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College of Veterinary Medicine

Jaagsiekte Sheep Retrovirus (JSRV)

from virus to lung cancer in sheep

A Graduation Project Submitted to the Department Council of the Internal and Preventive Medicine-College of Veterinary Medicine/ University of Al-Qadisiyah in a partial fulfillment of the requirements for the Degree of Bachelor of Science in Veterinary Medicine and Surgery.

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فَتَعَٰلَى ٱللَّهُ ٱلۡمَلِكُ ٱلۡحَقُّۗ وَلَا تَعۡجَلۡ بِٱلۡقُرۡءَانِ مِن قَبۡلِ أَن يُقۡضَىٰٓ
إِلَيۡكَ وَحۡيُهُۥۖ وَقُل رَّبِّ زِدۡنِي عِلۡمٗا ﴿١١٤﴾

صَدَقَ اللهُ العَظِيمُ

من سورة طه

Certificate of Supervisor

I certify that the project entitled (Jaagsiekte Sheep Retrovirus (JSRV) from virus to lung cancer in sheep) was prepared by **Ali shamki Idan and Hussain Kazem Jawed** under my supervision at the College of Veterinary Medicine / University of Al-Qadisiyah.

Supervisor

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-- / -- / 2021

Certificate of Department

We certify that Ali shamki Idan and Hussain Kazem Jawed had finished their Graduation Project entitled (Jaagsiekte Sheep Retrovirus (JSRV) from virus to lung cancer in sheep) and candidate it for debating.

Instructor

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-- / -- / 2021

Abstract

Jaagsiekte Sheep Retrovirus (JSRV) is a betaretrovirus infecting sheep. This virus is re-sponsible for a pulmonary adenocarcinoma, by transformation of epithelial cells from the bronchioli and alveoli. This animal cancer is similar to human bronchioloalveolar cancer (BAC), a specific form of human lung cancer for which a viral aetiology has not yet been identified. JSRV interacts with target cells through the membrane receptor Hyal2. The JSRV genome is simple and contains no recognised oncogene. It is now well established that the viral envelope protein is oncogenic by itself, via the cytoplasmic domain of the transmembrane glycoprotein and some domains of the surface glycoprotein. Activation of the PI3K/Akt and MAPK pathways participates in the envelope-induced transformation. Tumour development is associated with telomerase activation. This review will focus on the induction of cancer by JSRV.

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INTRODUCTION

Ovine pulmonary adenocarcinoma (OPA) is a contagious tumour originat-ing in the distal lung after infection by Jaagsiekte Sheep Retrovirus (JSRV). The disease was initially described in 1915 in South Africa and is present worldwide. JSRV belongs to the *Retroviridae* family and the *Betaretrovirus* genus. OPA is similar to a peculiar form of human cancer, bronchioloalveolar cancer (BAC), with which it shares clinical, radiologi-cal and histopathological features [51]. Although the molecular mechanisms of JSRV induced- tumorigenesis are still only partially understood, the significant recent efforts in the field of OPA research rein-force the for.

JSRV is the virus that is the cause of the contagious lung tumors in sheep called ovine pulmonary adenocarcinoma (OPA). The disease has also been called "jaagsiekte", after the Afrikaans words for "chase" (jaag) and "sickness" (siekte), to describe the respiratory distress observed in an animal out of breath from being chased, indicating the breathing difficulty experienced by infected sheep. Transmission of virus is through aerosol spread between sheep.

The exogenous infectious form of JSRV has an endogenous counterpart which is present in the genomes of all sheep and goats.[1] The sheep genome has around 27 copies of endogenous retroviruses (enJSRVs) that are closely related to JSRV. Endogenous JSRV has several roles in the evolution of the domestic sheep as they are able to block the JSRV replication cycle and play a critical role in sheep conceptus development and placental morphogenesis.[2]

Although OPA resembles human lung cancer, human lung cancer is not known to be caused by betaretroviruses.[3] Even though a possibility of a viral cause has been eliminated in bronchoalveolar cancer, understanding the molecular mechanisms leading to the transformation of lung epithelia by JSRV may be of interest in the context of therapeutic approaches in human lung cancers in general and bronchoalveolar adenocarcinoma (BAC) in particular.[

OPA: A VIRUS-INDUCED CANCER

Natural history

Transmission of OPA among sheep has been suspected for almost two centuries. The first report dates back to 1825, with a letter written by a farmer who complained about the loss of many of his sheep. The disease was called “Jaagsiekte”, after the Afrikaans words for “chase” (Jaag) and “sickness” (sieckte), to describe the respi-ratory distress observed in an animal out of breath from being chased [2]. The first evidence of a viral cause came from the observation of retrovirus particles in the lungs from sheep presenting clinical signs of cancer [1], and was further clearly con-firmed by experimental induction of the disease by intratracheal inoculation of viral particles with a reverse transcriptase activ-ity [4], cytoplasmic fractions of tumoral cells [2-1] or pulmonary secretions [1].

The disease can also be efficiently trans-mitted to goats by experimental inocula-tion [3-1]. JSRV has been definitively demonstrated as the aetiological agent of OPA by experimental inoculation of par-ticles produced from a JSRV-molecular clone [1].

OPA is present on all continents. Its incidence is difficult to evaluate in the ab-sence of an appropriate screening tool. The virus is transmitted between animals by close contact, mainly through aerosolized particles. The breeding conditions are of major importance for the dissemination of the virus. The incubation period in nat-urally infected animals ranges between 2 and 4 years [3], but the cancer may be diagnosed as early as a few months af-ter birth. The incubation period may vary according to the type of infection (experi-mental versus spontaneous infection), and the age of the animals [5]. Interestingly, injection of tumoural tissues into newborn lambs rapidly induces the disease in 3–6 weeks [7]. In natural conditions, the rapid development of tumoral lesions in young animals suggests a greater susceptibility of the developing lung to JSRV [8]. In utero transmission to the fetus has been sug-gested [8].

Pathogenesis

JSRV is transmitted by the respiratory route and may also infect lymphocytes and myeloid cells, in addition to the lung epithelia. Expression of the JSRV Envelope protein activates signalling cascades that promote cellular proliferation and malignant transformation of the cells. Initially, the tumour cells grow along the alveolar walls in a pattern reminiscent of human BAC, but subsequently become more invasive and metastasize to the local lymph nodes. Larger tumours may be necrotic and fibromatous at their centre. As the tumour grows, fluid production in the lung increases and this is likely to promote virus spread to other sheep. Only when the tumour reaches a size large enough to compromise lung function, do clinical signs appear. Critically, the majority of infected animals in endemic areas never show outward signs of infection, but they may be shedding virus, thus promoting inadvertent introduction of the disease into previously unaffected flocks and new geographical areas

JSRV: a member of the *Betaretrovirus* genus

JSRV is the virus responsible for the induction of OPA. JSRV belongs to the family *Retroviridae*, to the subfamily *Or- thoretrovirinae* and the genus *Betaretro-virus*. The *Betaretrovirus* genus also com-prises Mouse Mammary Tumour Virus (MMTV) responsible for a mammary ade-nocarcinoma in the mouse, Mason-Pfizer Monkey Virus (MPMV) isolated from a Rhesus monkey, and Squirrel Monkey RetroVirus (SMRV)(7). In 2003, Dolly the sheep, the first mammal cloned from an adult cell, died after being diagnosed with JSRV and lung cancer in sheep(3)

Virus and genomic organisation

Retroviruses are RNA viruses infect-ing vertebrate species and many non-vertebrates. Virions (80–100 nm in diam-eter) are spherical and surrounded by an envelope, with spikes composed of virus-encoded glycoproteins. The envelope is composed of viral proteins and elements of the host-cell membrane (lipid bilayer and proteins). The virions carry two copies of the genome, composed of linear, positive, single-stranded RNA. The 7.58 kb genome of the infectious virus comprises four main genes, organised as 5'- *gag- pro- pol- env* - 3' (Fig. 1), which encode the virus proteins (reviewed in [4-6]). Interestingly, while the nucleotide sequences of *gag*, *pro* and *pol* are homologous to their counterparts in MPMV, the *env* gene of JSRV is more related to that of MMTV and Human En-dogenous Retrovirus -K (HERV-K). JSRV is organised as a simple retrovirus, with an additional open reading frame, named ORF-

x, that overlaps the 3’ end of the *pol* gene. ORF-x is unique among retroviruses and may encode a putative accessory pro-tein of 166 amino acids. Although the existence of the protein is debated, ORF-x is strongly conserved in various isolates, and sequence analyses suggest a selective pressure for its conservation [6- 8] (and our unpublished data). Interestingly, two sub-genomic mRNA with splice ac-ceptor sites within or in the vicinity of ORF-x have been identified, suggesting that this putative gene may actually be tran-scribed [3]. We have also identified these two mRNA in tumoral lungs (unpublished data).

The JRSV genome contains non-coding regions at the ends of the genome, that are essential for the virus replication: R re-peated at both ends; U5 unique to the 5’ end and U3 unique to the 3’ end. The inte-grated genome is flanked by the long termi-nal repeat (LTR) composed of the 3 regions U3-R-U59(2). The LTR serve as the sites of transcriptional initiation. The U3 region contains several elements important for vi-ral transcription and tropism. The *gag* gene (*group-specific- antigen*) encodes a single polyprotein that is cleaved into at least three proteins: the matrix (MA), the major capsid protein (CA) and the nucleocap-sid (NC). The *pro* gene encodes a protein compatible with already-described dUT-Pase in its 5’ part and a protease (PRO) in its 3’ end. Whereas the protease cleaves the precursor polyproteins, the dUTPase (reviewed in [8]) prevents the incorpora-tion of deoxyuridine triphosphate (dUTP) by the reverse transcriptase [1]. The *pol* gene is predicted to encode the enzymatic activities: Reverse Transcriptase (RT) and integrase (IN), respectively implicated in the replication of the viral RNA and in the integration of the retrotranscribed DNA provirus into the host genome. The RT is a RNA-dependent DNA polymerase, essen-tial for the conversion of viral RNA into DNA. The *env* gene encodes the surface (SU) and transmembrane (TM) glycopro-teins. The SU glycoprotein interacts with the cellular receptor of JSRV in sheep, Hyal-2, a glycosylphosphatidylinositol an-chored hyaluronidase-2 [7]. The TM gly-coproteins presumably anchor SU into the

lipid bilayer and are composed of a hy-drophobic stretch of amino acids followed by a short cytoplasmic tail. The JSRV en-velope is a major determinant for the cel-lular transformation as discussed in detail below.

JSRV is phylogenetically related to the Enzootic Nasal Tumour Virus (ENTV), the agent responsible for nasal adenocarci-noma, a contagious tumour of the mucosal nasal glands affecting sheep and goats. In infected animals, epithelial cell prolifer-ation is responsible for continuous nasal discharge, respiratory distress, exophthal-mos and important skull deformations (for review see [8]). Co-infection of ENTV and JSRV has been reported [4,13].

A family of endogenous retroviruses, enJSRV (endogenous JSRV) closely re-lated to JSRV, is present in domestic and wild sheep and goats [3-4]. JSRV and en-JSRV genomes are highly related with 90–98% homology in deduced amino-acid sequences [5]. Endogenous retroviruses (ERV) are vertically transmitted as sta-ble Mendelian genes in the germline of most eukaryotes. They derive from the in-tegration of exogenous viruses in the host genomes, followed by genetic stabilisation through accumulation of mutations. Sev-eral families of HERV such as HERV-F, HERV-FRD, HERV-K, HERV-R, HERV-T and HERV-W (defined by the tRNA com-plementary to their putative primer binding site using the one letter code for the tRNA's corresponding amino acid) have been de-scribed in the human genome. Eight to twelve copies of enJSRV have been lo-cated on metaphase chromosome spreads of sheep and goats using fluorescent in situ hybridisation [8,14] (Fig. 2).

The biological significance of ERV is still largely debated. Expression of ERV has been described in the placenta and gen-ital tract of mammals including humans with HERV-W. In the female genital tract, enJSRV expression is limited to the epithelia and is particularly abundant in the

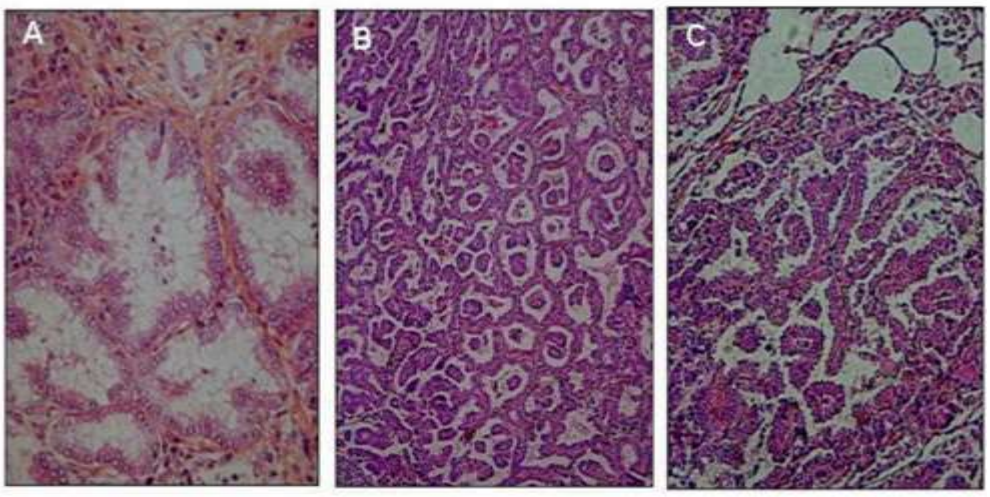

Figure 1. Subtypes of lesions observed in OPA: bronchioloalveolar (A), acinar (B) and papillary (C). (A color version of this figure is available at www.edpsciences.org/vetres.)

wheelbarrow test") is the flow of abun-dant mucoid fluid (up to 500 mL per day in advanced disease) from nostrils when the rear legs of the animal are raised. Extra-thoracic metastases are rare. Macroscopic examination shows enlarged lungs infil-trated with tumoural areas, varying from small nodules (1–30 mm) to lobar consol-idation [8,12]. The disease is multifocal, disseminated in both lungs, pneumonic in appearance, with the airways filled with fluid produced by the tumoural cells.

According to the latest WHO classify-cation for human lung cancers [7], OPA should be referred to as a mixed adeno-carcinoma with associated bronchioloalve-olar, papillary and/or acinar subtypes. The bronchioloalveolar differentiation is characterised by the expansion of cells fol-lowing the alveolar septa, also referred to as the lepidic spread, without destruc-tion of the alveolar architecture. The pap-illary subtype is defined by the pres-ence of papilla-like structures protruding above the epithelial layer and replacing the underlying alveolar architecture. Fi-nally, the acinar subtype is composed of duct-like structures or acini and tubules composed of cells resembling bronchial glands. In JSRV-induced adenocarcinoma, these three histopathological subtypes may be present within the same tumoural tissue(6,10).

The OPA tumoural cells derive from epithelial cells of the distal lung, namely alveolar type II cells (for ∼80% of the cells) and Clara cells (for ∼15% of the cells) [7]\. Type II pneumocytes produce different components of surfac-tant, a tensio-active agent that allows the maintenance of alveolar integrity.

Interestingly, tumoural cells over-express CD208/DC-LAMP (Dendritic Cell Lyzosomal Associated Membrane Protein) [4], a protein belonging to the LAMP family of proteins (Lysosomal-Associated Membrane Protein), and initially described in activated dendritic cells. CD208/DC-LAMP is also con-stitutively expressed in human, murine and ovine type II pneumocytes, and is over-expressed in human bronchioloalve-olar carcinoma and OPA [7]. In type II pneumocytes, CD208 is expressed in the constitutive membranes of the lamellar bodies, specific vesicles specialised in surfactant production. The role of CD208 over-expression in tumoural development is still unknown.

Mechanisms of oncogenesis

Oncogenic retroviruses have been historically divided into two groups

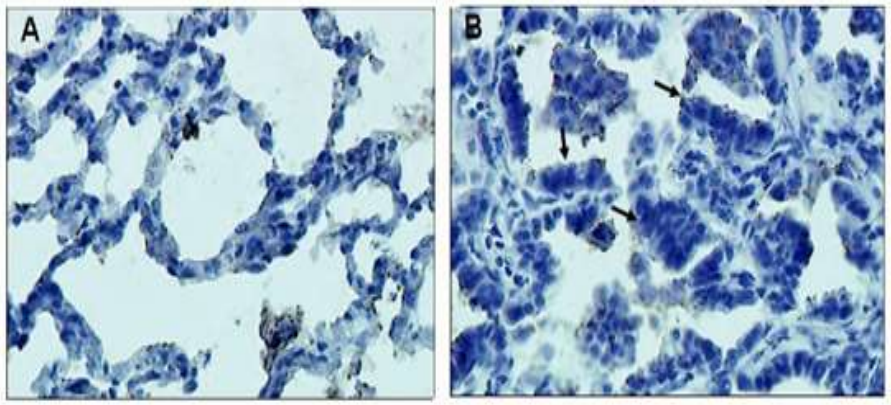

Figure 2. Microscopic pattern of lesions from OPA. Typical aspect of a non-tumoural (A) and tumoural ovine lung (B) labelled with an anti SP-A (Surfactant Protein A) antibody. Arrows show tumoural cells, i.e. type II pneumocytes labelled with and anti SP-A antibody. (A color version of this figure is available at www.edpsciences.org/vetres.)

depending on the speed of disease induc-tion. Acute and non acute retroviruses cause tumours with a short or long latency period respectively. Acute retro-viruses have been described in mice, birds, primates and are oncogene-bearing retroviruses. Viral oncogenes are derived from normal cellular genes or proto-oncogenes, involved in regulation of cell proliferation. Once

captured by the virus, proto-oncogenes undergo mutations that lead to uncontrolled cell proliferation. Rous Sarcoma Virus (RSV) is an example of avian retrovirus bearing an oncogene, *v-src*, deriving from a mammalian cellular kinase.

Typical lesions of OPA may be observed in just a few weeks following experimental inoculation of concentrated JSRV particles [6,4, 8]. This timeframe of disease in-duction and the multifocal pattern of OPA are compatible with the presence of an oncogene in the JSRV genome [8]. JSRV DNA transfection in murine NIH 3T3 fi-broblasts induces foci of transformed cells, clearly indicating that the JSRV genome contains an oncogenic element [4, 7]. However, to date no sequence homolo-gous to

any cellular oncogene has been detected in the JSRV genome [7,9]. The open reading frame (orf-x) of JSRV might be a potential oncogene, although it does

not present any sequence homology with known oncogenes [6, 7], and its deletion does not prevent transformation in vitro.

It is now clearly established that JSRV induces tumours via the oncogenic prop-erties of its envelope, which is both nec-essary and sufficient to induce transfor-mation. The transforming property of the JSRV envelope has been demonstrated in vitro in various cell lines including murine NIH 3T3 fibroblasts [4], rat 208F fibrob-lasts [7], avian DF-1 fibroblasts [4, 3], bronchial human BEAS-2B epithelial cells [1], canine kidney MDCK epithelial cells [3], and rat kidney RK3E cells [6]. The oncogenic property of the JSRV en-velope has also been shown in vivo in an immuno-deficient mouse model [8] and recently in sheep [7]. Expression of the JSRV envelope in mice using a replication-incompetent adeno-associated virus vector, AAV6, results in lung tumours similar to those observed in sheep [7]. The bron-chioloalveolar localisation of the tumours and the expression of the surfactant protein SP-C show that the transformed cells are derived from type II pneumocytes [8]. Us-ing a replication-defective virus carrying the *env* gene under the control of the JSRV LTR, it has been shown that the JSRV envelope is sufficient to induce lung tu-mours in sheep. The envelope of the related ENTV virus displays the same oncogenic property both in vitro [2, 3] and in vivo [8,11].

Deletion experiments show that the TM (transmembrane) region of the envelope is the main determinant for cell trans-formation [1, 3, 8]. In addition to the TM region, deletions of the SU (sur-face) glycoprotein (going from the signal peptide to the junction between the SU and TM subunits) also abolish transfor-mation induced by the envelope, suggest-ing that multiple domains of SU may be involved in cellular transformation. The cytoplasmic tail of TM, composed of 43 amino acids, is essential for the trans-formation process in MDCK and NIH-3T3 cells [4, 6,12]. cor-responding to a potential consensus site (phosphorylated on tyrosine Y) linked to the SH2 domain of the p85 subunit of PI3K (Phosphatidyl-Inositol-3 Kinase), a kinase that activates Akt. The PI3K-Akt signalling pathway is determinant in cel-lular proliferation and survival (for review [1]). Following a membrane stim-ulus such as a growth factor binding to its receptor, PI3K is recruited to the cell mem-brane. Phosphorylated-PI3K phosphory-lates the second messenger PIP2 (phos-phatidylinositol (4,5) biphosphate) into active PIP3 (phosphatidylinositol (3,4,5,13) triphosphate). PIP3 can then recruit PDK1 (phosphatidylinositol-dependent kinase 1), which in turn phosphorylates Akt. The ki-nase Akt can phosphorylate diverse sub-strates involved in signalling cascades con-trolling cellular proliferation, survival and metabolism. Akt phosphorylation inhibits proteins such as GSK-3 (Glycogen Syn-thase Kinase 3), FOXO (forkhead box

tran-scription factor), p24 or Kip1, and activates mTOR (mammalian target of rapamycin), an important regulator of cell growth.

The mechanisms leading to JSRV-induced cell transformation are in fact much more complex than previously con-sidered. Several experiments rule out a direct role for the YXXM motif in Akt ac-tivation. In JSRV-transformed cells, phos-phorylation of the Y590 residue of the intra-cytoplasmic TM tail, or interaction between the p85 subunit of PI3K and the envelope (a prerequisite for Akt activa-tion), have never been shown [4, 3]. Mutations of the YXXM motif do not abol-ish Akt phosphorylation, so that the exact role of this motif remains to be deter-mined [2, 4, 6]. Moreover, implication of the YXXM motif may differ between cell types in in vitro experiments [4, 6, 1]; while it is essential for transformation of NIH 3T3 fibroblasts, it is not required for transformation of avian DF-1 fibroblasts. Nevertheless, the pres-ence of the YXXM motif seems to affect the efficiency of envelope-mediated trans-formation [3]. Since the YXXM motif does not explain the oncogenic properties of JSRV, the mechanism of Akt activation in transformed cells still need to be de-termined. Interestingly, treatment of cells with LY294002, a PI3K-specific inhibitor, drastically reduces Akt phosphorylation in NIH 3T3 cells [2,5,11,14], suggesting that PI3K-dependent Akt activation may occur.

CONCLUSION

Over the last few years, research on JSRV and the resulting OPA has focussed on the molecular mechanisms of cell trans-formation. Interesting results came from the discovery that the virus envelope acts as a potent oncogene. Several cellular pathways seem to occur in the cell trans-formation.

To conclude, research into the biology of JSRV and mechanisms leading to the development of OPA is of great interest both for the naturally induced cancer in sheep and for BAC, the related human cancer. Even though a viral agent remains uncer-tain in BAC patients, understanding the steps leading to the transformation of lung epithelia may be of interest in the context of therapeutic approaches in human lung cancers in general and BAC in particular.

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الخلاصة

- Jaagsiekte Sheep Retrovirus (JSRV) هو فيروس بيتاريتروفيروس يصيب الأغنام. يمكن إعادة رعاية هذا الفيروس لسرطان غدي رئوي ، عن طريق تحويل الخلايا الظهارية من القصيبات والحويصلات ، وهو شكل محدد من سرطان (BAC) الهوائية. يشبه سرطان الحيوان هذا سرطان القصيبات السنخي البشري مع الخلايا المستهدفة من خلال مستقبل الغشاء JSRV الرئة البشري لم يتم تحديد مسبباته الفيروسية بعد. يتفاعل بسيط ولا يحتوي على أي مادة أورام معترف بها. لقد ثبت الآن جيدًا أن بروتين JSRV إن جينوم .Hyal2 الغلاف الفيروسي هو منشئ الورم في حد ذاته ، عبر المجال السيتوبلازمي للبروتين السكري عبر الغشاء يشارك في التحول MAPK و PI3K / Akt وبعض مجالات البروتين السكري السطحي. تنشيط مسارات الناجم عن المغلف. يرتبط تطور الورم بتنشيط التيلوميراز. ستركز هذه المراجعة على تحريض السرطان JSRVبواسطة