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Tumorigenesi del Mesotelioma Maligno: Il ruolo chiave della genetica

Introduzione

La revisione della letteratura proposta in questa sezione vuole sottolineare alcuni dei concetti chiave riguardanti la genetica e le vie coinvolte nella tumorigenesi del Mesotelioma Maligno.
Circa 250 articoli sono stati analizzati a questo proposito e se ne propone una sintesi schematica che non ha la presunzione di essere esaustiva in ogni dettaglio e pertanto, qualora si necessitasse di ulteriori approfondimenti, si rimanda alla bibliografia riportata alla fine del testo.

Biologia molecolare del mesotelioma

Come è noto, il mesotelioma maligno (MM) è una neoplasia che deriva da un'anomala proliferazione tumorale della pleura, del pericardio, del peritoneo, della tunica vaginale, del testicolo o dell'epitelio ovarico (1,2).
Ha un'incidenza in crescita, ed è purtroppo legato ad una prognosi spesso infausta (3,4). Varie sono le ipotesi patogenetiche di questa malattia ed esse sono state indagate approfonditamente (5-8).
Il MM è caratterizzato da una lunga latenza prima delle sue iniziali manifestazioni che portano alla diagnosi e, in questo lungo periodo, alterazioni genetiche possono avere luogo e caratterizzare le alterazioni neoplastiche (9-11). E' proprio sulla genetica e sulle vie patogenetiche legate a questa neoplasia che si punterà l'attenzione in questa revisione bibliografica.

Geni

I cromosomi maggiormente colpiti in questa neoplasia sono: 1, 3, 4, 6, 9, 13 e 14 (12). Le anomalie genetiche che più comunemente caratterizzano il mesotelioma pleurico maligno e che analizzeremo singolarmente sono le seguenti: $p16^{INK4a}$ /$p14^{ARF}$ (13,14), NF2 (15,16), p53 (17-20), PTEN (21-23), BAP-1 (24), LATS2 (25), PI3K/AKT/mTOR (22,26), EGFR (27,28), VEGF (29-31), pRb (32,33), BCL-2 (34-36), hippo (37-39) e Wnt (40,41).

$p16^{INK4a}$/$p14^{ARF}$

Il gene $p16^{INK4a}$ /$p14^{ARF}$ è conosciuto anche come CDKN2A/ARF ed è localizzato sul cromosoma 9p21.
Si tratta di un importante gene oncosoppressore che codifica per due proteine: $p16^{INK4a}$ e $p14^{ARF}$ (42-43).
La proteina $p16^{INK4a}$ è una proteina inibitrice di CDK che porta all'inattivazione di pRb.
La proteina $p14^{ARF}$, invece, regola la funzione di p53 inibendone la degradazione attraverso l'interazione con MDM2 (27,44,45).
Queste modificazioni giocano un ruolo fondamentale nella regolazione del controllo del ciclo cellulare; inoltre, queste alterazioni genetiche sembrerebbero legate ad una maggiore aggressività tumorale e ad una prognosi più infausta (13,14).
In particolare, questi geni sono implicati nello sviluppo di differenti tipologie di neoplasie (46-48). Allo stesso modo, possono esservi mutazioni genetiche di questo tipo nel mesotelioma pleurico maligno (13, 50-54).
Esperimenti scientifici hanno dimostrato che se questo gene viene "spento", si può verificare una sorta di "accelerazione" nella cancerogenesi dovuta all'esposizione ad amianto (55-59).
Studi di terapia genica sono volti alla riattivazione del gene $p16^{INK4a}$ /$p14^{ARF}$, per ripristinare le funzioni che vengono perse quando questo gene risulta mutato. Queste ricerche hanno dimostrato che, riattivando il gene in questione, si ottiene un arresto del ciclo cellulare delle cellule di mesotelioma, una inibizione della fosforilazione di pRb, una diminuzione della crescita cellulare. Tutte queste modificazioni potrebbero essere legate, dunque, ad un aumento della sopravvivenza, un incremento dei livelli di proteina p53, una spinta verso l'apoptosi cellulare (60-63,12). La terapia genica, volta al ripristino delle funzioni alterate dalla mutazione di

questo gene, sembrerebbe avere dei risultati preliminari promettenti.

NF2

NF2 è una sigla che si riferisce al gene neurofibromatosi di tipo 2 ed è una caratteristica genetica che viene ereditata in modo autosomico dominante e che comporta la predisposizione ad una sindrome tumorale, caratterizzata dallo sviluppo di schwannomi vestibolari bilaterali dell'VIII nervo cranico e altre neoplasia cerebrali, inclusi meningiomi ed ependinomi.
Questa sindrome deriva dalla mancata espressione del gene NF2 che è un oncosoppressore.
Inoltre, questo gene, sebbene sia conosciuto per la sindrome menzionata, risulta associato al mesotelioma maligno (64-69).
La mancata attività proteica legata alla codificazione del gene mutato sembrerebbe legata ad una maggior possibilità di carcinogenesi, rispetto a quei pazienti che non hanno questa alterazione genetica. Questo dato risulta sicuramente incrementato per i pazienti che sono stati esposti ad amianto (22,70). Tuttavia, la precisa definizione delle funzionalità di questo gene non è stata ancora completamente determinata.
La terapia genetica legata a questo gene riguarda il tentativo di "over-esprimere" il gene in questione utilizzando dei vettori virali. Questi studi hanno dimostrato risultati interessanti come il controllo del ciclo cellulare e della proliferazione (71-75).
Sicuramente la riespressione del gene NF2 nei pazienti affetti da mesotelioma maligno potrebbe contribuire in modo significativo all'inibizione della proliferazione cellulare e dell'invasività tumorale (76).

BAP-1

Alcuni studi clinici hanno cercato di comprendere come mai in alcuni villaggi sembrava essere presente una sorta di predisposizione genetica al mesotelioma pleurico. In queste ricerche, tra i geni alterati e dunque considerati coinvolti in questa patogenesi, è stato riscontrato anche BAP-1 (77-79).
Inoltre, recenti studi hanno dimostrato che BAP-1 è un onco-soppressore localizzato sul cromosoma 3p21 che sembrerebbe avere un ruolo nella regolazione del ciclo cellulare e nella risposta al danno del DNA (80-81).
Questa alterazione genetica è stata riscontrata in pazienti affetti da mesotelioma maligno, soprattutto nell'istotipo squamoso piuttosto che in quello epitelioide (82-84).
In particolare, questa modificazione genetica patologica sembrerebbe legata ad una peggior prognosi (85-86), oltre che allo sviluppo di neoplasie (87).
La terapia genica è in corso di studio non solo per arrivare a proporre un trattamento efficace per i pazienti che presentano l'alterazione genica di questo gene, ma anche per prevenire eventualmente il mesotelioma maligno in soggetti che risultato mutati per BAP-1.

LATS2

Il Large Tumor Suppressor (LATS) è stato il primo marcatore tumorale identificato nella drosophila (88).
Nell'uomo questo gene si trova in una regione del cromosoma 13 (13q11-12) e risulta frequentemente alterato nei tumori (89-90).
Sono state identificate due forme di LATS: LATS1 e LATS2. In particolare, LATS2 è una proteina centrosomale che sembra sia implicata nella suddivisione mitotica (91), nella regolazione dell'inibizione della crescita di Hippo (37) e nell'attivazione di p53 (92-93).
Questo gene é stato studiato nel mesotelioma maligno ed in particolare in linee cellulari caratterizzate da una delezione del cromosoma 13q11-12. Per queste analisi sono state utilizzate delle tecniche di ibridazione genomica comparativa, confermate poi tramite PCR. Questi test hanno dimostrato la presenza di mutazioni geniche di LATS2 nelle cellule di mesotelioma maligno (25).

Secondo queste ricerche, LATS2 sembrerebbe avere un ruolo nella proliferazione e nella sopravvivenza cellulare. Tuttavia, ulteriori studi sono necessari per confermare se questo gene giochi un ruolo effettivamente causale nello sviluppo di mesotelioma maligno.

Metilazione del DNA

Nel mesotelioma maligno studi riguardanti la metilazione del DNA hanno mostrato risultati promettenti.
E' stato dimostrato che il profilo di metilazione può essere considerato come un discriminante tra la pleura fisiologica e le sue alterazioni patologiche, in particolare quelle caratteristiche del mesotelioma (94).
Vi sono studi che ritengono che il profilo di metilazione possa addirittura essere considerato come un marcatore diagnostico utile per identificare neoplasie della pleura primitive e secondarie (95).
Altre ricerche si sono soffermate sulla relazione tra l'outcome dei pazienti e il loro stato di metilazione ed hanno notato interessanti differenza riguardanti la sopravvivenza in relazione con questa alterazione genetica (96).
Altri studi hanno analizzato anche la diagnosi e l'eventuale approccio terapeutico epigenetico (15,97).

MicroRNA

L'espressione dei miRNA é un ulteriore meccanismo importante nello sviluppo di tumori, secondario alla loro capacità di controllare differenti processi biologici.
Per questo motivo, molti ricercatori hanno soffermato la loro attenzione sul profilo dei miRNA per verificare eventuali discrepanze/associazioni tra queste diverse espressioni genetiche e la pleura (98-103).

Altri geni

Il gene salvador (SAV), componente della cascata Hippo è stato scoperto nella drosofila 81349 ed è considerato uno dei geni soppressori alterati in differenti forme neoplastiche (16, 104-105). Recentemente, è stata dimostrata la delezione a livello del cromosoma 14q22 in circa il 5% delle linee cellulari di mesotelioma; tuttavia, il reale ruolo di questo gene nella patogenesi di questa malattia è ancora in corso di studio (25).
Inoltre, a livello delle linee cellulari di mesotelioma maligno è stata riscontrata anche una delezione a livello del gene della β-catenina (CTNNB1) in circa il 10% dei casi (106). Il CTNNB1 sembrerebbe essere un fattore di stimolazione della crescita cellulare in differenti forme tumorali (107),sebbene anche in questo cqso ulteriori studi potranno chiarirne l'eventuale ruolo patogenetico.
Recenti studi hanno suggerito che la via di segnale Hedgehog è attivata nelle linee cellulari di mesotelioma maligno (108). Infatti, questa via di comunicazione sembrerebbe regolata da 13 geni nella patogenesi cancerosa. Tuttavia solo tre di questi geni sono risultati mutati nelle linee di mesotelioma maligno: PTCH1, SMO and SUFU (108-110).
Il ritmo circadiano è regolato da differenti geni e proteine che riguardano diversi processi: il sonno, la temperatura corporea, gli ormoni, la risposta immunitaria e tanti altri (111).
Diversi studi hanno dimostrato una possibile correlazione tra le alterazioni del ritmo circadiano e lo sviluppo di cancro (112-113). Nell' ambito del mesotelioma maligno sono in corso studi su differenti geni tra i quali i seguenti: the clock genes PER (period), CRY (cryptochrome) BMAL1 (aryl hydrocarbonreceptor nuclear translocator-like) (114-116).

Conclusioni

Le alterazioni genetiche associate al mesotelioma maligno sono in corso di studio: molte sono state identificate e tante altre sono in via di definizione.
Tutte queste ricerche sono volte al raggiungimento di una maggior conoscenza anche della genetica del

mesotelioma maligno, per comprendere come mutazioni genetiche possano correlare a questa patologia. Definirne il ruolo patogenetico ed eventualmente causale aprirebbe a nuove prospettive di ricerca e sicuramente a possibili strategie terapeutiche sperimentali volte a ripristinare, qualora possibile, una corretta genetica che in queste malattie appare distorta.

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