrays expanded this list even further, and gene expression profiles indicate that some genes show transient up regulation, whereas others — particularly those involved in protein synthesis and cell growth— are elevated throughout the main proliferative response in the regenerating liver [3, 11, 16].

Specific transcription factors, such as nuclear factor NF- κ B, signal transducer and activator of transcription STAT3 and AP1, are rapidly activated in remnant hepatocytes minutes after partial hepatectomy. The intracellular-signalling pathways that involve mitogen-activated protein kinase (MAPK) and, more specifically, pERKs (phosphorylated extracellular signal-regulated kinases), jun amino-terminal kinase (JNK) and receptor tyrosine kinases, are rapidly activated according to a similar time frame, thereby providing clues to the initiating signals [3, 9, 15].

Genetic and pharmacological approaches have confirmed that regeneration is a complex process. However, it is now possible to connect many of the proteins that are involved to two distinct linear pathways that are either cytokine or growth-factor dependent, and to identify regions of overlap between these two main regulatory mechanisms [2, 25]. Cytokines bind to their cellular receptors, thereby generating intracellular signals that lead to transcription-factor activation.

Restoration of liver mass is achieved without the regrowth of the lobes that were resected at the operation. Instead, growth occurs by enlargement of the lobes that remain after the operation, a process known as compensatory growth or compensatory hyperplasia. In both humans and rodents, the end point of liver regeneration after partial hepatectomy is the restitution of functional mass rather than the reconstitution of the original form [15, 26]

Almost all hepatocytes replicate during liver regeneration after partial hepatectomy. Because hepatocytes are quiescent cells, it takes them several hours to enter the cell cycle, progress through G1, and reach the S phase of DNA replication. The wave of hepatocyte replication is synchronized and is followed by synchronous replication of nonparenchymal cells (Kupffer cells, endothelial cells, and stellate cells).

There is substantial evidence that hepatocyte proliferation in the regenerating liver is triggered by the combined actions of cytokines and polypeptide growth factors. With the exception of the autocrine activity of TGF- α , hepatocyte replication is strictly dependent on paracrine effects of growth factors and cytokines such as HGF and IL-6 produced by hepatic nonparenchymal cells. There are two major restriction points for hepatocyte replication: the G0/G1 transition that bring quiescent hepatocytes into the cell cycle, and the G1/S transition needed for passage through the late G1 restriction point. Gene expression in the liver regeneration proceeds in phases, starting with the immediate early gene response, which is a transient response that corresponds to the G0/G1 transition. More than 100 genes are activated during this response, including the proto-oncogenes *c-FOS* and *c-JUN*, whose products dimerize to form the transcription factor AP-1. *c-MYC*, which encodes a transcription factor that activates many different genes; and other transcription factors, such as *NF- κ B*, *STAT-3*. The immediate early gene response sets the stage for the sequential activation of multiple genes, as hepatocytes progress into the G1 phase. Quiescent hepatocytes become competent to enter the cell cycle through a priming phase that is mostly mediated by the cytokines TNF and IL-6, and components of the complement system. Priming signals activate several signal transduction pathways as a necessary prelude to cell proliferation.

Under the stimulation of HGF, TGF α , and HB-EGF, primed hepatocytes enter the cell cycle and undergo DNA replication. Norepinephrine, serotonin, insulin, thyroid and growth hormone, act as adjuvants for liver regeneration, facilitating the entry of hepatocytes into the cell cycle. Individual hepatocytes replicate once or twice during regeneration and then return to quiescence in a strictly regulated sequence of events, but the mechanisms of growth cessation have not been established.

Conclusions

Experimentally, hepatocyte proliferation is blocked by the use of the chemical substances during long-term administration. It was described an increasing number of cells with mixed biliary and hepatocytic gene expression patterns, as well as some markers of their own [15]. These cells have been called “oval” cells, from the shape of their nucleus. Oval cells proliferate intensely in the periportal areas of the hepatic lobule and they are heavily infiltrated by stellate cells; the latter intertwine with the oval cells and produce HGF, FGF1, FGF2, and VEGF [6, 8, 9, 15]. Oval cells express both albumin and alpha-fetoprotein. The origin of the oval cells has been much debated. A strong argument for their origin from biliary cells is their early gene expression patterns which strongly resemble biliary cells, and the fact that biliary cells begin expressing hepatocyte-associated transcription factors before oval cells appear. There is no histologic observation demonstrating an oval cell population in any nonbiliary compartment in a normal liver. Cells equivalent to oval cells, called “ductular hepatocytes,” are also seen in humans during fulminant hepatitis following extensive liver injury (by chemicals, viruses, etc.) and they are assumed to play a role similar to oval cells in restoring hepatocyte populations.[14, 17]

It should be noted that pancreatic ductules have also been viewed as the source of progenitor cells for both acinar cells and islet cells of the pancreas [8, 9]. In addition, *in vitro* studies have demonstrated the possibility of development of hepatocytes and oval cells from bone marrow stem cells that are functionally multipotent, capable of self-replication during symmetric cell division and give rise to progenitor cells during asymmetric cell division, but it was not properly identified *in vivo* [9]. The self-renewal is a unique property of stem cells, and progenitor cells, which are its progenitors, proliferate and differentiate in population of somatic cells, but are not saved in tissue. They may have one or multilinear potential, but are only able to short-term of tissues restoration [4, 5].

Despite the fact the adult liver contains undifferentiated stem cells, these cells are not activated either during the postnatal growth or regeneration after partial hepatectomy [15]. In these cases, normal growth is due to proliferation of adult hepatocytes. The optional reserve stem cells of the liver are recruiting only during functional failure when hepatocytes lose the ability to reproduce.

References

1. Currier, A. R. et al. Plasminogen directs the pleiotropic effects of uPA in liver injury and repair. *Am. J. Physiol. Gastrointest. Liver Physiol.* 2003. 284, G508–G515.
2. Fausto N. Lessons from genetically engineered animal models. V. Knocking out genes to study liver regeneration: present and future. *Am. J. Physiol.* 1999. 277, G917–G921.
3. Fey GH, Hattori M, Hocke G, Brechner T, Baffet G, Baumann M, Baumann H, Northemann W. Gene regulation by interleukin 6. *Biochimie* 1991;73:47–50.
4. Heinrich, P. C. et al. Principles of interleukin (IL)-6-type cytokine signaling and its regulation. *Biochem. J.* 2003. 374, 1–20.
5. Kirillova I, Chaisson M, Fausto N. Tumor necrosis factor induces DNA replication in hepatic cells through nuclear factor kappaB activation. *Cell Growth Differ* 1999;10:819–828.
6. Koniaris, L. G., McKillop, I. H., Schwartz, S. I. & Zimmers, T. A. Liver regeneration. *J. Am. Coll. Surg.* 2003. 197:634–659.
7. LeCouter J, Moritz DR, Li B, Phillips GL, Liang XH, Gerber HP, Hillan KJ, Ferrara N. Angiogenesisin dependent endothelial protection of liver: Role of VEGFR-1. *Science* 2003; 299:890–893.
8. Lindroos PM, Zarnegar R, Michalopoulos GK. Hepatocyte growth factor (hepatopietin A) rapidly increases in plasma before DNA synthesis and liver regeneration stimulated by partial hepatectomy and carbon tetrachloride administration. *Hepatology* 1991;13:743–750.
9. Michalopoulos G. K. Liver Regeneration. **J Cell Physiol.* 2007 November ; 213(2): 286–300.

10. Mars WM, Zarnegar R, Michalopoulos GK. Activation of hepatocyte growth factor by the plasminogen activators uPA and tPA. *Am J Pathol* 1993;143:949–958.
11. Matsumoto K, Nakamura T. Emerging multipotent aspects of hepatocyte growth factor. *J Biochem* 1996;119:591–600.
12. Michalopoulos, G. K. & DeFrances, M. C. Liver regeneration. *Science*. 1997. 276, 60–66.
13. Nussler AK, Di Silvio M, Liu ZZ, Geller DA, Freeswick P, Dorko K, Bartoli F, Billiar TR. Further characterization and comparison of inducible nitric oxide synthase in mouse, rat, and human hepatocytes. *Hepatology* 1995;21:1552–1560.
14. Satyanarayana, A. et al. Telomere shortening impairs organ regeneration by inhibiting cell cycle re-entry of a subpopulation of cells. *EMBO J*. 2003. 22, 4003–4013.
15. Taub R. Liver regeneration 4: Transcriptional control of liver regeneration. *Faseb J* 1996;10:413–427.
16. Taub R. Liver regeneration: From myth to mechanism. *Nat Rev Mol Cell Biol* 2004;5:836–847.
17. Taub, R., Greenbaum, L. E. & Peng, Y. Transcriptional regulatory signals define cytokine-dependent and-independent pathways in liver regeneration. *Semin. Liver Dis.* 1999. 19, 117–127.
18. Wheeler, M. D. et al. Impaired Ras membrane association and activation in PPAR α knockout mice after partial hepatectomy. *Am. J. Physiol. Gastrointest. Liver Physiol.* 2003. 284, G302–G312.
19. Гарбузенко Д. В., Механизмы компенсации структуры и функции печени при ее повреждении и их практическое значение. *РЖЖГИ*. 2008, 6, 14-21.

ROLUL PAPILOMAVIRUSURILOR ÎN APARIȚIA NEOPLAZIILOR EPITELIALE.

Lucian Rudico

Catedra Histologie, Citologie și Embriologie

Summary

Role of papillomaviruses in development epithelial neoplasia

It is demonstrated that papillomaviruses are ethyological factors of crucial importance in appearance and progression of epithelial neoplastic lesions. In spite of their heterogeneity and polymorphism, these causal agents are able to infect epithelial sites of the species. In case of humans they may provoke abortive infections, usually with no clinical expression. In case of concomitant infections papilomaviruses may lead to neoplasia with high risk of malignant transformation. Papillomaviruses affect exclusively epithelia, using identical mechanisms of invasion, differences being represented by the ability of the viral genome multiplication that depends on cellular microenvironment, immune response of the host and proliferative potential of the infected epithelium.

Rezumat

Este demonstrat ca papilomavirusurile sunt factorii etiologici cruciali în apariția și progresia, a neoplaziilor epiteliale. În pofida la polimorfismul și heterogenitatea lor, acești agenți cauzali sunt capabili să infecteze site-uri epiteliale la una și aceeași specie și dacă ne referim la specia umană, ei pot cauza infecții abortive mai des inaparente și în cazul patologiilor concomitente pot duce la neoplazii epiteliale cu risc înalt de malignizare. Papilomavirusurile sunt în exclusivitate epiteliotrope iar mecanismele de invazie sunt identice, diferența fiind reprezentată de capacitatea virusului de a-și multiplica genomul reieșind din specificul celulei gazdă, statutului imun a macroorganismului reactivitatea lui și nu în ultimul rând de capacitatea de proliferare a epitelului.