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AKNA as Genetic Risk Factor for Cervical Intraepithelial Neoplasia and Cervical Cancer

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1. Introduction

Cervical cancer (CC) is the second most common cancer among women worldwide. The highest incidence rates of CC are reported in Central and South America, East Africa, South and Southeast Asia and Melanesia. In 2005 there were, according to WHO projections, more than 500, 000 new cases and 274, 000 deaths from CC (WHO, 2007). This is due to the fact that the majority of women in the world do not have access to cervical screening, which can prevent up to 75% of CC cases (Ferlay et al., 2001). Predictions based on the passive growth of the population and the increase in life expectancy say that the expected number of CC cases in 2020 will increase by 40% worldwide, corresponding to 56% in developing countries and 11% in the developed parts of the world (Ferlay et al., 2001).

The development of CC is preceded by a series of cellular abnormalities characterized by cytological and histological changes in cytoplasm maturation and nuclear irregularities. The disease starts as an atypical proliferation of epithelial cells that invade epithelial thickness and degenerate into more serious injuries that invade the stroma. The development of precancerous lesions of the cervix involves several events: exposure to a high-risk Human Papilloma Virus (HR-HPV) causes an initial infection of the squamous epithelium in the transformation zone, followed by morphological and biological alterations of the HPV infected cells (Walboomers et al., 1999).

As the understanding of the natural history of the disease has improved, the classification of these lesions has received different names: PAP I to V, moderate dysplasia, severe carcinoma in situ, cervical intraepithelial neoplasia (CIN) I, II, III, low grade squamous intraepithelial lesions (LSIL) and high grade squamous intraepithelial lesions (HSIL). Microscopically, the evolution of the lesion is characterized by the differentiation of epithelial cells that proliferate and invade the epithelial tissue. Progression is described in terms of increase in the degree of dysplasia (mild, moderate, severe) and carcinoma in situ (El-Ghobashy et al., 2005). Early lesions are now considered manifestations of HPV infection, which are characterized by the presence of nuclear changes and cell proliferation of the epithelium. These cellular abnormalities tend to regress spontaneously, but some of

these lesions, particularly those caused by highly oncogenic HPV (16, 18, 31, 33, 35, 45, 56, 58) can modify the thickness of the epithelium and the disease (Nobbenhuis et al., 2001). LSIL and CIN II, have a diploid or polyploid DNA content, which correlates with their tendency to reverse. In contrast, CIN III is often aneuploid, has a greater degree of cellular atypia and is more likely to persist, or progress (Grubisic et al., 2009).

The causal role of HPV in CIN and CC has been firmly established biologically and epidemiologically (Walboomers et al., 1999). Current meta-analysis of the literature shows that the most common HPV types worldwide, in descending order of frequency, are HPV 16, 18, 45, 31, 33, 52, 58 and 35. These are responsible for about 90% of all CC worldwide. The distribution is very similar to that of pre-invasive HSIL (Muñoz et al., 2004; Smith et al., 2007). Since the main route of transmission of genital HPV is sexual, certain patterns of sexual behavior (age of onset of sexual activity, number of sexual partners and sexual behavior of the couple) are associated with an increased risk of infection with genital HPV. But persistent infection with HR-HPV is necessary for carcinogenesis, and cofactors such as multiparity, prolonged use of oral contraceptives, smoking and co-infection with HIV, enhance the progression of infection to cancer (Almonte et al., 2008).

HPVs are species-specific and induce epithelial or fibroepithelial proliferations of benign skin and mucosa in humans and in several animal species. These viruses have a specific tropism for squamous epithelial cells and their production cycle only happens in these cells. HPV infection begins in the basal cells, which are mitotically active. After infection, the virus can lie dormant, replicate and produce infectious particles or become integrated into the cellular genome. Productive infection is divided into several stages depending on the state of differentiation of the epithelial cells. The full cycle that includes viral DNA synthesis, production of viral capsid proteins and assembly of virions, occurs selectively in terminally differentiated keratinocytes (Doorbar, 2006). The basal layer cells proliferate; despite containing HPV DNA, they appear to be very active in the expression of some viral proteins. Apparently, there are cellular factors that negatively regulate viral transcription in these cells.

This regulation is released when the infected cells migrate upward from the epithelium in the granular layer, where they undergo differentiation until they can no longer divide. First, transcription of early and late viral genes is activated in these cells, viral proteins are then synthesized and viral particles are assembled in some superficial cells (Longworth et al., 2004). Although most HPV infections are transient and subclinical, progression is strongly associated with HPV persistence. This process often leads to viral breakthrough in the E1/E2 regions and integration of viral DNA into the cell. The rupture releases the viral E6/E7 promoters and increases the expression of these transformer genes (Moody et al., 2010; Ghittoni et al., 2010). Infection with a HR-HPV acts as a trigger for the cascade of events in which the mechanisms of repair or correction of cell replication, mediated by p53 and retinoblastoma protein (Rb) are altered. Thus, the cell cycle is controlled by the virus, which triggers cellular changes that culminate in the transformation and immortalization of epithelial cells, thus establishing conditions for the start of cancer (Pim & Banks, 2010).

Most HPV infections are transient and intermittent. Epidemiological studies have shown that HPV clearance in healthy, immune competent individuals, takes 8 to 12 months (Woodman et al., 2007). Cohort studies have shown that the continued presence of HR-HPV

is necessary for the development, maintenance and progression of HSIL (Ho et al., 1998; Bory et al., 2002; Muñoz et al., 2003; Dalstein et al., 2003; Cuschieri et al., 2005). To establish a persistent infection, HPVs gain access to mitotically active basal-layer keratinocytes, where low-copy replication begins. The viral DNA persists as a nuclear episome in infected cells. In the non-productive stage of infection, HPVs replicate at low copy number in mitotically active basal layer cells within stratified epithelia (Howley, 1996). HPV genomes can persist in proliferating keratinocytes for years or decades. This persistent phase of the viral lifecycle is characterized by detectable levels of viral genome, but the absence of virus production (Stubenrauch & Laimins, 1999), which is most likely a strategy to evade immune surveillance. So, there are two well-defined phenomena in the development of neoplasia - first, there is an alteration in the cellular immune response that allows the persistence of the virus for many years (Walboomers et al., 1999; Nobbenhuis et al., 2001) and second, the phenomena of transformation in epithelial cells produced by oncogenic virus proteins (E6 and E7) through degradation of p53 and pRb (Scheffner et al., 1990; Boyer et al., 1996) and alteration in the expression of proto-oncogenes such as c-Myc and Ras (Marangoz et al., 1999).

Genetic factors intrinsic to the host immune system play a role in susceptibility and/or resistance to the development of CC. Genetic factors associated with CC are polymorphisms in genes coding for tumor necrosis factor alpha (TNF- α) (Wilson et al., 1997; Kirkpatrick et al., 2004), matrix metalloproteinase 1 (Lai et al., 2005), p53 (Dokianakis et al., 2000; Makni et al., 2000), Human Leukocyte Antigen-HLA (Apple et al., 1994; Hildesheim & Wand, 2002) and Fas (Lai et al., 2003). In a complete genome scan in families with more than one child with CC, it was found that in the long arm of chromosome 9 there is a susceptibility locus for the development of cervical carcinoma. In this locus, candidate genes could be potentially involved in genetic predisposition to this disease (Engelmark et al., 2006). Genes such as IKBKAP, PTPN3, TSCOT, AMBP, *akna*, TNFSF15, TNFSF8 and DEC1, have important roles in the development of the immune response.

Among these is the *akna* gene, which is located in band 32 (9q32) on chromosome 9 (HGNC: 24108) and consists of 24 exons (<http://www.ncbi.nlm.nih.gov/gene/80709>) (Figure 1A). Up to 9 different *akna* transcripts have been identified, resulting from alternative promoter usage, splicing and poly-adenylation. Of the 9 reported transcripts, the 3.1 kb F1 transcript has been functionally tested by our research group (Sims et al., 2005; Perales et al., 2010).

The AKNA protein encoded by this gene is a nuclear protein consisting of 633 amino acids with an approximate weight of 63 kDa. AKNA contains an AT-hook motif of nine amino acids, RTRGRPADS (arginine, threonine, arginine, glycine, arginine, proline, alanine, aspartic acid, serine), which satisfies the consensus requirements of an AT hook DNA-binding motif. The AT-hook is a small motif with a typical sequence signature, in which the tripeptide GRP (Gly⁵⁸, Arg⁵⁹ and Pro⁶⁰) is the centre of the DNA-binding domain (Siddiqua et al., 2011). Besides, AKNA contains multiple PEST protein-cleavage motifs, which have been shown to target proteins of rapid turnover (Chevallier, 1993; Siddiqua et al., 2001) and has three domains located in the PEST regions: Leu10-Thr43, H149-Ser171, and P616-T63. These regions are sites of protein degradation so AKNA is considered to have a short half-life (Siddiqua et al., 2001) (Figure 1B).

It has been demonstrated that AKNA expresses at least nine transcripts, some of which are expressed in a tissue-specific manner, reflecting its functional diversity. Besides, several of

these transcripts are predicted to encode proteins of 155, 137, 100 and 70 kDa. However, only two isoforms (70 and 100 kDa) are expressed in B- and T- cell lines, and both bind to the promoters of the costimulatory molecules of the immune response - CD40 and CD40L (CD40 ligand) (Sims et al; 2005). It has been shown that PEST-dependent cleavage of AKNA is key to its DNA binding function, because in the absence of the PEST-dependent cleavage, the expression of AKNA alone is not sufficient to induce CD40 expression (Sims et al., 2005; Ma et al., 2011).

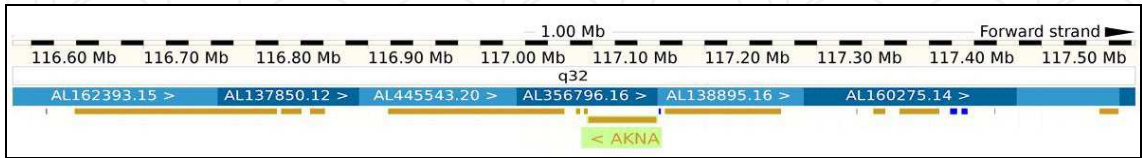


Fig. 1A. Akna gene localized in chromosome 9Q32

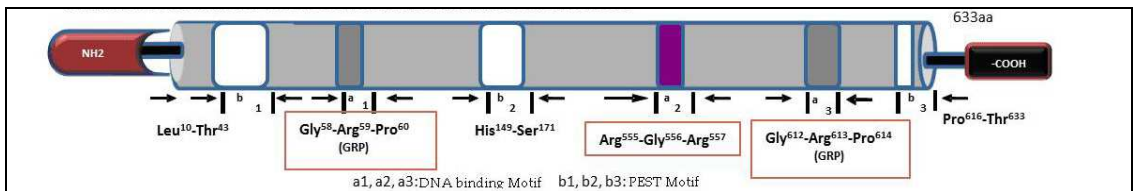


Fig. 1B. Protein at-hook-containing transcription factor

AT-hook proteins have been mainly recognized within the high mobility group A (HMGA) family, which includes chromatin remodeling proteins that coordinate transcriptional complexes to regulate gene expression (Cui & Leng, 2007). However, non-HMG AT-hook proteins have been identified and characterized. Among these, proteins with AT-hook-like motifs (ALMs) have been found to be capable of binding A/T-rich gene targets and regulating their transcription (Senthilkumar & Mishra, 2009; Gordon et al., 2010). In keeping with this notion, the human AKNA gene is a non-HMG transcription factor, which contains N- and C- terminus AT-hook motifs (Siddiqa et al., 2001; Sims et al., 2005). In addition, the AT-hook motif is considered to be the key to upregulation of expression of immune system co-activator molecules, since it has been shown to be directly involved in inducing the expression of molecules belonging to the TNFR family members. AKNA is mainly expressed in secondary lymphoid organs; it is expressed by germinal centre B lymphocytes during B-lymphocyte differentiation and by natural killer (NK) cells and dendritic cells (Siddiqa et al., 2001). AKNA binds the A/T-rich regulatory elements of the CD40 and CD40L promoters (a key receptor-ligand pair that is critical for antigen-dependent B cell development) and induces its expression (Siddiqa et al., 2001).

Thus, in this chapter we will discuss the findings of our research group with respect to the immune response against HPV, CIN and CC, and associated genetic factors of susceptibility to the disease that we found in population studies, particularly the *akna* gene.

2. Immune response against HPV & CIN

In the HPV cycle in keratinocytes, mature virions are shed from the epithelial surface of infected keratinocytes. HPV infection is poorly immunogenic because it is productive (produces no characteristic local inflammation) and during infection there is little presentation of viral antigens to the immune system by professional antigen presenting

cells, both locally and systemically (Feller et al., 2010). There is no significant evidence in the literature of inflammation being a risk factor for lesion progression, as observed in several tumor models. On the contrary, the inflammatory infiltrate in patients with established lesions seems to display anti-inflammatory or suppressor characteristics, like the absence of inducible NO synthase (iNOS) expression by macrophages (Mazibrada et al., 2008) and indoleamine 2,3'-deoxygenase expression by dendritic cells (Kobayashi et al., 2008).

Interestingly, the number of infiltrating macrophages seems to increase in correlation with lesion grade (Hammes et al., 2007; Kobayashi et al., 2008; Mazibrada et al., 2008). T lymphocytes also infiltrate cervical HPV associated lesions, where the phenotype, abundance and balance between different populations are important in determining the fate of lesions or tumors (Piersma et al., 2004; van der Burg, 2007; Woo et al., 2008). Cellular immune response plays an important role in the control and course of HPV infection; this response varies depending on the degree of injury and the oncogenic potential of HPV. There is evidence that HPV interferes with cell cycle control, secondary to the accumulation of genetic abnormalities; this accounts for viral persistence and the progression of lesions. In many patients secondary factors, such as inadequate immune response, play an important role (Riethmuller & Seilles, 2000).

At the cervical level, after infection of epithelial cells by HPV, a non-specific response is triggered accompanied by chemoattraction of neutrophils, activation of macrophages, activation of NK, natural antibodies and complement system; this is a first defensive barrier of specific immunity. Reticular cells of Langerhans (RCL) and some keratinocytes act as antigen presenting cells (APCs). RCLs are immature dendritic cells of myeloid origin residing in the squamous epithelium, including genital mucosa. RCL recognize the viral particles, capture antigens by micropinocytosis or mannose receptors, process captured proteins and transform them into immunogenic peptides, start the activation process (which includes a surface antigen polypeptide chain with HLA class II, CD40 and B7), migrate to local lymph nodes and present viral peptides to T cells in the context of the major histocompatibility complex (MHC) and costimulatory molecules (CD80, CD86 and CD40). Thus, native lymphocytes are activated and direct their differentiation into effector cells, initiating the antigen-specific immune response (Stern, 2008).

During a primary immune response, depending on the microenvironment and the signals received from certain cytokines, naive CD4⁺ T cells can differentiate into three to four major subsets of Th cells, with distinct patterns of cytokine secretion that drive different types of immune responses (Seder et al., 2003; Weaver et al., 2006). Briefly, IFN- γ and Interleukin (IL)-12 induce differentiation of Th1 cells to produce more IFN- γ , which enhances the clearance of viruses and the proliferation of specific CD8 cytotoxic T lymphocytes (CTL); on the contrary, if the local context does not express IL-12, it promotes the Th2 pathway which induces activation and expansion of B cells; these evolve, differentiating into plasma cells producing antibodies to viral proteins and inducing the expression of interleukins type IL-4, IL-5, IL-6 and IL-10 (Stern, 2008). The mediators of cell-mediated immunity against HPV infected cells and some tumors are CTL, which eliminate virally infected cells by means of antigen-specific, cell-mediated cytotoxicity. Additionally, CD4⁺ T helper cells participate in the control of these processes. Under certain conditions, the Tumor Growth Factor Beta (TGF- β 1) or IL-10 alone drives regulatory CD4⁺ T cell (Treg) differentiation which regulates

immune responses by several distinct mechanisms (Damoiseaux, 2006; Robertson & Hasenkrug, 2006). Thus, together with CTL, the only Th subset that is desirable in pre-malignant CC lesions is that of Th1 cells, as IFN- γ favors immune responses against viral infections.

The natural history of these tumors is long and includes the following steps: infection, persistent infection, viral genome integration into the host cell genome, genomic alterations, immortalization and transformation of epithelial cells. During all these steps, evasion of the immune system is an obligatory feature. The immune evasion mechanisms displayed by the infected cells include absence of cell death (Tindle, 2002), blocking of type I Interferon signaling and reduction of antigen presentation by MHC-I (Ashrafi et al., 2005; Stern, 2008).

2.1 Cellular immune response

Local cellular immune response detected in SIL is characterized by a moderate infiltrate and a decreased inverted Th/Tc (CD4/CD8) ratio, with decreased proliferative capacity (Santin et al., 2001). An imbalance in the pattern of cytokines, as by an increase in type II interleukin (IL-4, IL-10, suppressing the cellular immune response) and a concomitant reduction in interleukin type I [(IL-2, gamma interferon (IFN- γ)], has been reported in women with SIL and CC (Giannini et al., 1998; Clerici et al., 1998; Bor-Ching et al., 2001). Anti-tumor immunity in CC is activated by Th1 cytokines and inhibited by Th2 cytokines. Cytokines such as IL-4, IL-12, IL-10 and/or TGF- β 1, produced by various cell types (macrophages, dendritic cells and keratinocytes) have been involved in the suppression of cellular immune response (Giannini et al., 1998).

The pattern of cytokines and their expression in women with CC biopsies has been analyzed. 80% of the tumors express low levels of mRNA of CD4 T lymphocytes and high levels of CD8 CTL. Most tumors express the mRNA of IL-4 and IL-10 and 100% of them express the mRNA of TGF- β 1 and IFN- γ . None of the tumors express the IL-12 mRNA, IL-6 mRNA or TNF- α (Alcocer et al., 2006). Immunohistochemical analysis of tumors has demonstrated the presence of IL-10 in tumor cells and cell koilocytes, but not in infiltrating lymphocytes, suggesting that the cells producing IL-10 can be transformed by HPV. On the other hand, a correlation has been found between the immunostaining of IL-10 protein, the level of mRNA IL-10 expression and the supernatants of HPV transformed cell lines expressing IL-10 and TGF- β 1 (Alcocer et al., 2006). These findings show a predominant expression of immunosuppressive cytokines, which help to downregulate tumor specific immune response in the tumor microenvironment (Alcocer et al., 2006).

In a recent study, the functionality of peripheral blood T lymphocytes (PBL) and tumor-infiltrating lymphocytes (TIL) of women with SIL and CC was assessed, including proliferation, mRNA expression of IL-2, IFN- γ , IL-4, IL-10 and TGF- β 1, as well as the expression of CD3 ζ . Using immunohistochemistry, we have seen that TIL is distributed in the stroma more than in epithelium in advanced stages of the disease where CD8 CTL prevail. PBL stimulated with phytohemagglutinin in patients with CC, proliferate less than in SIL patients and healthy subjects. Also, a significant difference is observed in the PBL stimulated with anti-CD3, between patients with CC and healthy subjects. This shows that women with CC have a poor proliferative PBL response and a lack of response to TIL (Díaz et al., 2009).

Antigen recognition of cells with cytotoxic capacity is mediated by receptors. In T cells, these are called T-cell receptors (TCR), which consist of a heterodimer of $\alpha\beta/\gamma\delta$ chains and four $\epsilon, \delta, \gamma, \epsilon$ chains, which together are recognized as TcR-CD3. These receptors are in turn associated with two "zeta" strings which are responsible for the transmission of activation signals within the cell. Zeta chains are also present in the receptor for NK cell antigens. Molecular studies have shown a decreased expression of the dimer formed by the zeta chain, in both T cells and NK cells, contributing to the inefficiency of the effector mechanisms of lymphocytic infiltrate present in the lesions. It has been demonstrated that there is a decreased expression of CD3-zeta chain in patients with CC and CIN (Kono et al., 1996; Shondel et al., 2007), and that suppression *in vivo* can be the result of a circulating factor (Shondel et al., 2007). We found that IL-10 and TGF- β 1 produced by HPV-transformed cells are responsible for CD3-zeta suppression in CC patients (Diaz et al., 2009). These processes are regulated by local factors derived from tumor cells.

As there is an imbalance of cytokines in the microenvironment of these lesions, this affects the transcriptional level. Lymphocytic infiltrate present in the cervical lesions reflects an ineffective immune response (De-Gruijl et al., 1999). A significant correlation between low lymphocyte proliferation and decreased mRNA expression of CD3 ζ has been reported in T lymphocytes stimulated with anti-CD3, indicating that T cell function decreases with the progression of CC (Díaz et al., 2009). These changes result in a loss of control of certain HPV 16-18 genes and deregulation in the mechanisms of antigen presentation. Thus, the expression of HLA antigens is reduced or absent (Wang et al., 2002) and there is partial or total absence of Langerhans cells, considered to be they key antigen-presenting immune response against the tumor (Hachisuga et al., 2001).

2.1.1 Role of AKNA in immune response

Proteins containing AT hooks bind A/T-rich DNA through a nine amino-acid motif and are thought to co-regulate transcription by modifying the architecture of DNA, thereby enhancing the accessibility of promoters to transcription factors (Reeves & Nissen, 1990; Friedmann et al., 1993). AKNA is a human AT-hook protein that directly binds the A/T-rich regulatory elements of CD40 and CD40L promoters and coordinately regulates their expression. Consistent with its function, AKNA is a nuclear protein that contains multiple PEST protein-cleavage motifs, which are common in regulatory proteins with high turnover rates (Chevaillier, 1993).

AKNA is mainly expressed by B and T lymphocytes, NK cells and dendritic cells. During B-lymphocyte differentiation, AKNA is mainly expressed by germinal centre B lymphocytes, a stage in which receptor and ligand interactions are crucial for B-lymphocyte maturation (Berek et al., 1991; Liu et al., 1991; Jacob & Kelsoe, 1992; McHeyzer-Williams et al., 1993; Clark & Ledbetter, 1994; MacLennan, 1994; Arpin et al., 1995; Liu et al., 1996). These findings show that an AT-hook molecule can coordinately regulate the expression of a key receptor and its ligand, and point towards a molecular mechanism that explains homotypic cell interactions (Siddiga et al., 2001).

Human AKNA is a transcription factor with N- and C- terminus AT-hook motifs (Siddiga et al., 2001; Sims et al., 2005). Thus, it is possible that AKNA expression plays a role in

mechanisms that, if altered, could result in systemic and potentially fatal disorders. Human AKNA is encoded by a single gene located within the FRA9E region of chromosome 9q32 (Sims et al., 2005), a common fragile site (CFS) linked to loss-of-function mutations that often lead to inflammatory and neoplastic diseases (Thye et al., 2003; Landvik et al., 2009; Savas et al., 2009). Based on this reasoning, two independent gene-targeting mouse models were engineered to assess *in vivo* the physiological significance of *akna* gene expression. It was found that the phenotypes resulting from the deletion of the putative C-terminus ALM sequence (AKNA KO) or disruption of AKNA's exon 3 (AKNA KO2) were by and large similar: a) mice died prematurely at neonatal age; b) probable causes of sudden death included acute inflammatory reactions and alveolar destruction; c) triggering of the observed inflammation appeared to be pathogen-induced; d) systemic neutrophil mobilization and alveolar infiltration were routinely observed and; e) concerted activation of neutrophil-specific chemokine, cytokine and proteolytic enzyme expression seemed to be the norm. The central goal of the AKNA function was provided and supports the hypothesis that AKNA expression plays an important role in the mechanisms that regulate the magnitude of inflammatory responses to pathogens (Ma et al., 2011).

It was reported that deletion of murine *akna* gene results in small, frail mice that die suddenly at 10 days of life. Besides, AKNA KO mice present systemic inflammation, predominantly in the lungs, that is accompanied by enhanced leukocyte infiltration (mainly neutrophils) and alveolar destruction. Because AKNA functions as an AT-hook transcription factor, Ma and colleagues investigated expression of genes related to neutrophil function and found a significant enrichment in genes encoding inflammatory cytokines (IL-1 β , IFN- γ), inflammatory proteins [neutrophilic granule protein (NGP), cathelin-related antimicrobial peptide (CRAMP), S100A8/9] and proteases (matrix metalloprotease-9; MMP-9), which are implicated in alveolar damage. Given that AKNA deficiency results in an increase of MMP-9, IL-1 β , IFN- γ , NGP, and CRAMP S100A9 gene expression, it is possible that AKNA functions as a multi-faceted transcriptional repressor that can coordinately temper pathway-specific gene transcription (Ma et al., 2011; Moliterno & Resar, 2011).

It has been suggested that AKNA's function is necessary to regulate the magnitude of pathogen-elicited neutrophil activation, proliferation and tissue infiltration by coordinately restricting autocrine/paracrine cytokine and chemokine. This implies that when AKNA is productively expressed, neutrophil reactions are increased to neutralize and destroy pathogens. However, loss of AKNA expression could exacerbate neutrophil activation and cause irreparable tissue damage. This hypothesis is in tune with the enhanced MMP-9, IL-1 β , IFN- γ , and NGP expression and the resulting lethal syndrome associated with AKNA deficiency, in which transcriptional repression is seemingly lost (Ma et al., 2011). It is interesting to note that a significantly decreased expression of AKNA in CD4⁺ T cells has been reported in active patients with Vogt-Koyanagi-Harada Syndrome (VKH, a systemic autoimmune disease). It is unknown whether a decreased AKNA could play a role in VKH syndrome via downregulation of CD40 and CD40L (Mao et al., 2011). In conclusion, it will be interesting to determine if loss-of-function mutations, polymorphisms or epigenetic alterations in *akna* contribute to myeloid function, inflammation and neoplastic transformation.

2.1.2 Evasion of immune surveillance

There is evidence of CIN regression to normal epithelium and it has been suggested that cellular immune response is responsible for HPV clearance (Woo et al., 2010). The cellular immune response mechanisms against HPV are similar to other responses used against viral infection. However, sometimes these mechanisms fail; allow HPV persistence and tumor development. There are several mechanisms for immune response evasion; however, three operate in HPV-infected women: 1) the expression of immunosuppressor cytokines such as, IL-10 and TGF- β 1; 2) Fas ligand expression in HPV-transformed cells, and 3) the presence of Treg cells (de Gruijl et al., 1999; Bor-Ching et al., 2001; Alcocer et al., 2006) which are associated with HPV persistence (Molling et al., 2007) and CIN development (Scott et al., 2009). The presence of immune suppressor cytokines in HPV-CIN patient sera has been demonstrated (Clerici et al., 1997).

It is well known that IL-10 and TGF- β 1 expression are initiated at the onset of HPV infection and increase as the disease progresses. This allows us to postulate IL-10 as an HPV escape mechanism of the cellular immune response (Bermúdez-Morales et al., 2008). IL-10 and TGF- β 1 are expressed in HPV-transformed cells and are induced by HPV E2, E6 and E7 proteins (Bor-Ching et al., 2001; Peralta et al., 2006; Bermúdez et al., 2011).

A susceptibility factor for the development of CC is an alteration of the immune response in patients. This immunosuppression produces a decrease of CTL and NK activation, cells that play an important role in tumor cell elimination. Consequently, HPV-transformed cells do not express antigen presenting molecules, HLA class I and II, an effect mediated by IL-10 and TGF- β 1 and by the presence of Treg (Keating et al., 1995; Ploegh, 1998; Nakamura et al., 2007). IL-10 and TGF- β 1 also decrease CD3 ζ chain expression of the T-cell antigen receptor (Díaz et al., 2009; Patel & Chiplunkar, 2009), which is responsible for antigen recognition. Additionally, it is well known that there are infiltrating T-lymphocytes in CIN and CC, predominantly CD8 CTL; however, these lymphocytes have a low proliferation rate and the absence of costimulatory molecules of cellular immune response. Thus, there is no activation of CTL and no elimination of neoplastic cells (Alcocer et al., 2006; Díaz et al., 2009).

2.2 Humoral immune response

Regarding the humoral response, variability has been reported in antibody titers, regardless of the high levels of circulating immune complexes, especially in those patients with tumors in advanced stages. In early lesions, high levels of IgG antibodies against HPV oncogenic proteins E6/E7 and E4 have been observed, as a result of greater antigenic stimulation, with a decreased IgG1/IgG2 ratio; this is a reflection of the Th1/Th2 imbalance (Matsumoto et al., 1999; Pedroza-Saavedra et al., 2000). In advanced tumors, higher titers of IgA and IgM decrease proportionally as the disease progresses, perhaps due to an impaired immune system (Baay et al., 1997).

3. Genetic susceptibility and AKNA polymorphisms

3.1 Cancer genetic susceptibility

Scientific advances have enabled us to predict susceptibility to developing diverse diseases, including breast, ovarian, and other cancers like CC. With this new knowledge we are able to identify, in a specific population, who are at greater risk of developing a disease.

Cancer is a complex disease that should be considered as a genetic disease. In this respect, genetic factors are not considered to be a direct cause of disease but, in combination with environmental factors, have effects on the resistance or susceptibility to diseases as cancer. Furthermore, cancer risk assessment includes the collection and interpretation of multiple factors that contribute to carcinogenesis. These factors include personal and family health history, reproductive history and hormone use, environmental risk factors such as HPV infection and lifestyle habits associated with cancer risk, as well as any genetic/genomic information (Jenkins, 2009) (Figure 2).

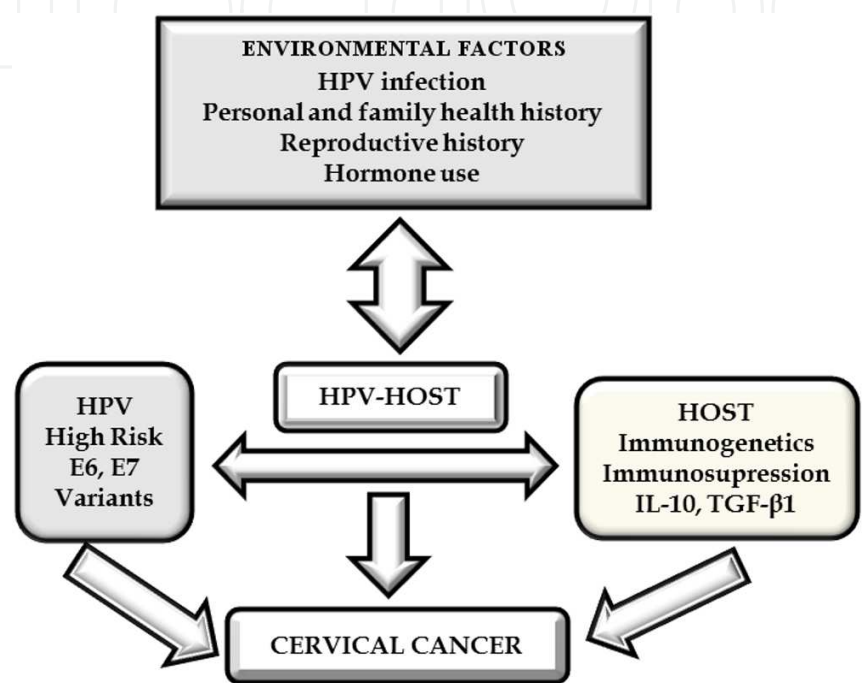


Fig. 2. Factors affecting the persistence of HPV infection and cervical cancer onset

A number of mechanisms leading to cancer have been identified through the discovery of structural alterations of genes called oncogenes and tumour suppressor genes. Somatic and germinal mutations are rare but play a determinant role in the emergence of cancer, while common and frequent variations (polymorphisms) play a role in cancer susceptibility and in the effects of anticancer drugs (efficacy and toxicity)(Robert, 2010; Hildesheim & Wand, 2002).

The susceptibility of a woman to developing CC is largely attributed to the type of HPV infecting the cervix and the persistent HPV infections associated with a high viral load; these are considered to be the major risk factors for persistent cervical lesions (Schlecht et al., 2003; de Araujo Souza & Villa, 2003). Persistence of infections by HR-HPV types is the single greatest risk factor for malignant progression. Although prophylactic vaccines have been developed that target HR-HPV types, there is a continuing need to better understand the virus–host interactions that underlie persistent benign infection and progression to cancer (Bodily & Laimins, 2011). Even though HPV is considered to be a necessary but not sufficient cause for CC, the hereditary component has been reported and several studies indicate that genetic background of the host is important for CC susceptibility and for the carcinogenic process. (de Araujo Souza & Villa, 2003; Hemminki et al., 1999; Magnusson et al., 2000; Wank & Thomssen, 1991).

To study the genetic background and to explore the differences in individual cancer susceptibility, a recent focus of research efforts has been on SNPs (single nucleotide polymorphisms). SNPs are the most common known form of human genetic variation and are defined as stable single-base substitutions with a frequency of greater than 1% in at least one population (Taylor et al., 2001; Meyer et al., 2008). For cancer research, the focus has been on SNPs that alter the function or expression of a gene, to attempt to explain observed associations with a pathogenic mechanism. Indeed, genetic polymorphisms in functionally critical genes such as immune response genes have been suggested as risk factors for the development of a variety of cancers including CC (Taylor et al., 2001; Milam et al., 2007). There are several reports about genes related to immune response (e.g. MHC genes), cytokine genes, genes involved with cancer development (e.g. p53) and CC susceptibility (Glew et al., 1992; Haukin et al., 2002; Sierra-Torres et al., 2003).

Concerning HLA polymorphisms and the risk of CC, discordant results have often been observed among different populations, where the most consistent reports are for the DRB1*13 and DRB1*0603 alleles as a protection factor with OR 0.3-0.4 (Hildesheim & Wand, 2002; Apple et al., 1994; Maciag et al., 2002) and increasing risk for the DQB1*03 and DRB1*1501-DQB1*0602 with OR 2.9 and for the DRB1*0301-DQB1*0201 haplotype, which was associated with a two-fold reduction in risk for transient and persistent HPV infections. DRB1*1102-DQB1*0301 showed a lower risk effect only for persistence. DRB1*1602-DQB1*0502 and DRB1*0807-DQB1*0402 were associated with seven- and three-fold increases in risk for persistence, respectively (Hildesheim & Wand, 2002; Apple et al., 1994; Maciag et al., 2002). More recently, a study of CC cases that were HPV-16 positive and controls, carried out in Mexican population, showed consistent results of association between the HLA-DRB1*15 (OR, 3.9; 95 % CI, 1.6-10.2) and the DRB1*15 DQB1*0602 haplotype (OR, 4.1; 95 % CI, 1.4-12.7) in CC cases, compared with the control group. Also for the HLA class I, the haplotypes HLA-A2-B44-DR4-DQ*0302, HLA-A24-B35-DR16-DQ*0301 and HLA-A2-B40-DR4-DQ*0302 showed a positive association with CC (OR > 1), while HLA-A2-B39-DR4-DQ*0302, HLA-A24-B35-DR4-DQ*0302 and HLA-A68-B40-DR4-DQ*0302 showed a negative association (OR < 1) (Hernández et al., 2009).

Also TNF- α has been implicated in direct and indirect control of HPV infection through induction of apoptosis and stimulation of inflammatory responses. Two types of polymorphism have been described in TNF- α gene. One involves several polymorphisms in the TNF- α promoter region, including SNPs at positions -76, -161, -237, -243, -308 (G→A), -375, -568, -572, -575, -857 and -863; the second involves SNPs in DNA microsatellites (Martin et al., 2006). Evidence suggests that the GG genotype of SNP G/T at position -308 in the TNF- α promoter region, has been associated with CC precursor lesions (Kirkpatrick et al., 2004). Other TNF- α SNPs with reported associations with CC include -237, -572, -857 and -863, and haplotype analysis has again strengthened these regions as potential targets for determination of CC susceptibility. The other TNF- α polymorphisms associated with CC are the microsatellite polymorphisms TNF- α 2, TNF- α 8 and TNF- α 11, with significant associations between CIN I and the TNF- α 8 allele, CIN III and the TNF- α 2 allele in patients who are HPV-18 positive, and TNF- α 11 with HPV-16 infection and CIN, in combination with HLA DQB allele (Martin et al., 2006).

Also, p53 polymorphism in codon 72 has been associated with CC. It has been observed that the p53 variants differ biochemically from each other and that the p53-Arg is more

susceptible to HPV E6-mediated degradation than the proline variant (Madeleine et al., 2002; Beckman et al., 1994). Furthermore, Storey et al., have shown that individuals who were homozygous for the arginine allele had a seven times higher persistence of HPV associated to CC than heterozygous proline/arginine women (Storey et al., 1998). However, similar analyses performed in other populations did not confirm the association between such polymorphism of the p53 gene and the risk of developing HPV-associated lesions (Minaguchi et al., 1998; Hildesheim et al., 1998). Beside MHC and p53 polymorphism, polymorphisms in cytokine genes can influence immune responses to HPV infection, possibly modifying risks of CC. (Kirkpatrick et al., 2004; Howell & Rose, 2006; Bidwell et al., 1999; Haukin et al., 2002; Stanczuk et al., 2002; Matsumoto et al., 2010).

IL-10 and TGF- β 1 polymorphisms have also been reported in diverse populations. G allele of SNP (A/G) at position -1082 in interleukin-10 promoter region, has been associated with high levels of IL-10, which increases with disease severity ($p < 0.001$) (Farzaneh et al., 2006; Singh et al., 2009; Matsumoto et al., 2010). On the other hand, CC patients with -509TT showed marginal low risk for stage I cancer ($p = 0.04$, OR = 0.95, 95% CI = 0.91-0.99) but -509TT genotype of TGF- β 1 was associated with increased risk for stage II cancer ($p = 0.07$, OR = 3.13, 95% CI = 0.87-11.14) (Singh et al., 2009).

3.2 AKNA polymorphism

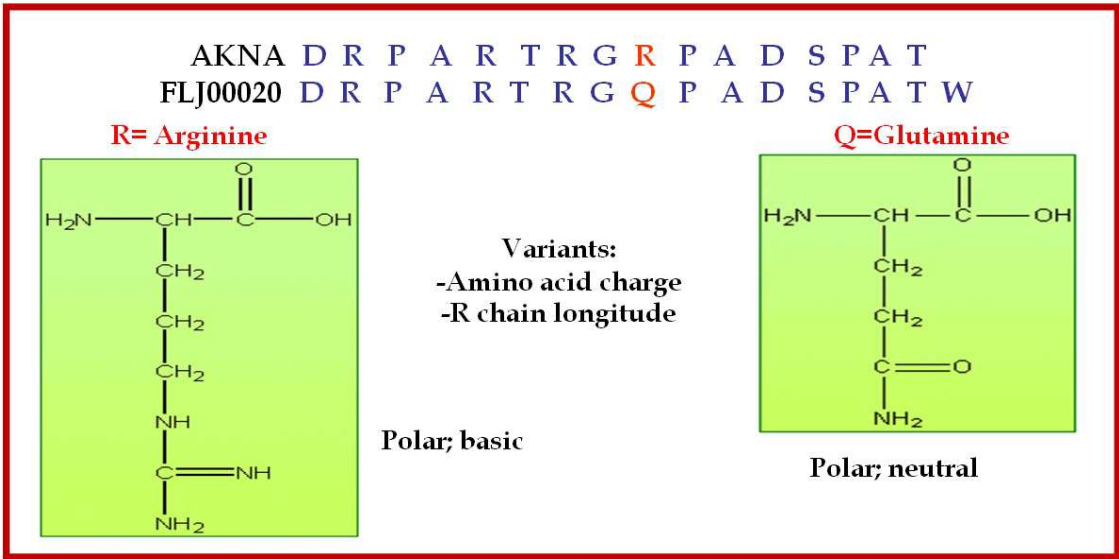
A number of genetic susceptibility factors have been proposed, but with the exception of the HLA class II, have not shown consistent results among studies. The first genome-wide linkage scan was performed using 278 affected sib-pairs to identify loci involved in susceptibility to CC. This study found that 9q32 contains the susceptibility locus for CC, and some of these candidate genes are potentially involved in the genetic predisposition to this disease; among these genes is *akna* (Engelmark et al., 2006).

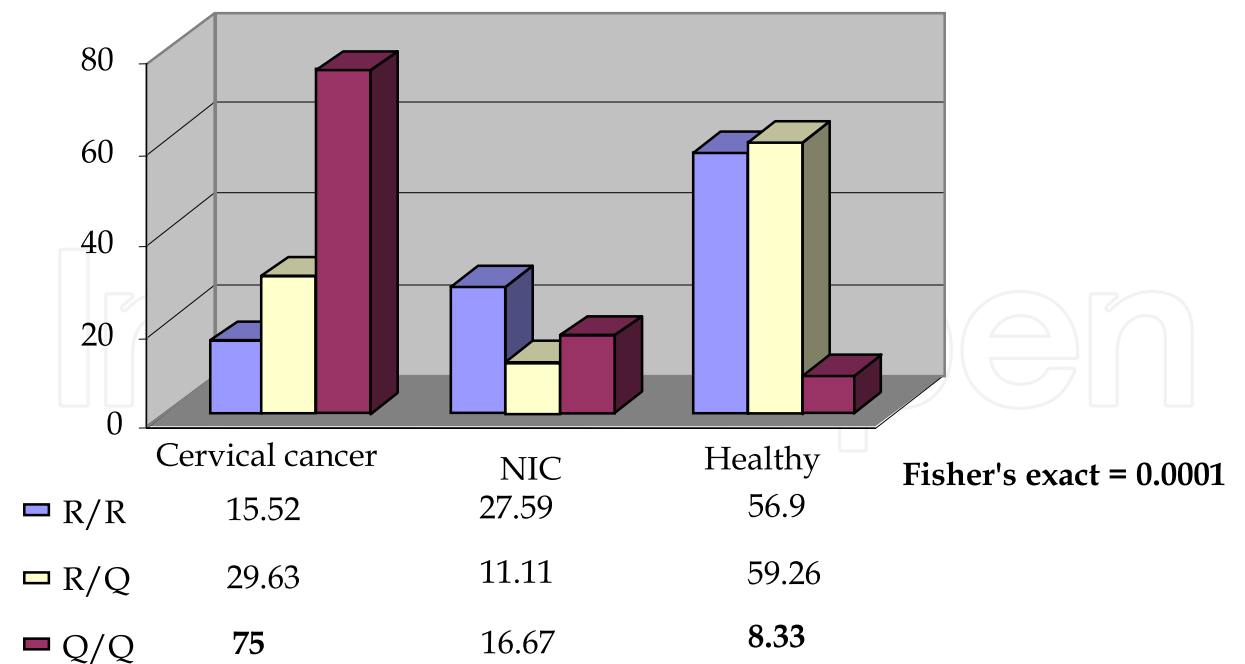
AKNA is a transcriptional factor that is involved in lymphocyte maturation and in the up-regulation of signaling molecules, such as CD40L (Siddiqi et al., 2001; Sims et al., 2005). Even though the precise molecular mechanisms for AKNA function have not been defined, AT-hook transcription factors have emerged as multifaceted regulators that can activate or repress broad A/T-rich gene networks. Thus, alterations of AT-hook genes could affect the transcription of multiple genes causing global cell dysfunction which could mediate DNA bending and chromatin rearrangement (Cairns et al., 1999; Ma et al., 2011).

Although functional data concerning AKNA are scarce, sequences of *akna* genes deposited in the GenBank databases are increasing. SNP analysis in the Genecard site (<http://www.genecards.org/>), at the 313 SNPs, reported that, for all *akna* genes, only 11 of them are coding non-synonyms. Among all the SNPs reported for *akna*, SNP (rs3748178) involving the transition G/A, at nucleotide 114189600(-) of chromosome 9 (accession no. AK024431) (Ota et al., 2004), appears to be functionally relevant. This mutation produces an R to Q amino acid change at codon 1119 (protein accession NP_110394). Such R/Q mutation occurs at an important AT-hook DNA binding motif within the highly conserved core that has a typical sequence pattern centered around a glycine-arginine-proline (GRP) tripeptide (codons 1118-1120). This short conserved sequence is relevant because it is necessary to bind DNA (Aravind & Landsman, 1998). The importance of producing a GQP core motif, instead

of a GRP, is because glutamine lacks the positive charge that arginine has and thus potentially affects its DNA-binding capacity (Reeves & Nissen, 1990; Huth et al., 1997).

The AT-hook motif interacts directly with the minor groove of DNA in AT rich regions. Although some sequence specificity is present in the AT hook itself, and this may affect the main function of this motif (which is to anchor to the proteins in the minor groove of the DNA, near sequences targeted by other regions of the AT hook proteins), it is probably dependent on the spacing between successively interacting AT-hooks and their binding sites may be crucial for conformational changes of the DNA (Huth et al., 1997; Aravind & Landsman, 1998). A SNP at codon 1119 of the *akna* gene, yields a potentially relevant amino acid change (R1119Q) located at the DNA binding AT-hook motif; the AT hook may serve as a contact which affects the specificity and affinity of the DNA binding protein (Figure 3).





akna genotype distribution, Modified from Perales G, et al., Biomarkers, 2010

Fig. 4. *akna* genotype distribution

	ORc	CI 95%	P value	ORa	CI95%	P value
CACU	3.66	1.35, 9.94	0.01	4.22	1.3, 13	0.01
NIC	0.6	0.18, 1.93	0.39	0.61	0.18, 2.0	0.42

CI, confidence interval; CIN, cervical intraepithelial neoplasia; Multinomial logistic regression: ORc, unadjusted odds ratio; ORa, adjusted OR by age. Modified from Perales G, et al., Biomarkers, 2010

Table 1. Risk of Cervical cancer associated with Q/Q *akna* genotype

The AT-hook *akna* motif studied in this work is present in all reported *akna* isoforms except in the C1 and C2 isoforms (Sims et al., 2005). Therefore, the relevance of our observation is valid for the wide range of isoforms potentially expressed by the *akna* gene (Sims et al., 2005). The observed frequencies of *akna* Q/Q genotype in this group of 194 studied chromosomes, and the demonstration of a statistically significant association between a mutation in the *akna* gene (that results in an R-Q amino acid change) and susceptibility to CC, is of high relevance to biological knowledge of the development of CC. Whether this mutation contributes to an alteration of AKNA protein structure and immune function, and to CC development, is under investigation (Perales et al., 2010).

4. Conclusions and perspectives

HPV infection has two different cycles, the productive cycle and the transforming cycle. In the productive cycle of HPV, which occurs in keratinocytes, mature virions are shed from the epithelial surface of infected keratinocytes. HPV infection is poorly immunogenic because it is productive (produces no characteristic local inflammation) and during infection there is little presentation of viral antigens to the immune system by professional antigen-presenting cells, both locally and systemically. In some cases, HPV infection produces a non-

inflammatory reaction. There is no adequate cellular immune response, due to excessive secretion of immunosuppressor cytokines, essentially IL-10, which produces a reduction of antigen-presenting and co-stimulatory molecules, and hence no recognition by the surrounding CD8 CTL. The AKNA transcription factor that induces the expression of stimulatory molecules, such as CD40 and CD40L, may play an important role in regulating the immune response against HPV. We found a genetic variant of the *akna* gene that has high frequency in patients with CC. Consequently, we believe that this genetic variant plays an important role, as a risk factor in CC development; the absence of AKNA protein may play an important role in the immune response against HPV. Thus, at the cervical level, after infection of epithelial cells by HPV, a nonspecific response is triggered that is accompanied by chemoattraction of neutrophils. Therefore, this interesting information about *akna*-KO raises important questions and further avenues for biomedical research. For instance, the enrichment of AKNA in wild-type neutrophils, and excess neutrophil counts in the absence of AKNA, suggests that this protein is important in the negative regulation of myeloid differentiation or neutrophil survival. It is of high relevance to determine whether loss-of-function mutations, polymorphisms or epigenetic alterations in *akna* contribute to myeloid diseases, such as myeloproliferative neoplasias, and CC. In conclusion, AKNA appears to be an important genetic factor associated with the progression of CC and genes regulated by this transcription factor could be involved in the resistance to CC progression.

5. References

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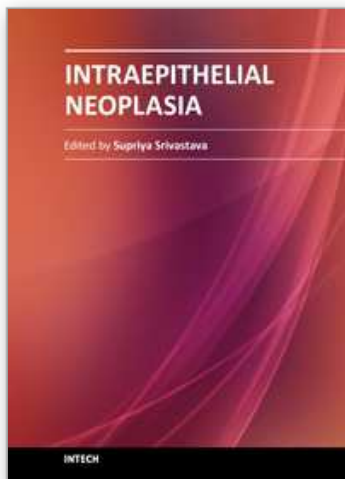
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The book "Intraepithelial neoplasia" is till date the most comprehensive book dedicated entirely to preinvasive lesions of the human body. Created and published with an aim of helping clinicians to not only diagnose but also understand the etiopathogenesis of the precursor lesions, the book also attempts to identify its molecular and genetic mechanisms. All of the chapters contain a considerable amount of new information, with an updated bibliographical list as well as the latest WHO classification of intraepithelial lesions that has been included wherever needed. The text has been updated according to the latest technical advances. This book can be described as concise, informative, logical and useful at all levels discussing thoroughly the invaluable role of molecular diagnostics and genetic mechanisms of the intraepithelial lesions. To make the materials easily digestible, the book is illustrated with colorful images.

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